Comments and Communications

In Praise of Chisholm's "Social Responsibility"

Dr. George Brock Chisholm's article "Social Responsibility" (*Science*, January 14, p. 27) merits more than the rather limited distribution afforded by *Science*. I am convinced there are many hundreds of intelligent non-scientists who would welcome these fundamental analyses of social phenomena that can lead to war.

Naturally, I am considerably interested in any intelligent means of preventing further destructive wars. I saw the beginnings of World War I in Berlin and London and, as an interned Japanese prisoner in Manila, personally felt the intensely evil effects of World War II.

It seems to me that there must be many other members of the AAAS who will share my belief that we should employ every means possible to prevent a return to another medieval period in the world. Scientists have a stake in this matter, not alone in protecting their own interests but in upholding and buttressing the kind of social pattern suggested by Dr. Chisholm, which is a workable plan and which means their survival.

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Concerning the Nutritive Value of Breads

In a recent publication (November 1948) entitled "Outlook for Bread and Flour Enrichment" (prepared by the Committee on Cereals, Food and Nutrition Board, National Research Council) the following reference is made to certain data reported in one of our publications (Guerrant and Fardig. *J. Nutrition*, 1947, 34, 523).

"Using various forms of bread to the extent of 30 percent of the diets of young rats, these authors showed the following gains in weight during an 8-week feeding period: whole wheat bread, 82 grams; non-enriched bread, loss; enriched bread, 95 grams; dark bread, 15 grams; milk bread, 20 grams. An important feature of these experiments is that they illustrate the importance of the non-bread components in the dietary in determining the relative nutritional merits of the breads. The presence of 20 percent purified casein in all diets insured the presence of adequate protein for the high demand of young growing rats—much higher than those of slower growing human beings."

Inasmuch as the foregoing statements have led to a misinterpretation of our data, a word of explanation is hereby presented. To this end it seems necessary to point out again that the studies referred to above were concerned particularly with the various flours and breads made therefrom as sources of *thiamine* and *riboflavin*. This we attempted to make clear in the title and elsewhere in our publication. Since this point is not made clear in the report prepared by the Committee on Cereals, and certain pertinent details of our studies are not included, it is my desire at this time to emphasize that we regarded growth rates reported as indications of the relative *thiamine* and *riboflavin* content of the respective breads, and only in these respects are they a measure of the relative nutritive values of the breads.

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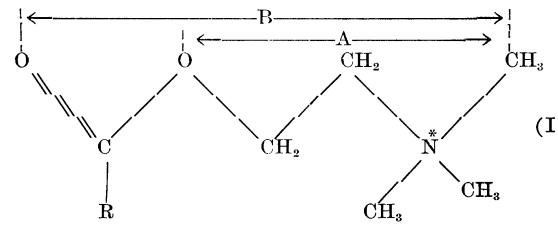
The Structure-Action Relationships of the Choline Group

In an interesting recent article (*Science*, 1948, 107, 94) Pfeiffer has suggested that all the numerous drugs which possess parasympathetic stimulant action "contain a ketone oxygen group adjacent to an ether oxygen linkage with a methyl substituted nitrogen at a distance of two saturated carbon atoms," as in (I):



(I)

He assumes further that these three groups, carbonyl oxygen, ether oxygen, and N-methyl, are prosthetic groups and proceeds to calculate from models the interprosthetic distances A and B. It may be noted in passing that this is an unusual use of the term "prosthetic," which literally means "something added in order to make up a deficiency" and has come to refer in immunology and enzymology to groups which must be added to an inert molecule (usually protein) in order to render it physiologically active (e.g. antigenic or enzymically active); in this sense, the obvious prosthetic group of acetylcholine is the acetyl group which converts the relatively inert substance choline into the highly potent parasympathetic transmitter. It would seem more fitting to refer to the three groups as pharmacologically *active* or *pharmacodynamic* groups. But leaving aside such niceties of terminology, it would indeed be welcome if the complexities of the pharmacology of parasympathetic drugs could be seen to have an underlying basis as simple as Pfeiffer suggests. Unfortunately, his assumptions are beset with difficulties, of which two may be briefly considered: (1) not all molecules containing the three groups disposed spatially as required show parasympathetic stimulant actions and (2) some molecules show such actions but do not contain all three groups.

(1) Not all choline esters of carboxylic acids are parasympathetic stimulants although they contain the three groups at the appropriate mean distances apart. The extraordinary potency of the acetic ester compared with that of its near homologues, such as the formic and propionic esters, is well known, but higher homologues, e.g. the butyric and valeric esters, have scarcely any parasympathomimetic activity (H. C. Chang and J. H.

Gaddum. *J. Physiol.*, 1933, 79, 255; R. Hunt and R. de M. Taveau. Bull. No. 73, Hygienic Laboratory, U. S. Treasury, 1911) and, when a phenyl nucleus is introduced, as in the benzoic, phenylacetic esters, etc., the compounds appear to have purely nicotine-like properties (R. Hunt and R. de M. Taveau. Bull. No. 73, Hygienic Laboratory, U. S. Treasury, 1911); the benzilic ester is atropine-like (H. R. Ing, G. S. Dawes, and I. Wajda. *J. Pharmacol.*, 1945, 85, 85). Similarly in the carbamic esters, alkyl substitution in the carbamyl group leads to a sharp decline in parasympathetic stimulant actions which are completely absent in the phenylcarbamic ester (M. B. Bender, M. A. Spirtes, and D. B. Sprimson. *J. Pharmacol.*, 1943, 77, 107); the dibutyl- and diamylcarbamic esters are atropine-like (K. C. Swan and N. G. White. *Amer. J. Ophthal.*, 1944, 27, 933).

It may be argued, and probably with justice, that the emergence of atropine-like properties in the benzilic and dibutylcarbamic esters means that these esters have an affinity for parasympathetic endings but block the action of acetylcholine. There would appear to be a gradation of properties which pass through a stage when the esters have little or no affinity for parasympathetic endings and neither stimulate nor paralyze them; thus Swan and White (K. C. Swan and N. G. White. *Amer. J. Ophthal.*, 1944, 27, 933) found in the dialkylcarbamic esters of choline that the diethyl member was a weak miotic, the di-*n*-propyl member inactive, and the dibutyl member was mydriatic. Similarly, the lower fatty acid esters of choline have stimulant effects at parasympathetic endings; benzoic, phenylacetic esters, etc. have no action, and benzilic and tropic esters paralyze them.

(2) The ethers of choline contain no carbonyl oxygen, but the simple alkyl ethers have well-established parasympathomimetic properties; indeed Dale (*J. Pharmacol.*, 1914–15, 6, 147) noted that choline ethyl ether resembled muscarine more closely than it did acetylcholine in that its nicotine-like effects were less prominent; the ethyl ether of β-methylcholine is even more like muscarine and is a powerful miotic. Finally, true parasympathomimetic effects, e.g. on the heart and blood pressure, are shown by alkyltrimethylammonium salts which lack both the carbonyl oxygen and the ether linkage (J. H. Burn and H. H. Dale. *J. Pharmacol.*, 1914–15, 6, 417; R. Hunt. *J. Pharmacol.*, 1926, 28, 367; R. Hunt and R. R. Renshaw. *J. Pharmacol.*, 1925, 25, 315; 1926, 28, 367).

It seems clear therefore that although the carbonyl oxygen, ether oxygen, and N-methyl group occur in many parasympathomimetic drugs, these groups are not all indispensable and their presence in a molecule does not necessarily ensure parasympathetic stimulant action.

One of the most interesting features of Pfeiffer's article is the prominence which is given to the spatial relations of the so-called prosthetic groups. There is indeed suggestive evidence that the actual molecular dimensions of members of the choline group have an important influence on the potency of these drugs. Two dimensional factors appear to be important: (1) the size of the "cationic head" of the molecule and (2) the length of the chain attached to it.

(1) The most active members all contain the $\overset{+}{N}Me_3$-group as cationic head; there appears to be no exception to this rule. Successive replacement of methyl groups by either hydrogen or ethyl leads to a steep decline in parasympathomimetic activities (Table 1). The replacement of one or more methyl groups by hydrogen (R. L. Stehle, K. J. Melville, and F. K. Oldham. *J. Pharmacol.*, 1936, 56, 473) leads to relatively weak bases. The dissociation constants of these bases are not known, but they would not necessarily decrease in the order of successive replacement of methyl by hydrogen; nor if they did is it likely that they would decrease sufficiently steeply to account for the progressive decline in activity. No doubt both the instability of the cations containing one or more hydrogen atoms and the absence of methyl groups play their part in the observed decline in activity.

TABLE 1

$-\overset{+}{X}$	Mols $AcO \cdot C_2H_4\overset{+}{X}$ = 1 mol acetylcholine		
	Cat's blood pressure	Rabbit intestine	Frog's heart
$-NMe_3$	1	1	1
$-NMe_2H$	50	> 40	> 50
$-NMeH_2$	> 500	> 1,000	> 500
$-NH_3$	> 2,000	20,000	40,000
$-NMe_2Et$	3	2.5*	2
$-NMeEt_2$	400	700*	1,500
$-NEt_3$	> 2,000	1,700*	> 10,000
$-PMe_3$	13	12	12
$-AsMe_3$	66	90	83

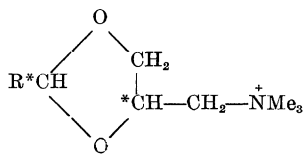
* These figures refer to guinea pig ileum.

The successive replacement of methyl by ethyl groups does not produce so dramatic an effect until at least two methyl groups are replaced.[1] The high activity of the mono-ethyl member of the series is particularly interesting. A possible explanation of this observation will be discussed elsewhere. The replacement of three methyl groups by ethyl reduces the muscarine activity of the cation to negligible proportions; this effect of the triethylammonium group (and the similar effect of higher trialkylammonium groups) has also been observed in the analogous ethers (R. Hunt and R. R. Renshaw. *J. Pharmacol.*, 1929, 37, 309; 1933, 48, 105), in betaine esters (R. Hunt and R. R. Renshaw. *J. Pharmacol.*, 1933, 48, 105), in tetra-alkylammonium salts (J. H. Burn and H. H. Dale. *J. Pharmacol.*, 1914–15, 6, 417; R. Hunt. *J. Pharmacol.*, 1926, 28, 367; R. Hunt and R. R. Renshaw. *J. Pharmacol.*, 1925, 25, 315), and in Bovet's acetal compounds (formula II: E. Fourneau, D. and F. Bovet, and G. Montezin. *Bull. Soc. Chim. biol.*, 1944, 26, 134, 516).

The replacement of the N-atom in acetylcholine by P or As (A. D. Welch and M. H. Roepke. *J. Pharmacol.*, 1935, 55, 118) also increases the size of the cationic head of the molecule and leads to a decline in activity (Table 1); this result is interesting because the three methyl groups and the high basicity are retained. The change will, of course, increase the "interprosthetic" distances A and B in formula I, but only slightly.

[1] Unpublished work by Mrs. P. Holton in this Laboratory.

(2) If parasympathetic drugs of the general type R–$\overset{+}{N}Me_3$ are considered, it will be found that the most active member of any group of homologues will usually be the one containing a 5-atom chain (excluding hydrogen atoms) in the group R. In the esters, acetylcholine is much more active than either formyl- or propionylcholine[2]; similarly N-alkylcarbamylcholines are less active than carbamylcholine. Both the nitrous and the nitric esters of choline, which Dale (*J. Pharmacol.*, 1914–15, 6, 147) found to have considerable muscarine activity, contain 5-atom chains, but the higher and lower homologues have not been studied; the former compound was for many years called "synthetic muscarine." Pyruvylcholine (H. C. Chang and J. H. Gaddum. *J. Physiol.*, 1933, 79, 255), which contains a 6-atom chain, is moderately active, but its lower homologue, glyoxylylcholine, has not been studied. The acetic esters of formocholine ($HO \cdot CH_2 \cdot \overset{+}{N}Me_3$) and γ-homocholine ($HO \cdot CH_2CH_2CH_2\overset{+}{N}Me_3$) are both less active than acetylcholine (R. Hunt and R. de M. Taveau. Bull. No. 73, Hygienic Laboratory, U. S. Treasury, 1911). In choline ethers, the ethyl ether is more active than either the methyl or propyl ethers (H. H. Dale. *J. Pharmacol.*, 1914–15, 6, 147). Similarly, in formocholine ethers, $RO \cdot CH_2\overset{+}{N}Me_3$, where R is CH_3, C_2H_5, C_3H_7, or C_4H_9, the most active member is the *n*-propyl ether (A. J. Ewins. *Biochem. J.*, 1914, 8, 366). Bovet's compounds (II) are interesting; they should exist in



(II)

diastereoisomeric pairs, but, since the distance across the ring between the asterisked carbon atoms will be only slightly less (about 8%) than that between the α and γ carbon atoms in a normal chain, we can regard (II) when R is CH_3 as the nearest approach to the 5-atom chain type; in fact, the compound in which R is CH_3 is markedly more active than the compounds in which R is H or C_2H_5 (E. Fourneau, D. Bovet, F. Bovet, and G. Montezin. *Bull. Soc. Chim. biol.*, 1944, 26, 134, 516).

In the alkyltrimethylammonium series, the *n*-amyl member was found by Raventos (*Quart. J. exp. Physiol.*, 1937, 27, 99) to be the most active on the frog's auricle; lower members were less active, and higher members inactive or antagonistic.

There appear to be very few exceptions to this 5-atom chain rule.[3] Simonart (*J. Pharmacol.*, 1934, 50, 1) recorded that the methyl ether of β-ethylcholine was a more powerful vasodilator than the ethyl ether, but the reverse was true of the corresponding ethers of β-methyl- and β-propylcholine. Hunt and Renshaw (*J. Pharmacol.*, 1932, 44, 151) found that in the series of thioethers, $RSCH_2\overset{+}{N}Me_3\}$ I, where R was CH_3, C_2H_5, C_3H_7, and C_4H_9, the *n*-propyl and ethyl ethers were about equally active vasodilators. Among betaine esters ($RO \cdot CO \cdot CH_2\overset{+}{N}Me_3$) the methyl and ethyl esters were also about equally active vasodilators (R. Hunt and R. R. Renshaw. *J. Pharmacol.*, 1925, 25, 350; 1926, 29, 17). Finally Kulz (*Arch. exp. Path. Pharmak.*, 1928, 98, 337) found in the alkyltrimethylammonium series that the *n*-butyl member was the most active on the frog's heart.

This brief survey of the available data suggests that the actual dimensions of what we have called the cationic head and the chain in members of the choline group have an important effect upon the intensity of the action at parasympathetic endings; such a result seems to indicate that a fairly precise fit between the drug-cation and some macromolecular structure in the living cell is required if a high degree of activity is to be observed.

We have so far been considering only the muscarinic properties of members of the choline group. It is unfortunate that the relations between structure and the nicotine-like actions of the group are much more obscure. There is some evidence that the size of the cationic head has an important effect upon the stimulant-nicotinic properties (e.g. on sympathetic ganglia) because they are diminished by replacing the N-atom of acetylcholine by P or As and abolished by replacing the three N-methyl groups by ethyl or larger radicals. Among onium salts also, only those containing three methyl groups attached to the central atom (N, P, As, or S) produce contracture of the frog's rectus abdominis (H. R. Ing and W. M. Wright. *Proc. roy. Soc.*, 1933, **114B**, 48). There are indications that particular radicals, e.g. *n*-butyl, benzyl, etc., intensify stimulant-nicotinic activity; thus the butyl ether of choline (A. Simonart. *J. Pharmacol.*, 1932, 46, 173) and the methyl ether of β-butylcholine (A. Simonart. *J. Pharmacol.*, 1934, 50, 1) both have striking nicotinic effects on blood pressure. It is generally assumed that β-methylcholine derivatives fail to show stimulant-nicotinic effects; this appears to be frequently but not invariably true: thus, whereas the *n*-butyl ether of β-methylcholine, in contrast to that of choline, has only a slight pressor action after atropine administration, Renshaw, *et al.* (*J. Amer. chem. Soc.*, 1938, 60, 1765) found that acetyl β-methylthiocholine ($CH_3CO \cdot SCHMeCH_2\overset{+}{N}Me_3$) had an intense nicotinic effect on blood pressure not only after, but even before, the administration of atropine.

The paralyzing nicotine-like action on sympathetic ganglia appears to be, like the curariform action in striated muscle, a general property of "onium" cations. There is no evidence, however, that the paralysis of ganglion cells runs parallel with that of voluntary muscle; indeed, what evidence there is suggests a reciprocal relation—that high curariform activity is associated (in onium cations) with low paralyzing activity on ganglion cells and vice versa. Tetraethylammonium is the best-known example of this inverse relation.

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[2] In the esters $C_nH_{2n+1}\ CO \cdot O \cdot CH_2CH_2\overset{+}{N}Me_3$ the chain length is $n+4$; i.e. formylcholine ($n=0$) has a 4-atom chain. If the carbonyl oxygen of formylcholine were regarded as part of a 5-atom chain, this ester would have to be compared with the formic esters of formocholine and γ-homocholine.

[3] We have neglected the small differences in length between 5-atom chains arising from the different atomic radii of C, O, and N because they would be insignificant in comparison with the differences in the lengths of homologous chains.