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Polarizing Forces of the Muscarinic Moiety

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As an extension of some recent discussions (*1–6*) concerning the chemical constitutional characteristics of the muscarinic drugs, the following treatment dealing with a quantitative evaluation of the polarizing forces of moiety components has been found to be of particular value. Moreover, since it is a general type procedure which may well find application in other chemical constitution biologic activity problems, a brief communication of the basic approach is illustrated here.

The method of evaluation developed by Price (*7*) was applied in the estimation of the polarizing forces of the moiety components of the well-known muscarinic agents outlined in Table 1. Insofar as possible, the over-all intramolecular distances of the agents compared in each series are nearly constant. It will be seen that decreases in potency in each series are strongly correlated with the absolute difference in polarizing force of the component examined from that corresponding component in acetylcholine.

As is well recognized by other workers in this field, acetylcholine appears to be a "two-headed" moiety, although a quantitative expression of the character of the two heads has been lacking. Somewhat vague references to groups of "high" or "low" polarity and to the degree of methylation of the nitrogen do not

TABLE 1

	Polarizing force of bracketed function in dynes × 10^{-4}	Potency	
		Depressor	Gut stimulation
Series I			
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-\left[-O-\overset{O}{\overset{\|}{C}}-\right]-CH_3$	− 0.32	1	1
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-O-CH_2-]-CH_3$	− 1.21	1/3	1/10–1/20
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-CH_2-CH_2-]-CH_3$	+ 0.77	1/6	1/25–1/30
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-\left[-CH_2-\overset{O}{\overset{\|}{C}}-\right]-CH_3$	+ 0.89	1/70	1/50–1/100
Series II			
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-\left[-O-\overset{O}{\overset{\|}{C}}-\right]-CH_3$	− 0.32	1	
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-I]$	− 0.39	≈ 1	
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-Br]$	− 0.55	1/10–1/50	
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-Cl]$	− 0.68	1/20–1/100	
$(CH_3)_3\overset{+}{N}-CH_2-CH_2-[-OH]$	− 1.46	1/200–1/1000	
Series III			
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2-\left[-\overset{+}{N}(CH_3)_3\right]$	+ 3.21	1	
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2-\left[-\overset{+}{N}H(CH_3)_2\right]$	+ 3.02	1/50	
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2-\left[-\overset{+}{N}H_2(CH_3)\right]$	+ 2.88	1/500	
$CH_3\overset{O}{\overset{\|}{C}}OCH_2CH_2-\left[-\overset{+}{N}H_3\right]$	+ 2.64	1/2000	

directly allow for quantitative evaluation in the more exact sense that model measurements do in the evaluation of steric factors. The evaluation of polarizing forces as illustrated above may fulfill to some extent this gap in the theoretical tools of the "structure-activity" pharmacologist.

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Hypothesis of the Biological Action of Radiation

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Numerous investigations on the effect of radiation on living organisms have brought us to a stage where the mechanism of action of radiation on cells may be clarified by mathematical interpretation. The studies of the late D. E. Lea (*1*) initiated such an approach.

Lethal effects of radiation have been studied by a number of authors with a wide variety of experimental materials, partly because of the ease with which experiments can be done in which the criterion of the effect of radiation is the death of the organism or cell, and partly because of the practical importance of the lethal action of radiation on cells in the treatment of cancer.

The manner in which radiation effects the killing of bacteria, or the inactivation of viruses, is becoming clearer. With viruses, the biological effect is believed to be due to a single ionization in the virus; with these materials exponential curves are typical in plots of inactivation vs. dosage. With bacteria, in some cases, such plots give sigmoid curves. Lea attributes sigmoid response curves to the tendency of some bacteria to clump. However, most of the survival curves for cells of higher organisms are also of a sigmoid nature. The formula of Blau and Altenburger (*2*), which is known as the multihit theory, is considered as explaining the facts of the case reasonably well. There are some discrepancies in it, in the experimental results from some studies, which cannot be fitted even by modifications of their formula.

Comparisons have been made between experimental data and the formula arising from the following hypothesis.

Rather than consider that there is only one radiation-sensitive region in a cell, which is the viewpoint of the multihit theory, assume that there are in a cell n molecules essential to the continued existence of the cell. Assume that the cell can survive if no more than r molecules out of the n are damaged by ionization from radiation—that is, the cell dies if more than a certain percentage of the n molecules are damaged, and that each molecule is damaged by one ionization. Then the following considerations arise:

a) Just as in the disintegration of radioactive elements, the probability that a molecule escapes damage is $e^{-\sigma t}$ where σ = action coefficient and t = duration of radiation; accordingly, $1-e^{-\sigma t}$ represents the probability that a molecule is damaged.

b) If we take a large number of cells, each of which contains n molecules, the first term in the expansion of the formula

$$[e^{-\sigma t}+(1-e^{-\sigma t})]^n$$

gives the probability that a cell suffers no damage to any of the n molecules after time t, the second term that one in n is damaged, and the $(r+1)$st term gives the probability that r of the n molecules suffer damage.

If we suppose that the cell can survive if no more than r molecules are damaged, then the survival curve is given by the following formula:

$$y = e^{(-\sigma t)n} + ne^{(-\sigma t)(n-1)}\cdot(1-e^{-\sigma t}) + \ldots + {}_nC_r e^{(-\sigma t)(n-r)}\cdot(1-e^{-\sigma t})^r$$

$$= \sum_{i=0}^{i=r} {}_nC_i e^{(-\sigma t)(n-i)}\cdot(1-e^{-\sigma t})^i. \qquad (1)$$

For simplicity, we may substitute x for $e^{-\sigma t}$ and we may then write Eq. (1) as follows:

$$y = \sum_{i=0}^{i=r} {}_nC_i x^{n-i}(1-x)^i,$$

$$\frac{dy}{dx} = (n-r)\,{}_nC_r x^{n-r-1}(1-x)^r.$$

The integral of this last expression is

$$y = (n-r)\,{}_nC_r \int_0^x x^{n-r-1}(1-x)^r dx. \qquad (2)$$

The incomplete β-function is defined by

$$\beta_x(p,q) = \int_0^x x^{p-1}(1-x)^{q-1}dx,$$

so the indefinite integral in Eq. (2) can be expressed as

$$\beta_x(n-r, r+1).$$

The complete β-function is

$$\beta(p,q) = \int_0^1 x^{p-1}(1-x)^{q-1}dx = \frac{(p-1)!\,(q-1)!}{(p+q-1)!},$$

so that

$$\beta(n-r, r+1) = \frac{(n-r-1)!\,r!}{n!}.$$

The coefficient in (2) is

$$(n-r)\,{}_nC_r = \frac{n!}{(n-r-1)!\,r!}.$$

Thus the survival curve (2) can be expressed in the form

$$y = \frac{\beta_x(n-r, r+1)}{\beta(n-r, r+1)}, \quad x = e^{-\sigma t}. \qquad (3)$$