Although decamethonium (C_{10}) stimulates chick biventer muscle, increasing N-substitution with alkyl or aryl groups results in the appearance of antagonist properties (Thesleff & Unna, 1954). Two such antagonists are decamethylene 1,10-*bis*-dimethylbenzyl-ammonium bromide (DPC_{10}), and decamethylene 1,10-*bis*-dimethyl (1-naphthylmethylene) ammonium bromide (DNC_{10}). The 2-chloroethyl derivative of DPC_{10}, decamethylene 1-(N-benzyl-2-chloroethylamino)-10-dimethyl-benzylammonium chloride hydrochloride, bears the same relationship to DPC_{10} as does benzilylcholine mustard (BCM) to benzilylcholine (Gill & Rang, 1966), and may accordingly be termed $DPC_{10}M$. Like other 2-haloalkylamines, $DPC_{10}M$ undergoes cyclization in solution to yield an ethyleniminium ion. It was hoped that, as with dibenamine and BCM, this might irreversibly alkylate receptors.

$DPC_{10}M$ did indeed produce an irreversible type of antagonism to carbachol and suxamethonium. The following observations suggested that $DPC_{10}M$ acted specifically on acetylcholine receptors: (*a*) contractions produced by 3·9 mM caffeine were unaffected by a concentration of $DPC_{10}M$ sufficient to abolish the response to a large dose of carbachol; (*b*) application of tubocurarine together with $DPC_{10}M$ prevented the appearance of the long-lasting $DPC_{10}M$ block. In early experiments the amount of antagonism produced by $DPC_{10}M$ appeared to be highly variable. The explanation of this variability was found to be that, in contrast to the action of BCM, the degree of block produced by $DPC_{10}M$ depended not only on the concentration of the antagonist and the time for which it was applied, but also on whether agonist was applied concurrently: rather than acting as "protecting" agents, agonists were found markedly to increase the blocking action of $DPC_{10}M$. Thus $1{\cdot}1\times10^{-6}$M $DPC_{10}M$ (as ethyleniminium) applied on its own for 15 min produced a final dose ratio to carbachol less than 1·2; when 3×10^{-5}M carbachol was applied for 4 min during the exposure to $DPC_{10}M$, the dose ratio produced was 2·0. This enhancement was seen even when $1{\cdot}5\times10^{-4}$M carbachol, applied for 90 sec, preceded the application of $DPC_{10}M$ by as long as 15 min. It is argued that this effect is due to the agonist causing a change in the receptors, the $DPC_{10}M$ having a greater affinity for receptors in this altered state than it has for those in the unchanged state. This has been termed a metaphilic effect of agonists, denoting their ability to alter the affinity of receptors for other compounds.

DPC_{10} and DNC_{10} were reversible antagonists, but they showed an equivalent phenomenon, the metaphilic effect appearing as "enhanced desensitization" in the presence of antagonist (see Flacke & Yeoh, 1968).

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The quantitative estimation of the activity of fourteen analogues of the neurohypophysial hormones on strips of mammary gland *in vitro*

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Quantitative estimation of the milk-ejecting activity of neurohypophysial hormones and analogue polypeptides is generally done *in situ* (for review see Berde & Bois-

TABLE 1. *Activities on the lactating rabbit mammary gland*

Substance	Activity in i.u./μ-mole		No. of 4-point assays	Ratio of activity rat uterus / rat B.P.	*In vitro* activity if value *in situ* = 100%	Difference
	in situ	*in vitro*	*in vitro*			
Asp[4]-oxytocin	298±127	266±8	6	823	89·3±2·7	−10·7
Val[3]-oxytocin	206±13·9	176±14·6	4	590	85·5±7·1	−14·5
De-amino[1]-oxytocin	436±45	516±38	4	556	118·2±8·7	+18·2
Oxytocin	100*	100*		90	100*	0*
Ile[8]-oxytocin	330±21	301±24·6	4	46·2	91·1±7·4	−8·9
Arg[8]-vasotocin	~220	252±16	6	0·47	114·3±7·2	+14·3
(Nε-For-Lys)[8]-vasopressin	~81	73·7±13·8	6	0·4	90·9±17	−9·1
Orn[8]-vasotocin	96±6	143±8·9	6	0·4	149·0±9·3	+49
De-amino[1]-Arg[8]-vasopressin	85·5±32	62·3±23·3	6	0·07	72·9±27·3	−27·1
Orn[8]-vasopressin	~52	61·5±22·8	6	0·03	118·2±43·8	+18·2
Lys[8]-vasopressin	63±10·5	81±14·3	4	0·02	128·6±22·7	+28·6
De-amino[1]-Phe[2]-Arg[8]-vasopressin	~4	4·3±0·4	6	0·01	107·5±10	+7·5
Phe[2]-Lys-vasopressin	~2·6	3·1±1·1	5	0·01	119·2±16·9	+19·2
Phe[2]-Orn[8]-vasotocin	7±1·9	9·82±2·7	6	0·01	140·3±38·6	+40·3
Phe[2]-Orn[8]-vasopressin	~3	4·2±0·6	6	0·003	140·0±20	+40

* Arbitrarily set at 100.

sonnas, 1968). As *in vitro* methods with higher sensitivity have also been described (for review, see Bisset, 1968) a series of such compounds was investigated to see if agreement was good or bad between *in vitro* and *in situ* results and whether the *in vitro* method has other advantages.

The method was essentially that of Méndez-Bauer, Cabot & Caldeyro-Barcia (1960). Mammary gland strips from rabbits fifth day post-partum were suspended in 10 ml. organ baths; their contractions were registered by Statham Gold Cell transducers and a Texas recorder. The resting tension was 500 mg. Standard oxytocin concentrations were 0·2 and 0·4 m-u./ml.; all doses were given at 10 min intervals and allowed to act for 2 min. The bath was washed out for 15 sec. A 4-point assay design (Schild, 1942) was used.

Results are given as i.u./μmole in Table 1 (column 3). *In situ* values are given in column 2 and ratios of oxytocic to pressor activity (isolated rat uterus and rat blood pressure) in column 5 (from Berde & Boissonnas, 1968). The *in vitro* values found are not far from but not identical with *in situ* results.

Substances with vasoconstrictor activity such as adrenaline and vasopressin are known to modify the *in vivo* responses of the mammary gland to oxytocin (for review see Bisset, 1968). The ratio in column 5 lists the substances to take account of the degree of their pressor activity. An inhibitory effect *in situ*, due to vasoconstriction, might cause the *in vitro* values for strongly pressor substances to be higher. Such a trend is recognizable but does not apply to all compounds. Vasoconstrictor activity may be one—though not the only—factor interfering in the *in situ* method.

Advantages of the *in vitro* method were (*a*) it appears to be free of possible influence of vasoconstrictor activity; (*b*) it allows definite values to be obtained where this is impossible *in situ*.

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Modification by phospholipids of responses of the guinea-pig isolated ileum to drugs and transmural stimulation

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Cell membrane phospholipids include cephalin (phosphatidylethanolamine and phosphatidyl-L-serine) and lecithin (phosphatidylcholine). Since these phospholipids appear to play an important part in the control of membrane permeability and ionic transport (Tobias, Agin & Pawlowski, 1962; Wolfe, 1964), it was considered of interest to study their effect on the longitudinal contractions of the guinea-pig isolated ileum preparation promoted either by agonistic drugs or by transmural stimulation.