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RELATIONSHIPS BETWEEN STEREOSTRUCTURE AND PHARMACOLOGICAL ACTIVITIES

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Previous surveys (1–4) on the relationship between chemical structure and biological activity in these *Annual Reviews* have treated this subject in a comprehensive, though not exhaustive, fashion. In the present review attention is focused primarily on the role of stereochemical factors in the action of drugs on excitable tissue. More specifically, the material covered deals with steric factors arising from asymmetric centers and from conformational isomerism in molecules that exert their primary action at cholinergic, adrenergic, analgetic, histaminic, and serotonin receptors. Effort has been directed toward a highly-selective interpretive appraisal of the present status of the subject. Because of space limitations, the stereoselectivity[1] of drugs with enzymes has not been discussed. The literature coverage extends from January, 1966, through December, 1968. Older literature is cited where necessary.

The advent of configurational and conformational analyses of organic molecules and the development of newer methods for the determination of molecular geometry has stimulated interest in the shape of biologically active compounds. Since the earliest documented report by Cushny (5), who demonstrated a difference in activity between antipodes, numerous examples of stereoselectivity in drug action have appeared and a number of recent reviews are available which touch on this subject (6–10).

One of the major difficulties usually associated with interpreting relationships between structure and activity in congeneric series is that of factoring drug availability in the biophase from events at the receptor, particularly when the tests are carried out *in vivo*. Hansch (11) has made significant progress in this area by use of substituent constants but, until this method is refined further so that different processes which are dependent on the same physical parameters can be factored, it is difficult to interpret the

[1] The term "stereoselectivity" rather than "stereospecificity" will be employed in cases where pharmacological activity is found predominantly in one isomer, though not exclusively. The latter term implies that activity resides only in one isomer. Since the former situation is more widely observed, this term is also used in general discussions.

results of such studies at the receptor level. The fact that optical antipodes possess identical solubility, and diastereomers very similar physical properties, suggests that large potency differences between stereoisomers usually are due primarily to differences in affinity or intrinsic activity, or both (6). Indeed, the stereoselectivity usually seen in drug action is one of several lines of evidence supporting the receptor concept. (12).

Virtually nothing is known of the chemical constitution of receptors in excitable tissue. It is believed that these entities are composed of protein or lipoprotein components that are integrated into the membrane structure (13–16). The inherently dissymmetric properties of these components are most likely responsible for stereoselectivity in drug action. Proper alignment of key functional groups in the drug molecule with the receptor elements is

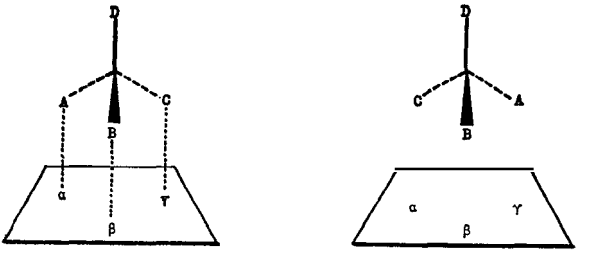

FIG. 1.

believed to trigger conformational changes (17, 18) that ultimately are observed as a pharmacological effect. A ligand not possessing the requisite stereochemistry may be inactive or less potent than its stereoisomer because proper alignment is not achieved. This can be due to low affinity or low intrinsic activity, or both (6).

The well-known Pfeiffer relationship (19) that predicts that the enantiomeric potency ratio of a variety of drugs is proportional to the effective dose suggests that highly potent asymmetric compounds should possess higher stereoselectivity if receptor complementarity is a factor in the drug-receptor interaction. This relationship holds true only for drugs whose asymmetric center interacts with a dissymmetric portion of the receptor (20). Easson & Stedman (21) advanced the hypothesis of three-point attachment to explain differences in potency between enantiomorphs containing a single asymmetric center. According to this model, the sequence of three key receptor elements and three substituents attached to the asymmetric carbon of the active antipode are complementary to one another so that "fit" can be achieved (Figure 1a). The antipode possessing the opposite configuration cannot align these groups to fit the receptor and consequently would be less active or inactive (Figure 1b). The antipodes could have comparable affinities if one or two of the three points of attachment

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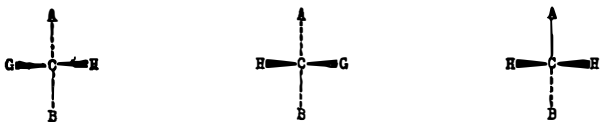
were not particularly strong. Whether or not the antipode possesses intrinsic activity would depend on the number of pharmacophoric groups properly aligned with the receptor. If only one or two pharmacophoric groups are required, it would be expected that the remaining group(s) could enhance or hinder drug-receptor association. This could result in optical antipodes having equal intrinsic activity but different affinities. Agonists differing only in affinity are quite common and, for example, cholinergic molecules such as (+)- and (−)-isomers of muscarine and of acetyl-β-methyl-choline (22–25) fall into this category. On the other hand, if intrinsic activity is dependent on the correct presentation of three pharmacophoric groups to the receptor, the model suggests that the pharmacologic effect would be stereospecific rather than stereoselective. In such a case the molecule possessing the "wrong" configuration may have little affinity or possess sufficient affinity to act as an antagonist of the active antipode. Examples of mutual antago-



a b c

FIG. 2

nism between antipodes have been reported for isoproterenol and related compounds (26–28). Utilizing the three-point attachment hypothesis, information on the contribution of a group to affinity may be obtained by comparing the optical isomers with the corresponding symmetrically substituted compound (Figure 2). If the isomer **a** is designated as the more potent antipode, with groups A and B essential for affinity, substituent G (usually methyl or alkyl) may affect the relative orders of affinities as follows: 1) **a**>>**b**∼**c**, 2) **a**>**c**>**b**, 3) **a**∼**c**>>**b**, and 4) **c**>**a**>>**b**. Other orders are also possible. The situation symbolized in the first case can be attributed to the ability of G to enhance association of **a** with the receptor; **b** would have G directed away from the receptor and hence have an affinity similar to that of **c**. Case 1 is approximated by muscarine if the C-2 asymmetric center is inverted or made symmetric without altering the relative stereochemistry of the remaining two centers (Table I). The methyl group must be *cis*-oriented to the quaternary group for high potency, although it can be noted that 2-methylmuscarine possesses this feature but has a low order of activity. The obstructive role of the additional methyl group (R′) cannot be easily accounted for in terms of a planar receptor model. However, if a portion of the receptor is located in a cleft, the presence of a second 2-methyl group could severely hinder drug-receptor association. Case 2 would be expected if G enhanced binding in **a** and hindered binding in **b**. An approximation of case 2 is found in comparing the potencies of

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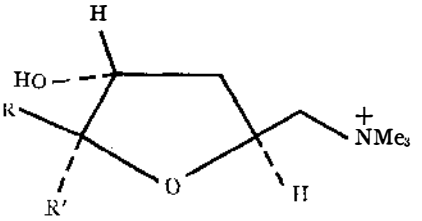
TABLE I

EFFECT OF MODIFICATION OF C-2 SUBSTITUENTS IN MUSCARINE



	Relative Muscarinic Potency[a]
(±)-muscarine R = Me, R′ = H	2.7
(±)-*epiallo*-muscarine R = H, R′ = Me	0.008
(±)-2-desmethylmuscarine R = R′ = H	0.008
(±)-2-methylmuscarine R = R′ = Me	0.0009

[a] From Ref. 21

methadone enantiomers with the desmethyl analogue (29) (Table II). The third case might suggest that G is not involved in the interaction of **a** with the receptor and that **b** has low affinity because of the steric hindrance offered by G. This appears to be represented by acetyl β-methylcholine whose optical antipodes possess intrinsic activities equal to that of acetylcholine (23). The (+)-isomer and acetylcholine have affinities of the same order of magnitude, but differ from the less active isomer by a factor of over 300 (Table III). The fourth case is consistent with G exhibiting steric hindrance to drug-receptor association in both **a** and **b**; the order of affinities would be caused by the absence of G in **c** and by the partial obstructive effect of G in **a** as compared to more severe steric hindrance from this group in **b**. An example that conceivably may represent case 4 is illustrated by the relative β-adrenergic blocking potencies of sulfonamidophenethanolamines (Table IV) (30). Although the racemates were not separated into optical antipodes, it is apparent that the desmethyl compound is more potent than either of the diastereomers which differ from one another by several orders

TABLE II

CONTRIBUTION OF THE 6-METHYL GROUP TO ANALGETIC ACTIVITY IN METHADONE

Compound	ED_{50}
R-(−)-methadone	0.8
S-(+)-methadone	25.7
6-desmethylmethadone	2.5

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TABLE III

CONTRIBUTION OF THE β-METHYL GROUP IN ACETYL-β-METHYLCHOLINE TO MUSCARINIC ACTIVITY

Compound	Relative Affinity
acetylcholine	100
S-(+)-acetyl-β-methylcholine	90
R-(−)-acetyl-β-methylcholine	0.3

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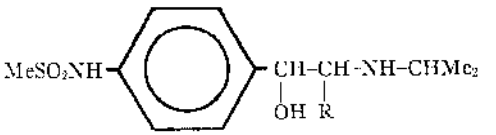
of magnitude. The possibility that the potency difference may be caused by a difference in conformational arrangement of ArCHOH and N-*i*-pr in ***erythro*** and ***threo*** isomers is unlikely, since proton magnetic resonance studies on these and related compounds (30, 31) indicate similar preferred conformations. The above cases all assume that the receptor can differentiate the two methylene protons in **c** even though this is a symmetrical molecule. This model was employed by Ogston (32) to depict how the active site of an enzyme might differentiate two carboxyl groups of a symmetric substrate.

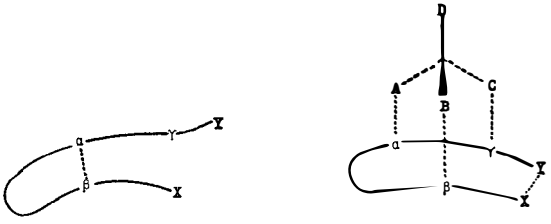
When taken literally, the three-point attachment concept implies that drug receptors are rigid templates. Nachmansohn (33) was early to recognize that acetylcholine may induce a conformational change in the receptor protein. It is now widely accepted that enzymes and noncatalytic proteins have the ability to undergo macromolecular reorganization upon interacting with a ligand. The conformational mobility of proteins has provided support for the induced fit hypothesis of Koshland (17) and has prompted the formulation of macromolecular perturbation theories of drug action (18, 34). The degree to which a drug can change receptor geometry is not known. It is possible that a range of flexibilities exists for different types of

TABLE IV

EFFECT OF THE 1-METHYL GROUP ON THE β-ADRENERGIC RECEPTOR BLOCKING POTENCY OF ARYLETHANOLAMINES



	Relative Blockade
(±), R=H	1
(±)-*erythro*, R=Me	0.4
(±)-*threo*, R=Me	0.00017



a b

FIG. 3

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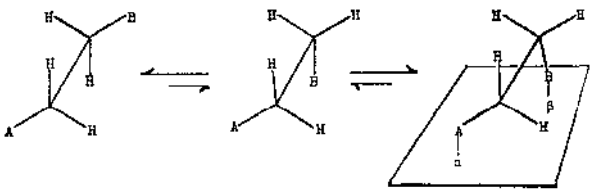
receptors. Receptor flexibility raises the question as to whether the pattern of key binding sites on a receptor in the resting state reflects the complementary arrangement of pharmacophoric groups in the drug molecule. For example, a receptor may undergo a conformational change in the drug-receptor interaction (Figure 3) because of a disruption of attractive forces ($\alpha \ldots \beta$) responsible for stabilizing the receptor in the resting state (figure 3a), with the concomitant creation of new points of attraction (X . . . Y) in the activated state (Figure 3b). In addition to receptor perturbation, it is quite possible that the preferred conformation of a drug can be transformed to one that is less favored when attached to a receptor. This has been aptly described by Ariëns & Simonis (35) as a "mutual molding of drug and receptor." Thus, an energetically favored ground state conformation of a drug molecule is not necessarily the pharmacophoric conformation, particularly if the energy barrier is not unusually high. A schematic representation of this process is illustrated in Figure 4. High affinities between substituents (A, B) in the drug molecule and the corresponding binding sites (α, β) on the receptor would result in the binding of the less favored conformer (Figure 4b). It is conceivable that ΔG for the conformational equilibrium, $\mathbf{a} \rightleftarrows \mathbf{b}$, could be as high as 2 Kcal./mole while still retaining affinity if the combined contribution of A and B to binding were in the range of -7 Kcal./mole.

In certain cases potency differences between flexible diastereomeric drugs may arise because the more active diastereomer has greater capability of



a b c

FIG. 4

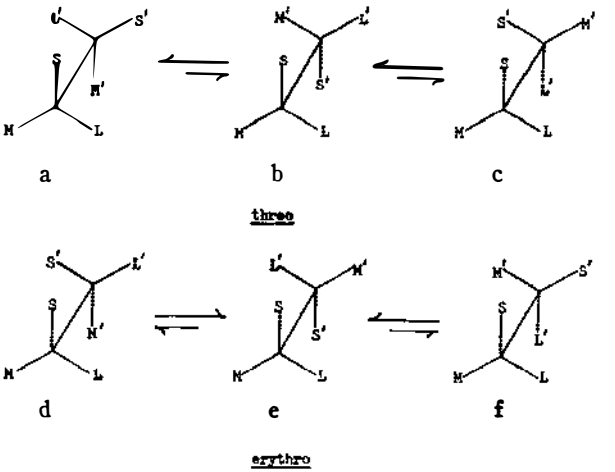


FIG. 5. Staggered conformational isomers of *threo* and *erythro* molecules containing small (S, S'), medium (M, M') and large (L, L') groups.

achieving a pharmacophoric conformation. For example, if the sequence of binding sites on a receptor is such that it can accommodate the preferred conformation of the *threo* isomer (Figure 5a) but not the most stable *erythro* conformer (Figure 5e), the latter would have to rotate to a less favorable conformation (Figure 5d) in order to attain an identical orientation of key groups for the receptor interaction (Figure 6). This would result in the *erythro* diastereomer having less affinity for the receptor. The simple model described above assumes that the S′ and L′ groups do not directly influence affinity of the drug for the receptor but rather do so in an indirect fashion. If steric hindrance to drug-receptor association or an additional point of binding depends on the positions of S′ and L′, a more complex version of the model would be more accurate. This can be illustrated by supposing that the large group (L′) in conformer **d** reduces affinity or intrinsic activity, or both, by sterically interfering with proper drug-receptor association. On the other hand, the conformer in the *threo* series (**a**) would contain a small group (S′) in an identical position and would not sterically interfere with binding or perhaps might aid binding by being engaged in an attractive interaction.

The primary difficulty in attempting to deduce a stereostructure-activity relationship through conformational analysis is that virtually nothing is known about the mutual conformational changes that occur in the drug molecule and receptor in the course of the drug-receptor interaction. At one extreme both the preferred and pharmacophoric conformation may be identical, and at the other extreme the receptor may place certain steric demands on the drug so that it is bound in an unfavorable conformation. Con-

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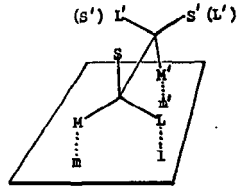

FIG. 6.

formationally rigid drug molecules may provide a solution to this problem. The advantages of this approach are that (*a*) key groups in the drug molecule are rigidly held in one position and (*b*) the chirality of the pharmacophoric conformation also can be investigated. The major disadvantage is that the prototype molecule under study must be modified to "freeze" it into a single conformation, and this may also influence activity unpredictably. The success of this approach depends largely on the moieties employed to confer rigidity. As a general rule, the rigid molecule should resemble as closely as possible the prototype drug.

In the following sections, I will attempt to show how these concepts and methods have been applied to the analysis of stereostructure-activity relationships.

AGENTS ACTING AT CHOLINERGIC RECEPTORS

Recent reviews (36–39) attest to the growing interest in the steric requirements for the ligands acting at cholinergic receptors. The possible allosteric nature of such receptors (19, 34, 40–42) adds an additional element of complexity to the task of correlating steric effects with activity. The fundamental importance of acetylcholine (ACh) has resulted in a number of attempts to define the most stable dihedral relationship in this flexible molecule. A nuclear magnetic resonance (n.m.r.) study of ACh in D_2O has led Culvenor & Ham (43) to conclude that a *gauche* orientation is preferred (Figure 7). The coupling constants determined in this study arise from a weighted average of all possible conformations and consequently no estimate of the fraction of *trans* conformer could be made. The structure of ACh as determined by Canepa, Pauling & Sorum by X-ray crystallography (44) has also been shown to have a *gauche* relationship. A similar arrangement has been reported for the N-C-C-O system in crystallographic studies of muscarine (45) and lactoylcholine (46). A variety of choline and ethanolamine derivatives not active in cholinergic systems also are *gauche* (47). This has been attributed to electrostatic attraction between the ether oxygen and the charged nitrogen atom and to intramolecular bonding between this oxygen and a proton of the N-methyl group (44, 46, 47). However, spectral studies in various solvents have yielded inconclusive results with regard to the latter possibility (48, 49). Shefter & Kennard (50) determined the conformational structure of acetylselenocholine by X-ray analysis and have

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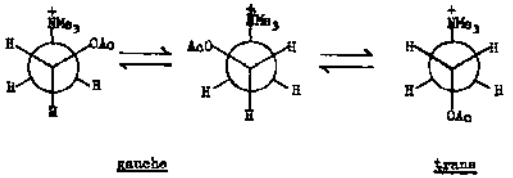

FIG. 7. Projection formulas illustrating staggered conformations of acetylcholine.

found the selenium atom and the quaternary group to be *trans*. Using molecular orbital theory, the minimum energy conformations for acetylcholine, muscarine, and muscarone have been calculated by Kier (51) to be essentially *gauche*. Theoretical conformational analysis by Liquori and co-workers (52) has led to the same conclusion for muscarine. However, a similar analysis (53) of the acetylcholine molecule predicted the presence of four conformations (two *gauche* and two *trans*) having energies separated by less than 1 Kcal/mole.

On the basis of some of the above studies, a *gauche* conformation (Figure 7) has been proposed for muscarinic activity (25, 36, 39, 44, 46, 50, 51). The relevance of structure determined by X-ray to the preferred conformation of cholinergic molecules in aqueous solution requires further experimental verification, since the packing restriction of the crystal lattice may change the conformational energy barrier. Although molecular orbital calculations hold great promise for conformational analysis, this technique will require considerable refinement in order to predict energy differences between conformers in aqueous solution. Presently, such calculations do not consider solvent effects that may play an important role on conformational free energy differences, particularly when charged and dipolar groups are in the molecule. Moreover, assuming that the *gauche* conformation is preferred, the conclusion that this arrangement is required for muscarinic action may be open to question if it is conceded that a preferred conformation can be converted in the receptor interaction to one that is not favored. The high affinity of muscarinic receptors for ACh (dissociation constant $= 2.08 \times 10^{-6}$) (54) makes it entirely possible that this may occur.

In contrast to the high stereoselectivity associated with muscarinic receptors, low steric requirements at the nicotinic sites are suggested by the relatively low enantiomeric potency ratios for substances such as nicotine (55), lactoylcholine (56), and acetyl-α-methylcholine (25, 57). Molecular orbital (58) and n.m.r. studies (59) on the nicotinium ion have suggested two conformations of similar energies (Figures 8a, b) and it was proposed that the internitrogen distance in conformer **a** is close to the distance between the nitrogen and carbonyl oxygen of ACh when in a *gauche* orientation (Figure 8c).

Attempts to circumvent difficulties associated with determining pharmacophoric conformations for cholinergic agents have led to the preparation

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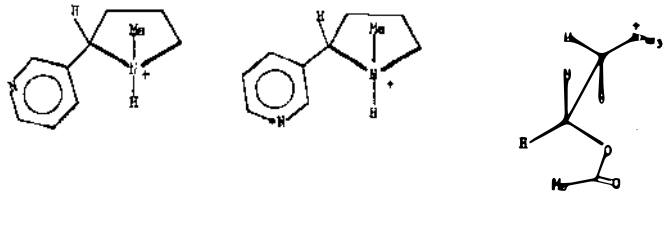
and testing of diastereomeric, conformationally restricted and rigid analogues of acetylcholine. Archer and associates (60) have prepared both diastereomers of 2-tropanyl acetate methiodide (Figure 9) and found that the



a b c

FIG. 8.

a b

FIG. 9.

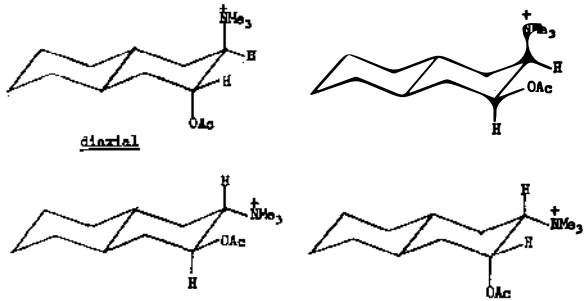


FIG. 10.

equatorial isomer (**a**) favors muscarinic action and that the axial compound (**b**) is primarily nicotinic. Both diastereomers had low potencies when compared to ACh. Based on the assumption that the conformations of both diastereomers are as depicted, it was concluded that muscarinic and nicotinic receptors favor the *trans* and *gauche* conformations (Figure 7), respectively. Smissman et al. (61) synthesized four *trans*-decalin analogues of ACh (Figure 10). The *trans* ring juncture prevents conformational inversion of the ring system. Although the boat conformation is possible, n.m.r. data suggested the chair form to predominate. The *trans-diaxial* racemate possessed 0.06 percent of the muscarinic potency of ACh and was the most active of the four diastereomers. Since the most active isomer is

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the only diastereomer which has the quaternary and acetoxy groups disposed in a *transoid* fashion, it was postulated that the *trans* conformation of ACh is responsible for muscarinic activity. In connection with the same study, the *erythro* racemate of α,β-dimethylacetylcholine was determined to have much greater (14 percent of ACh activity) muscarinic activity than the *threo* racemate, and this was attributed to the ability of the former to assume a *transoid* conformation more easily than the latter isomer (Figure 11). Nelson & Wilson (62) have prepared *cis* and *trans* bicyclo[2·2·2]oc-

FIG. 11.

FIG. 12.

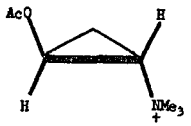

FIG. 13.

tane analogues of ACh (Figure 12). The *trans* isomer, which approximates the *transoid* arrangement of groups, was weakly muscarinic while the *cis* isomer showed no activity. Armstrong, Cannon & Long (63) have made enantiomers of *trans*-2-acetoxycyclopropyltrimethylammonium iodide (Figure 13). Unlike the previous ACh analogues, the N-C-C-O system in this molecule is conformationally rigid. The (+)-isomer was found to be as potent a muscarinic agent as ACh and 330 times more active than the (−)-isomer. Evidence was presented that indicated both isomers to be substrates of acetylcholinesterase. From this data it was concluded that the *trans* conformation of ACh (Figure 7) is involved in attachment to the muscarinic receptor. May & Triggle (64) have reported that bicyclic analogues (Figure 14) of the highly potent muscarinic agent, *cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide, have negligible activity and concluded that

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potent muscarinic molecules do not adopt any of the limiting conformations in the bicyclic dioxalones when attached to the muscarinic receptor. The chair and boat conformations illustrate the O-C-C-N moiety to be *gauche* and eclipsed, respectively. The inactivity of these compounds might be related to their inability to achieve a *transoid* conformation.

These studies appear to support the idea that a *transoid* O-C-C-N orientation is involved in the interaction with muscarinic receptors even though the preferred conformation for this moiety in ACh may be *gauche*. This would mean that a conformational change in the ACh molecule is induced upon interaction with the muscarinic receptor.

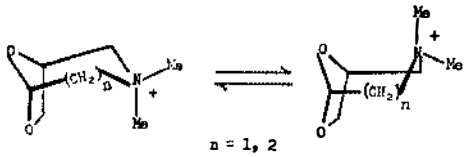

FIG. 14.

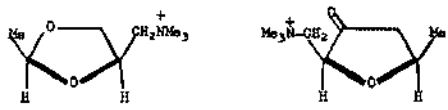

FIG. 15

Information on the mode of interaction of drugs with cholinergic receptors has also been obtained from correlations of absolute stereochemistry with activity. Belleau and coworkers (65, 66) have prepared optical antipodes of *cis*-F2268 (67) (Figure 15) and determined the more active isomer to possess the same absolute configuration as (+)-muscarine (68). The finding (24) that the more active antipode of muscarone has the opposite absolute stereochemistry and a greatly reduced enantiomeric potency ratio has been attributed to a difference in the mode of receptor interaction (65). The possibility that minor structural modification will alter the binding mode is not unique to cholinergics and appears to be a wide-spread phenomenon that also has been observed with other classes of drugs (69–73). Absolute configurational studies (23, 25) on acetyl-β-methylcholine have been carried out and its high stereoselectivity rationalized in terms of a spatial arrangement of groups similar to that found in (+)-muscarine (Figure 16). On this basis one might also expect the more active enantiomer of the cyclopropyl ACh analogue (63) to have the same configuration at the β-carbon (Figure 13). Although the (*S*)-configuration at the β-carbon atom is important for high muscarinic activity, Ellenbroek et al. (74) have reported that this is not the case for β-methylcholine esters having antagonistic properties.

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Thus, both stereoisomers shown in Figure 17 display very similar pA_2 values. On the other hand, marked stereoselectivity was found for esters containing an asymmetric α-carbon atom in the acid moiety. The concept of "accessory receptor areas" was formulated (37, 74) in an effort to rationalize the different stereoselectivities for agonists and antagonists. According to this view, the binding modes of muscarinic agents and antagonists differ in that the latter cover the receptor only partially. The accessory areas are topo-

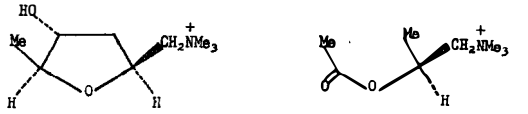

FIG. 16.

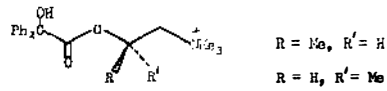

FIG. 17.

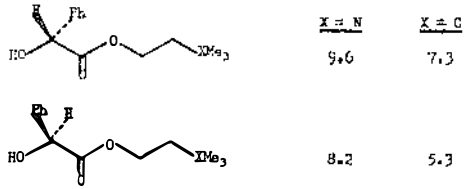

FIG. 18. pA_2 values for enantiomeric choline and carbocholine esters (refs. 37, 74).

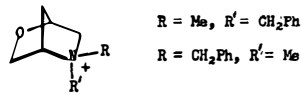

FIG. 19.

graphically asymmetric so that the configuration at the α-carbon of the acid moiety becomes the dominant feature governing affinity. Further support for this hypothesis was obtained with enantiomers of the ""carbocholine" esters (37), as it was found that the more active optical isomers in the nitrogen-free esters have the same configuration as the choline analogues (Figure 18). The low stereoselectivity associated with the choline moiety is also consistent with the observation (75) that compounds containing an asymmetric quaternary nitrogen atom (Figure 19) have comparable muscarinic blocking action. Similar concepts have been developed (76, 77) to explain transitions from agonist to antagonist in ascending a series of alkyltrimethylammonium ions.

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Agents Acting at Adrenergic Receptors

The well-known concept (78, 79) of *alpha* and *beta* adrenergic receptors and the development of selective agents (80–84) that act upon these receptor species have led to numerous attempts to delineate the steric requirements for adrenergic action. As most molecules that interact with adrenergic receptors contain at least one asymmetric center, the relationship of pharmacological activities with stereoisomerism represents an important part of structure-activity analysis and is particularly relevant to current adrenergic receptor hypotheses (85–87) that draw on these correlations.

The presence of an asymmetric center bearing the hydroxyl group endows both adrenergic agonist and antagonist molecules with high stereoselectivity. The more active antipodes usually are levorotatory and, where known (88–95), possess the (*R*) configuration. Agents acting on *beta* adrenergic receptors generally possess greater stereoselectivity than those interacting with *alpha* sites, as evidenced by higher (*R*)/(*S*) potency ratios for the former.

Patil and associates (96, 97) have investigated the relationship between absolute configuration and potency of a variety of *alpha* agonists in an effort to test the Easson-Stedman hypothesis (21), which states that (*R*) isomers enter into a three-point interaction involving the aromatic ring, hydroxyl group, and amine function (Figure 20). Accordingly, the (*S*) isomers are predicted to act like the desoxy derivatives because two-point contact not involving the hydroxyl group takes place. In normal tissues the desoxy analogues were found (96) to be more potent than (*S*) isomers; it was determined, however, that these compounds produced little effect and had marginal intrinsic activity when tested on reserpine pretreated tissue (97), thus indicating that the Easson-Stedman hypothesis is of predictive value for direct-acting *alpha* agonists but not for indirect effects. These studies suggest that compounds that produce adrenergic effects by promoting release of endogenous catecholamines generally are less stereoselective than those engaged in direct interaction with adrenergic receptors. The stereoselectivity of the uptake rates for norepinephrine antipodes appears to be concentration-dependent with little or no stereoselectivity exhibited at higher catecholamine levels (98–100). The *threo* and *erythro* racemates of α-methylnorepinephrine also are taken up equally well (101–106). On the other hand, retention appears to be highly stereoselective (105) so that (*R*)-iso-

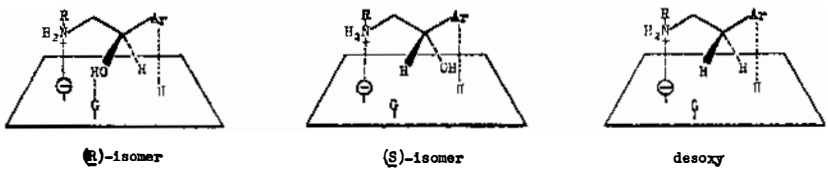

Fig. 20. An illustration of the Easson-Stedman hypothesis.

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mers and *erythro* compounds possess greater affinity than the (*S*) isomers and *threo* series, respectively (101–107). The marked stereoselectivity associated with the retention mechanism may prove to be of value in the design of highly specific false adrenergic transmitters (108). The mechanisms of retention, release, and uptake of brain catecholamines (109) may be similar to those found in peripheral nervous tissue and, if this is the case, it would be expected that agents that affect release and uptake would generally exhibit lower stereoselectivity than those that exert their effect by direct interaction with adrenergic receptors. Thus, (+)- and (−)-enantiomers of ephedrine and amphetamine exert their central stimulant effects in an indirect fashion and show low stereoselectivity while the action of pipradrol resides solely in the (*R*)-isomer and is direct-acting (110, 111). The fact that the more active enantiomers of amphetamine and (*R*)-pipradrol have opposite configurations supports the suggestion that they possess different modes of action.

It has been pointed out by Patil and associates (96) that the generalization that predicts (1*R*) stereoselectivity for *alpha* agonist action must be viewed with caution when applied to molecules containing two asymmetric centers. This conclusion was based on the finding that although both (−)-ephedrine and (−)-pseudoephedrine possess the requisite (1*R*) configura-

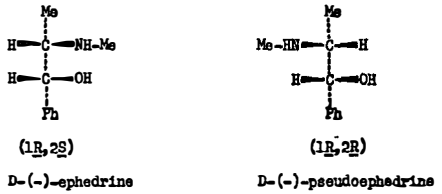


FIG. 21.

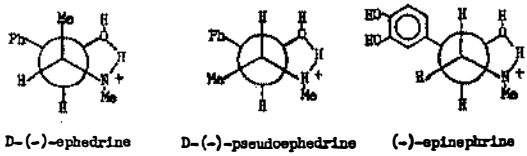
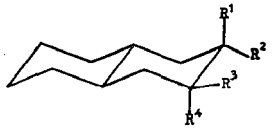


FIG. 22

tion (Figure 21), only the former is an agonist. The latter isomer was devoid of intrinsic activity but retained sufficient affinity to block the effects of (−)-ephedrine (112). Conformational analyses of these and related compounds were carried out by Portoghese (31) through n.m.r. studies and it was found that the preferred conformation of ephedrine (*erythro* isomer) and pseudoephedrine (*threo* isomer) are very similar with the exception of the orientation of the 2-methyl group (Figure 22). No firm conclusion could be drawn because it was not known whether the preferred conformation is

similar to that found in the drug-receptor complex; however, it was suggested that the methyl group in (—)-pseudoephedrine renders the molecule inactive by sterically preventing effective ion-pair formation with the receptor. It was proposed that epinephrine and norepinephrine assume similar conformations in agreement with the recent structure determination (X-ray crystallography) of norepinephrine hydrochloride by Carlström & Bergin (113). More recently Kier (114) has calculated the preferred conformations for ephedrine and pseudoephedrine. The conformation proposed for the latter compound did not agree with the experimental results obtained from the n.m.r. studies (31). In an effort to determine the effect of conformational isomerism on adrenergic activity, Smissman & Gastrock (115) have conformationally restricted phenethanolamine analogues (Figure 23) and have found all four racemates to be equipotent. No conclusions could be drawn because it was not known whether the activities were direct or indirect.



R^1	R^2	R^3	R^4
OH	Ph	H	NH_2
OH	Ph	NH_2	H
Ph	OH	NH_2	H
Ph	OH	H	NH_2

FIG. 23

The pattern of activity for *erythro* and *threo* isomers of α-methylnorepinephrine, α-methylepinephrine, and metaraminol parallels that found for the ephedrines in that only the (1*R*) isomers of the *erythro* series activate *alpha* receptors (102, 106, 116, 117). Since it is likely that these diastereomers adopt the same preferred conformations as the ephedrine isomers, steric hindrance by the α-methyl group in the *threo* isomers (31) may also account for the low potencies. The (1*R*) isomers in the *erythro* series are primarily direct-acting whereas the desoxy isomers are mainly indirect acting in conformity with the Easson-Stedman hypothesis (106).

With regard to action at *beta* adrenergic receptors, Tye et al. (118) reported that the (1*R*) isomers of both ephedrine and pseudoephedrine were primarily direct-acting while the diastereomers in the (1*S*) series possessed an appreciable indirect component. It is of interest that (1*R*,2*S*)-ephedrine, but none of the other isomers, was found to act as a partial agonist. The *beta* adrenergic action of *erythro* and *threo* diastereomers of α-methylnorepinephrine and the corresponding desoxy isomers have been tested on guinea pig trachea (106). All agents except (1*S*,2*R*)-α-methylnorepinephrine and the (—)-desoxy analogue were direct-acting. It was concluded that, so far as *beta* adrenergic receptors are concerned, the data are not in harmony with the Easson-Stedman hypothesis.

Although the more active antipodes of *beta* adrenergic receptor antagonists possess the (1*R*) configuration, introduction of a second asymmetric

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center may modify the blocking action or even render the compound inactive. The C-2 position is particularly sensitive to steric effects as exemplified by the fact that *threo* isomers of butoxamine and of ephedrine do not act as blocking agents while the *erythro* isomers having the requisite (1*R*) configuration are antagonists (118, 119). A somewhat similar relationship has been found among racemic *erythro* and *threo* sulfonamidoethanolamines (30). Both the relative and absolute stereochemical requirements for *beta* receptor antagonists and for *alpha* agonists appear to be analogous and Patil (119) has suggested that the steric hindrance by the 2-methyl group (31) in the *threo* isomers may be responsible for this phenomenon. Diastereomeric *beta* adrenergic blocking agents containing an asymmetric substituent at-

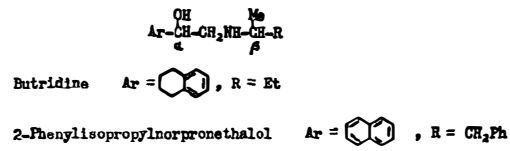

FIG. 24

tached to the basic nitrogen (Figure 24) have been investigated. Of the four butridine stereoisomers, those possessing the ($\alpha R,\beta R$) and ($\alpha R,\beta S$) configurations were responsible for the blocking activity, whereas the ($\alpha S,\beta S$) ($\alpha S,\beta R$) were devoid of any such action (120, 121). Similarly, *beta* blockade is associated mainly with the ($\alpha R,\beta R$) and ($\alpha R,\beta S$) isomers of phenylisopropylnorpronethalol (94). Although potency differences between the active isomers were noted, these studies indicate that the stereochemistry of the N-substituent is of minor importance and that the α-center plays a dominant role in the receptor interaction. The fact that a variety of pronethalol and propanalol analogues containing different N-substituents possess high antagonist activity (122, 123), coupled with the above data, suggests that the portion of *beta* adrenergic receptor which comes in contact with the N-substituent is neither highly dissymmetric nor structurally specific. Patil et al. (124) have concluded that the *alpha* receptor-protecting ability of *beta* blocking agents involves two-point interaction because optical antipodes show little or no difference in their protecting capacity. It is conceivable that *beta*-adrenergic receptors contain a hydrophobic region that is responsible for binding of the N-substituent and that proper alignment of the C-1 asymmetric center with the receptor is achieved in this fashion. A similar hydrophobic region does not appear to be present in *alpha* adrenergic receptors and it is possible that the hydrophobic N-substituents of beta blocking agents are in part responsible for the two-point interaction described by Patil (124).

Augstein et al. (125) have investigated the adrenergic neurone blocking activities of a series of aryloxyalkylguanidines and concluded that hydrogen-bonded cyclic conformations (Figure 25) are required for optimal potency.

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It was suggested further that *ortho* group in these series enhance biological activity by forcing the α-methylene group out of the plane of the aromatic ring. Monro et al. (126) prepared the *syn* and *anti* isomers of guanidoxan (Figure 26) and found only the former to possess adrenergic neurone blocking action. The conformational rigidity conferred by the cyclopropane ring allows only the *anti* isomer to assume a cyclic hydrogen-bonded conformation. The fact that this isomer is inactive suggests that the preferred cyclic conformation of the flexible blocking agents is not necessarily involved in the drug-receptor interaction.

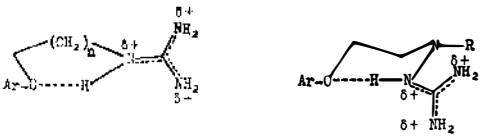

FIG. 25

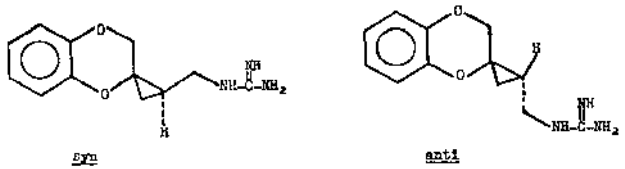

FIG. 26.

MISCELLANEOUS RECEPTOR CLASSIFICATIONS

This section includes agents whose mechanisms of action are not known or do not fall into the categories that already have been discussed.

Agents acting at analgetic receptors.—Steric aspects of the interaction of strong analgetics with receptors have been reviewed by Portoghese (9), and citations pertaining to this subject can also be found in recent comprehensive reviews on analgetic antagonists (127, 128). Marked changes in the absolute stereoselectivity of analgetics have been postulated (71) to be reflective of differing modes of interaction with analgetic receptors. Earlier reports (69, 72) that proposed that the modes of interaction between diampromide (and related N-substituted compounds) (Figure 27) and analgetic receptors are different from that of methadone have been corroborated by Casy & Hassan (129). The inversion of stereoselectivity of the analgetic receptors was rationalized in terms of possible differences in preferred conformations between the anilide analgesics (130) and methadone (131, 132). Another analgetic, α-methadol, was also suggested (71) to interact with receptors in a manner that is dissimilar to that of methadone. Since the absolute stereochemistries of the more active antipodes of the methadols (133), isomethadols (134), and normethadol (135) have in common the (3*S*) con-

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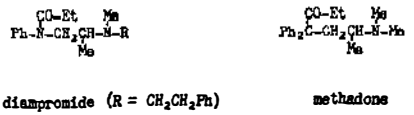
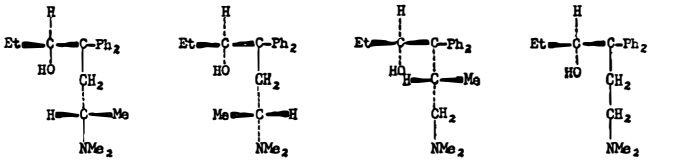


diampromide (R = CH_2CH_2Ph) methadone

FIG. 27.



(3S,6S) (3S,6R) (3S,5S) (3S)

(-)-α-methadol (-)-β-methadol (+)-β-isomethadol (-)-normethadol

FIG. 28. Absolute stereochemistries of the more active enantiomers of methadol and related compounds.

figuration (Figure 28), it appears that the hydroxyl group is of primary importance in orienting α- and β-methadol at the receptor surface with the 6-methyl group playing a relatively minor role. In the case of isomethadol the configuration at both asymmetric centers appears to be important, as only one optical isomer is active. Acetylation of the alcohol group of α-methadol results in a change from (6*S*) to (6*R*) receptor stereoselectivity. This phenomenon can be explained on the basis that such a conversion eliminates the hydrogen-bonding donating potential of the C-3 group with the receptor and thereby leads to a different mode of interaction. According to this interpretation (136) the different modes of interaction are characterized by high stereoselectivity at C-3 and low stereoselectivity at C-6 for the methadols, and the reverse in the methadol acetates. The binding mode of methadone is thought to resemble those of the methadol acetates because they all possess (6*R*) stereoselectivity and can enter into hydrogen bonding with the receptor only by acting as proton acceptors. Portoghese & Larson (137) have prepared enantiomers of α- and β-prodine and determined the configurations of the more potent enantiomers to be (3*R*,4*S*) and (3*S*,4*S*), respectively (Figure 29). The observation that 3-desmethylprodine possessed greater potency than either of the less active prodine antipodes, coupled with the fact that the C-3 asymmetric centers in the more potent isomers have opposite configurations, led to the suggestion that the unsubstituted side of the piperidine ring might play a major role in the receptor interaction. Casy (138) has postulated that the greater activity of (±)-β-

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prodine over (±)-α-prodine is related to the possibility that the former adopts a boat conformation in aqueous medium. Smissman & Steinman (139) have synthesized and tested conformationally restricted *axial-* and *equatorial*-phenyl analogues of prodine and found both diastereomers (Figure 30) equiactive. It was concluded that no definite requirements of the phenyl group are necessary for analgetic action. Portoghese and coworkers (140, 141) prepared diastereomeric, conformationally rigid meperidine analogues (Figure 31) and found the *endo*-phenyl epimer to be twice as potent

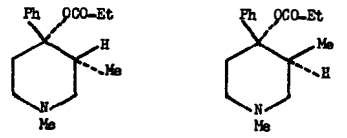

FIG. 29. Absolute stereochemistries of the more active prodine diastereomers.

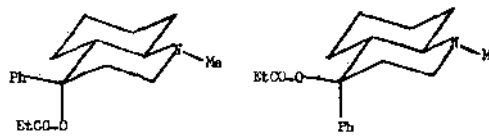

FIG. 30.

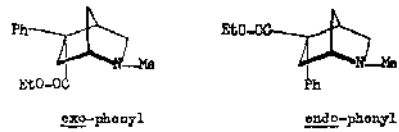

FIG. 31.

as meperidine and six times more potent than the *exo* isomer. In terms of brain concentrations, however, the *endo-exo* potency ratio was 3.7. Evidence was presented that quantitatively related the difference in brain levels to their partition coefficients. The minimal conformational requirements were rationalized (141) in terms of different modes of interaction, although it was pointed out that this does not necessarily mean that highly potent analgetics also have low conformational requirements.

May & Eddy (142) have reported the separation of physical dependence capacity (PDC) from analgetic activity by optical resolution of the *cis*-5,9-diethyl benzomorphan derivative (Figure 32). The (−)-isomer was as potent as morphine and yet possessed nalorphine-like antagonism while the (+)-isomer had weak analgetic activity and high PDC in morphine-depen-

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dent monkeys. Since the racemate had no PDC it was concluded that the (−)-isomer antagonized some of the effects of (+)-isomer. Similar relationships have been found (143, 144) among optical isomers of other 5,9-substituted benzomorphans. Tullar et al. (145) have prepared all possible stereoisomers (optical and *cis-trans*) of pentazocine, cyclazocine, and related compounds as narcotic antagonists. The (−)-antipodes were found to be more potent than the (+)-antipodes, but potency differences between *cis* and *trans* isomers were not large. Bentley et al. (146–151) have prepared several series of closely related derivatives of 6,14-*endo*-ethenotetrahydrothebaine and have found that many members in these series are powerful narcotic analgetics. One such member, etorphine (Figure 33), was 1000 to 80,000

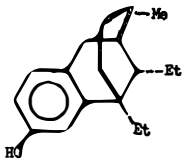

FIG. 32.

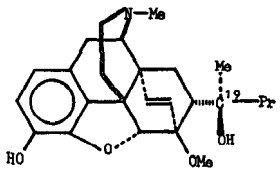

FIG. 33.

times more potent than morphine, depending on the test method employed (152). Although etorphine achieves higher brain levels than dihydromorphine this cannot fully account for its potency (153). Nuclear magnetic resonance (154) and X-ray crystallographic (155) studies have confirmed the structures of these molecules and indicate that the C-19 carbinol function is internally hydrogen bonded with the methoxy group. There is a substantial difference in potency between C-19 epimers, with the configuration depicted in Figure 33 being more active. This has led Bentley (156) to suggest that the *tertiary* hydroxyl group forms a point of specific binding to the receptor and that the alkyl chain, when properly positioned, leads to further enhancement of binding.

Agents acting on histamine receptors.—Hite & Shafi'ee (157) have pointed out that the hypothetical histaminic receptor formulated by Barlow (158), to predict the configuration of the more active pheniramine isomers, is not valid. This was confirmed by the finding (159) that the more active pheniramine antipodes (Figure 34) are in the (*S*)-series rather than the (*R*)-series predicted by Barlow (158) on the basis of a hypothetical receptor. No conclusions concerning the nature of the histaminic receptor were

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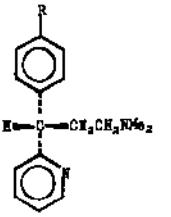

FIG. 34.

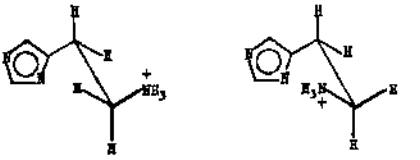

FIG. 35.

drawn, since there was no evidence that conformationally mobile antihistamines are bound to the receptor in the most stable conformation. Extended Huckel molecular orbital calculations on monoprotonated histamine led Kier (160) to conclude that two conformations (Figure 35) of nearly equal preference exist in solution. It was proposed that the *trans* conformation was involved in the interaction with histamine receptors in the guinea pig ileum and that the *gauche* arrangement might be accepted by receptors responsible for gastric secretory stimulation. Since diprotonated histamine should predominate at gastric pH, it would be of interest to determine its preferred conformation in that state. Under these conditions it might be expected that the *trans* conformation would predominate because of electrostatic repulsion between the two protonated groups. Nauta et al. (161) have speculated on the preferred conformation of benzhydryl ethers related to diphenhydramine and on the nature of the histamine receptor.

Agents acting on serotonin receptors.—Little is known about steric factors associated with serotonin receptors. On the basis of molecular orbital calculations (162), a single preferred conformation was proposed and a complementary receptor hypothesized. The relationship of the internitrogen distance of serotonin, in its predicted conformation, to that of LSD was offered as an explanation of LSD's antagonism.

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