from the bath into the "biophase" and that the competition at the receptors is a rapid process. The theories discussed in the next paragraphs make this theory unnecessary.

(e) Some drugs may produce a small effect themselves and yet block the effects of other drugs. Quantitative studies with such drugs led Stephenson (139, 141) to suggest that

(i) The effect of an agonist depends not only on its affinity for the receptors, but also on its ability to produce an effect when combined. This idea has been developed independently by Ariëns (4, 8) who speaks of the affinity and the intrinsic activity of drugs. According to this theory a drug may antagonize other drugs by occupying nearly all the receptors and yet produce a small effect itself.

(ii) The effect is not proportional to the number of receptors activated and a maximum effect may be produced when this proportion is small. This is the theory of spare receptors. The nature of the relationship between the effect and the number of active receptors is unknown, but, whatever it may be, this change in the theory does not affect the shape of the isobols, the value of the dose-ratio or pA_2, or even the parallelism of the log-dose-effect curves.

The original theory of competition explained the shape of one type of dose-effect curve. The new theory does not explain the shape of any dose-effect curves, but it preserves most of the old theory and explains the new facts. According to it, the reason that maximum effects can be produced even when most of the receptors are blocked is that only a small proportion of the receptors is in any case necessary for a maximum effect. So long as sufficient receptors remain free the shape of the log-dose-effect curve remains the same, but eventually with high concentrations of antagonist the proportion of free receptors becomes so small that the original maximum effect is not produced even by very large doses of agonist.

AFFINITY, INTRINSIC ACTIVITY AND DRUG INTERACTIONS

E. J. ARIËNS, J. M. VAN ROSSUM AND A. M. SIMONIS

Pharmacological Institute of the University of Nijmegen, Netherlands

TABLE OF CONTENTS

In the study of pharmacodynamics—the interaction between drugs and biological objects—the reaction mechanism underlying the interactions is of primary importance.

In pharmacology as well as in enzymology the principle of competitive inhibition is a tool in the study of the interaction of drugs or combinations of drugs with biological receptor systems. This principle is based on the use of the equation of Michaelis and Menten (105) and developed by Haldane (64, 65), Lineweaver and Burk (84), Clark (31), and Gaddum (51). In recent time a massive body of experimental evidence has been produced, confirming the significance of this principle (98, 124, 136, 147, 148).

Investigation of the action of drugs on isolated organs or tissue cultures has the advantage that the influence on the effect of resorption, transport, breakdown, and excretion is small and often need not be taken into consideration. The effect is mainly determined by the interaction of the drug and its specific receptor system, especially if equilibria are studied.

In order to produce an effect, the drug has to satisfy at least two conditions. There must be an *affinity* between the drug and the specific receptors, in other words, a pharmacon-receptor complex has to be formed and this complex must have the properties necessary to intervene with the biochemical or biophysical processes in such a way that an effect results. The contribution to the effect per unit of pharmacon-receptor complex is called *intrinsic activity*. The activity of a drug is a function of affinity and intrinsic activity (3, 4). Competitive antagonism implies the use of these terms, introduced by us in 1950.

Both the agonist A and the competitive antagonist B have an affinity for the same receptor system, while the intrinsic activity has a real value ($\alpha > 0$) for the agonist and is zero ($\beta = 0$) for the antagonist.

The intrinsic activity is analogous to the reaction velocity constant k_3, which determines the formation of the final product P in the case of an enzymological reaction as for instance:

$$[E] + [S] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [ES] \xrightarrow{k_3} [E] + [P]; \qquad (v_s = k_3[ES])$$

In the case of a pharmacological interaction the formation of the pharmacon-receptor complex is followed by a chain of reactions, finally resulting in the effect. The efficiency of the pharmacon-receptor complex with respect to this reaction chain is expressed by the intrinsic activity (3).

Various types of drug action will be approached from this point of view. The

term intrinsic activity is used in analogy to the intrinsic toxicity, which is the toxicity per quantity of toxon fixed to the biological object in the case of bacteria, used by Dagley (36). Stephenson (139) mentioned the principle, in discussing the ability of the drug-receptor complex to set in motion the mechanism of the cell.

I. DRUG-RECEPTOR INTERACTION

The drug A interacts in a reversible way with the receptor system R and produces an effect by means of the effector system E_R. This is represented by:

$$[A] + [R] \underset{k_2}{\overset{k_1}{\rightleftarrows}} [RA]$$

The effect resulting from the formation of the pharmacon-receptor complex RA is:

$$E_A = [RA]\alpha = \frac{\alpha[r]}{\frac{K_A}{[A]} + 1} \qquad \text{(I)}$$

in which $[A]$ is the concentration of the pharmacon A, $[R]$ is the concentration of free receptors, $[r]$ is the total concentration of receptors (free and occupied), $[RA]$ is the concentration of pharmacon-receptor complex, $K_A = \frac{k_2}{k_1}$ is the dissociation constant of RA, α is the intrinsic activity of A, $E_{A\max} = \alpha[r]$ is the maximal effect to be obtained with A.

An analogous equation is obtained if the formula for the adsorption isotherm according to Langmuir is used. From equation (I) it may be seen that the intrinsic activity is proportional to $E_{A\max}$, while $K_A = [A]$ if $E_{A\max}/E_A = 2$.

The supposition that the effect is a linear function of $[RA]$ and α, is, although not the most probable, the most simple one. We think it useful to start on the basis of this simplification. A comparison of theoretical and experimental curves will show whether a more complicated relation has to be introduced, and possibly which relation is preferable. The corrections and extensions which are necessary probably depend on the biological object and the drug concerned.

A study of the relations between chemical structure and pharmacological action often reveals gradual change in affinity with a change of the chemical structure in a homologous series of compounds. A gradual change in intrinsic activity as a function of the chemical structure may be expected as well. The values of the affinity and the intrinsic activity are correlated with certain, possibly different, chemical configurations in the structure, or, more accurately, with the physico-chemical properties related to these configurations. If the chemical structure is changed both terms may vary more or less independently (3). Experimental evidence for this is obtained with a series of bis-trialkylammonium compounds, tested as contracture-inducing agents on the frog rectus abdominis

TABLE I

Affinities (1/K) and intrinsic activities of some series of quaternary α-ω-di-ammonium compounds, tested as contracture producing agents on the rectus abdominis muscle of the frog

Substance No.	n	R_3	Intrinsic Activity α	"Dissociation Constant" K[1] mmol/l
$R_3N^+-(CH_2)_2-O-\overset{\overset{O}{\|}}{C}-(CH_2)_n-\overset{\overset{O}{\|}}{C}-O-(CH_2)_2-N^+R_3$				
M 115[2]	2	Me_3	1	2.0×10^{-3}
M 126	2	Me_2Et	0.9	8.4×10^{-3}
M 131	2	$Me\ Et_2$	0.05	1.9×10^{-2}
M 130	2	Et_3	0	2.2×10^{-2}
M 111	4	Me_3	1	3.6×10^{-4}
M 114	4	Me_2Et	0.9	3.8×10^{-4}
M 124	4	$Me\ Et_2$	0.4	4.3×10^{-2}
M 106	4	Et_3	0	1.1×10^{-2}
$R_3N^+-(CH_2)_n-N^+R_3$				
C 10	10	Me_3	0.75	2.9×10^{-3}
M 129	10	Me_2Et	0.35	1.4×10^{-2}
M 128	10	$Me\ Et_2$	0	4.7×10^{-2}

[1] The *K* values are not corrected for the deviation in the slopes of the curves (10).
[2] The M compounds were kindly supplied by the "Stickstoff-Werke", Linz, Austria.

muscle (5, 8, 10) and with series of F 2249 derivatives, tested on the rat jejunum (129). See also Table I.

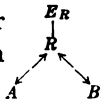
Unless compounds with equal intrinsic activities are compared, a comparison of various compounds is only possible by the study of dose-action curves and not by a simple comparison of equiactive doses.

In a study of a series of p-aminobenzoic acid (PABA) derivatives as a growth factor for a PABA-deficient strain of *Escherichia coli* (*E. coli* 273) a gradual change from growth factor to competitive inhibitor—compound with a sulfanilamide-like action—was found. The generation time of *E. coli* 273 with optimal concentrations of the various components was: with PABA 60 min, with 2-Cl-PABA 76 min, with 3-OH-PABA 90 min, with 3-Br-PABA 123 min, with 3-Cl-PABA 183 min, with 2-Br-PABA 220 min and with 2-CH_3-PABA ∞ min (6). The latter acted as a competitive antagonist of the others. A compound such as, *e.g.*, 3-Br-PABA has an intermediate intrinsic activity as a growth factor. PABA is incorporated into folic acid, a compound used in the formation of coenzyme F, which is essential for the production of methionine, serine, xanthine, and thymine (37). One has to expect that the compounds with intermediate intrinsic activity are used by the bacteria to synthesize folic acid, *etc.*, in which PABA is replaced by its derivatives. The lower intrinsic activities of these derivatives may be related to a lower turnover rate of the coenzyme F, which contains the PABA derivative. The fact that 2-aminopyridine-5-carboxylic acid

can also be used as a substitute for PABA by *E. coli* 273 supports the supposition of the formation of a coenzyme F containing 2-aminopyridine-5-carboxylic acid (7). The analogous compounds follow the reaction chain. Possibly this is also the case with 2-CH_3-PABA, sulfanilamide and its derivatives.

II. COMPETITIVE INTERACTION

The combination of compounds A and B, exhibiting an affinity for the same receptor system, results in a competitive interaction, which is represented by:



$$E_{AB} = [r]\frac{\alpha[A]K_B + \beta[B]K_A}{[A]K_B + [B]K_A + K_AK_B} = \frac{\alpha[r]}{\left(\frac{[B]}{K_B} + 1\right)\frac{K_A}{[A]} + 1} + \frac{\beta[r]}{\left(\frac{[A]}{K_A} + 1\right)\frac{K_B}{[B]} + 1} \quad \text{(II)}$$

As may be seen from this equation, the competitive interaction results in a mutual shift of the dose-action curves. $[B]$ shifts the dose-action curves for A along the log $[A]$ axis to higher values of $[A]$ and *vice versa* (4, 9, 10). Suppose a certain concentration of A is in contact with the biological object. The effect is E_A. Now B is added. The result of the addition of B depends on the intrinsic activities α and β of A and B.

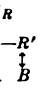
1. *Competitive synergism.* $\alpha = \beta$. The addition of B always results in an increase of the effect, unless $E_A = E_{A\max}$. Such a synergism or addition is obtained by combining the compounds M 111 and M 115 (Table I) (10).

2. *Competitive dualism.* $\alpha > \beta > 0$. Addition of increasing concentrations of B results in an effect $E_{AB} = E_{B\max}$ when this compound occupies all receptors. If $E_A > E_{B\max}$ addition of B causes a decrease of the effect, and if $E_A < E_{B\max}$, addition of B causes an increase of the effect. If $E_A = E_{B\max}$, addition of B does not change the effect at all. Such a dualism in action is obtained by combining the compounds M 115 and M 129 (Table I) (5, 10). d-Tubocurarine (dTc) and the acetylcholinomimetic compound decamethonium (C-10) produce a different type of block in the striated muscle. In contrast to the dTc-block, the C-10 block is not reversible by edrophonium N.N.R. (Tensilon). C-10 induces a contracture of the so-called "slow muscle fibres" as for instance those of the frog rectus abdominis muscle. This contracture is antagonized in a competitive way by dTc. A combination of both types of action in one compound, thus a competitive dualism in action, is often mentioned (22a, 57, 58, 99, 129, 142).

3. *Competitive antagonism.* $\beta = 0$, $\alpha > 0$. Independently of E_A, addition of B always decreases the effect. Finally, for high values of $[B]$, $E_{AB} = E_{B\max} = 0$. This type of interaction is obtained by combining the compounds M 115 and M 130 (Table I) (5, 10). If $\beta = 0$ in equation (II), the well known equation for competitive inhibition is obtained (31, 32, 84, 133, 143). Competitive inhibition is a special case of the general principle of competitive interaction.

III. NON-COMPETITIVE INTERACTION

The effect resulting from the interaction of a compound A with a receptor system R is changed as a result of the interaction of a compound B with the interdependent receptor system R'. A and B react independently and in a reversible way with their respective receptor systems[1]. The interaction of B with R' causes a change in the effect of A (8, 11):



a) By a change in the contribution of the pharmacon-receptor complex RAR' to the effect, and thus in the intrinsic activity.

$$E_A = [RAR']\alpha; \qquad E_{AB'} = [RAR']\alpha + [RAR'B]\alpha\,(1 + \beta')$$

in which β' is the intrinsic activity of B. b) By a change in the affinity between R and A, thus in the dissociation constant of RA. The dissociation constants for the pharmacon-receptor complexes RAR' and $RR'B$ are K_A and K'_B respectively. For $RAR'B$ the dissociation constant becomes $K_A K'_B(1 - \kappa_{AB'})$.

A. Non-competitive interaction resulting in a change in intrinsic activity

This type of interaction is represented by:

$$E_{AB'} = [rr']\frac{\alpha\dfrac{[A]}{K_A} + \alpha(1+\beta')\dfrac{[A][B]}{K_A K'_B}}{1 + \dfrac{[A]}{K_A} + \dfrac{[A][B]}{K_A K'_B} + \dfrac{[B]}{K'_B}} = \frac{\alpha[rr']}{\dfrac{K_A}{[A]} + 1}\left[1 + \frac{\beta'}{\dfrac{K'_B}{[B]} + 1}\right] = E_A\left[1 + \frac{\beta'}{\dfrac{K'_B}{[B]} + 1}\right] \tag{III}$$

From this equation it follows that addition of the antagonist B causes an increase or decrease of the effect E_A, without shifting the dose action curves along the log $[A]$ axis (11).

Suppose a certain concentration of the agonist A is in contact with the biological object. The effect is E_A. Now B is added. The result of the addition of B depends on the intrinsic activity β'.

1. *Non-competitive synergism.* $\beta' > 0$ and $E_{AB'} > E_A$. Compound B, which is inactive as such, increases the effect of A as though the biological receptor system were sensitized for A by B. We might call this a non-competitive sensitization (8, 11).

2. If $\beta' = 0$, compound B is inactive with respect to the effect induced by A. With respect to a compound C ($\gamma' \neq 0$), also interacting with R', B behaves as a competitive antagonist (11).

3. *Non-competitive antagonism.* $-1 \leqslant \beta' < 0$ and $E_{AB'} < E_A$. Compound B, which is inactive as such, decreases the effect of A. If $\beta' = -1$, for high values

[1] In the text and formula the interdependent receptor system is represented by RR', if occupied by the drug A by RAR', or $RR'A$ or $RAR'A$ respectively. The total number of receptors is represented by rr'.

of $[B]$, $E_{AB'}$ becomes zero. Then the well known equation for non-competitive inhibition is obtained (8, 27, 84, 101, 102, 134). Non-competitive inhibition is a special case of non-competitive interaction.

Experimental evidence for this type of interaction is available (8, 11, 27, 101), *e.g.*, in the effect of Bu-N^+-Me_3 combined with Dec-N^+-Me_3 on the frog rectus abdominis muscle.

B. Non-competitive interaction resulting in a change in affinity

This type of interaction is represented by:

$$E_{AB'} = \frac{\alpha[rr']}{\frac{K_A \cdot f_{AB'}}{[A]} + 1}, \quad \text{in which} \quad f_{AB'} = \frac{1 + \frac{[B]}{K'_B}}{1 + \frac{[B]}{K'_B}\left(\frac{1}{1 - \kappa_{AB'}}\right)} \qquad \text{(IV)}$$

The addition of B causes a change in K_A by the factor $f_{AB'}$. This means that, as a result of the addition of B, which is inactive as such, the dose-action curves for A are moved along the log $[A]$ axis to lower or higher concentrations, dependent on $\kappa_{AB'}$ (11).

Suppose a certain concentration of A is in contact with the biological object The effect is E_A. Now B is added. The result of the addition of B depends on the value of $\kappa_{AB'}$.

1. *Non-competitive synergism.* $0 < \kappa_{AB'} < 1$; $f_{AB'} < 1$ and $E_{AB'} > E_A$. The dose-action curves for A are moved up to lower values of $[A]$. We might call this a non-competitive sensitization.

The sensitization of the frog rectus abdominis muscle for various quaternary ammonium salts by the so-called anti-acetylcholine esterases as mentioned by Cohen *et al.* (33), is probably of this type (11).

2. If $\kappa_{AB'} = 0$, $f_{AB'} = 1$ and the compound is inactive with respect to the effect induced by A. With respect to a compound C ($\kappa_{AC'} \neq 0$), also interacting with R', B behaves as a competitive antagonist.

3. *Non-competitive antagonism.* $0 > \kappa_{AB'}$, $f_{AB'} > 1$ and $E_{AB'} < E_A$. The dose-action curves for A are moved up to higher values for $[A]$. If $\kappa_{AB'}$ becomes $-\infty$, equation (IV) becomes identical with the one for competitive inhibition. In competitive inhibition there is a virtual change in K_A; in this type of non-competitive antagonism, there is a real change in K_A.

IV. UNCOMPETITIVE INTERACTION

The effect of the interaction of an agonist A with a receptor system R is changed as a result of the interaction of a compound B with the receptor system RA. In fact, A takes part in the formation of the receptor system for B. This implies that the affinity of B to RA may vary with the agonists used.

$$\begin{matrix} E_R \\ \downarrow \\ R \\ \updownarrow \\ A \end{matrix} \text{ and } \begin{matrix} E_R \\ \downarrow \\ RA \\ \updownarrow \\ B \end{matrix}$$

$$[R] + [A] \rightleftarrows [RA]$$

$$[RA] + [B] \rightleftarrows [RAB']$$

The effect of the combination of A and B is:

$$E_{AB'} = \alpha[RA] + \alpha(1 + \beta')[RAB'] = [r]\frac{\alpha\frac{[A]}{K_A} + \alpha(1 + \beta')\frac{[A][B]}{K_A K'_B}}{1 + \frac{[A]}{K_A} + \frac{[A][B]}{K_A K'_B}} \quad \text{(V)}$$

The difference between uncompetitive interaction (equation V) and non-competitive interaction (equation III) is determined by the term $[B]/K'_B$ in the denominator of equation (III). Comparing these equations, it may be seen that this term only influences $E_{AB'}$ for small values of $[A]$, while if $[A] \gg K_A$ both equations become identical.

The intrinsic activity of B, β', determines the result of the interaction. Suppose a certain concentration of the agonist A is in contact with the biological object. The effect is E_A. Now B is added. The result of the addition of B depends on the intrinsic activity β'.

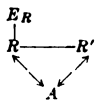
1. *Uncompetitive synergism.* $\beta' > 0$ and $E_{AB'} > E_A$. The compound B, which is inactive as such, increases the effect of A. We might call this an uncompetitive sensitization.

2. If $\beta' = 0$, the compound B is inactive with respect to the effect induced by A. With respect to a compound $C(\gamma' \neq 0)$, also interacting with RA, B behaves as a competitive antagonist.

3. *Uncompetitive antagonism.* $-1 \leqslant \beta' < 0$ and $E_{AB'} < E_A$. The compound B, which is inactive as such, decreases the effect of A. If $\beta' = -1$, the well known equation for uncompetitive inhibition is obtained (84).

In the case of a pharmacological interaction, the formation of the pharmacon-receptor complex is followed by a chain of reactions, offering many opportunities for a non-competitive interaction by a compound B. In enzymology the non-competitive antagonist B has to interact with the same enzyme molecule as compound A. This means that there is a greater chance that compound A in the complex RA takes part in the formation of the receptor for B, which results in an uncompetitive interaction. As far as we know, examples of uncompetitive inhibition are found only for enzyme actions (38). Plotting equations (III) and (V) according to Lineweaver and Burk yields curves clearly manifesting the difference between non-competitive and uncompetitive inhibition. The antagonistic action of Dec-N^+-Me_3, with respect to the contracture of the frog rectus abdominis muscle caused by Bu-N^+-Me_3, is of the non-competitive type, mentioned under IIIA3 (8, 11).

V. NON-COMPETITIVE AUTO-INTERACTION



Suppose a compound A has an affinity to both interdependent receptor systems, R and R'. As a result of the interaction of A with R', the dissociation constant or the intrinsic activity of the complex formed by R and A may be changed (8, 11).

A. Non-competitive auto-interaction resulting in a change in intrinsic activity

This type of interaction is represented by:

$$E_{AA'} = \frac{\alpha[rr']}{\frac{K_A}{[A]} + 1}\left[1 + \frac{\alpha'}{\frac{K'_A}{[A]} + 1}\right] = E_A\left[1 + \frac{\alpha'}{\frac{K'_A}{[A]} + 1}\right] \qquad \text{(VI)}$$

in which E_A is the effect of A if no auto-interaction takes place. This equation is analogous to the equation for non-competitive interaction (equation III).

Suppose the dissociation constant $K_A \ll K'_A$. The addition of A to the biological object causes an effect, which is changed as a result of the interaction of A with R' at higher concentrations of A. The change in the original effect of A, as a result of auto-interaction, depends on the intrinsic activity α' (11).

1. *Non-competitive auto-sensitization.* $\alpha' > 0$. The original effect of A increases as a result of the auto-interaction.

2. If $\alpha' = 0$, the compound does not exhibit an auto-interaction. With respect to a compound C ($\gamma' \neq 0$), also interacting with R', A behaves as a competitive antagonist.

3. *Non-competitive auto-inhibition.* $-1 \leqslant \alpha' < 0$. The original effect of A is reduced as a result of the auto-interaction. If $\alpha' = -1$ for high values of A, $E_{AA'}$ becomes zero.

In fact, the value of K'_A/K_A determines at which concentration of A the auto-interaction becomes apparent (8, 11).

a) If $K'_A/K_A > 1/\delta$, ($\delta = 0.01$) the auto-inhibition becomes manifest after the agonistic effect has already reached its maximal value. See Bu-N^+-Me_3, Figure 1.

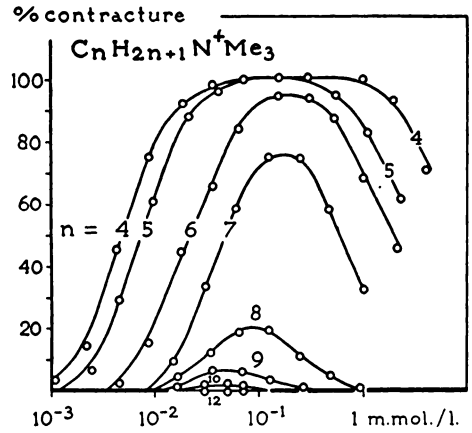


FIG. 1. *Contracture-producing action of alkyltrimethylammonium salts in the rectus abdominis muscle of the frog.* Dose-response curves of a homologous series of alkyltrimethylammonium salts (C_nH_{2n+1}—N^+—Me_3). The curves No. 4, 5, 6, *etc.* represent the n-butyl, n-amyl, n-hexyl, n-octyl, n-nonyl, n-decyl, and n-dodecyl derivative, respectively. Abscissae: concentration in mmol/l. Ordinate: contracture in % of the maximal contracture with Bu—N^+—Me_3. The compounds used clearly show auto-inhibition.

b) If $\delta < K'_A/K_A < 1/\delta$, the compound exhibits agonistic and non-competitive inhibitory properties at the same doses. See Hept-N^+-Me_3 and Oct-N^+-Me_3, Figure 1.

c) If $K'_A/K_A < \delta$, the receptor system R is occupied only after the receptor system R' is already saturated with A. See Dec-N^+-Me_3 and Dodec-N^+-Me_3, Figure 1. These compounds behave with respect to, *e.g.*, Bu-N^+-Me_3 and M 115 as non-competitive antagonists of the type mentioned under IIIA3. In the case of a non-competitive auto-inhibition, the dose action curves exhibit a maximum $E_{AA'max}$ at a certain concentration of A, $[A]_{max}$. Differentiation of equation (VI) shows that for

$$\frac{dE_{AA'}}{dA} = 0, \qquad [A]_{max} = \sqrt{K_A K'_A} \quad \text{and} \quad E_{AA'max} = \frac{\alpha[rr']}{(1 + \sqrt{K_A/K'_A})^2}$$

The phenomenon of auto-inhibition and its dependence on the value of K_A/K'_A has been demonstrated in various series of homologous compounds (8, 11, 14), *e.g.*, on the interactions of various cholinesters and ACh-esterase. In enzymology this phenomenon is mentioned under the name non-competitive substrate inhibition (71).

B. Non-competitive auto-interaction resulting in a change in affinity

An equation for this type of interaction is obtained if—in equation (IV)—B, K'_B and $\kappa_{AB'}$ are replaced by A, K'_A and $\kappa_{AA'}$. The shape of the dose-action curves varies, dependent on the intrinsic activities $\kappa_{AA'}$ and α, and on the ratio K_A/K'_A (11). If $\kappa_{AA'} = -\infty$, the equation becomes:

$$E_{AA'} = \frac{\left(\frac{1}{1 + K_A/K'_A}\right)\alpha[rr']}{\left(\frac{1}{1 + K_A/K'_A}\right)\frac{K_A}{[A]} + 1} \qquad \text{(VII)}$$

As $\kappa_{AA'} = -\infty$, a simultaneous occupation of R and R' in RR' by drug A is excluded. This means that the interaction of A with RR' results in the formation of RAR' and $RR'A$. Only RAR' contributes to the effect.

Suppose the intrinsic activity α is constant and larger than zero. Then the effect of A depends on the value of K_A/K'_A.

1) If $K_A/K'_A < \delta$; ($\delta = 0.01$), only R is occupied by A. With high doses of A the effect becomes $[RAR']\alpha = [rr']\alpha$. The drug A behaves as a competitive synergist of other agonists which interact with R.

2) If $\delta < K_A/K'_A < 1/\delta$, a part of the double receptors RR' is occupied at R, another part at R'. The quantity of RAR' determines the agonistic, the quantity of $RR'A$ the antagonistic properties of A. With respect to the compound mentioned under 1), A exhibits a dualism in action identical to the competitive dualism in action described in chapter II2.

3) If $K_A/K'_A > 1/\delta$, only R' is occupied by A. The drug behaves as a competitive antagonist of compounds, mentioned under 1).

A gradual change from agonist to competitive antagonist via compounds exhibiting a dualism in action as a result of a gradual change in the chemical structure of the compounds in a homologous series, may be caused by a change in the intrinsic activity (see chapter I and II) and may be originated by a change in K_A/K'_A in case of the non-competitive auto-interaction described in this chapter.

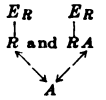
In practice there may be a two-way fit of the compound on the double receptor: an effective fit for the agonist, an ineffective one for the competitive antagonist and a mixed fit for the compounds with a dual mode of action.

On this basis also a differentiation in the time course between both components of the action of a compound with a dual mode of action is possible: $K'_A = k'_2/k'_1$ and $K_A = k_2/k_1$. If $k_1 \gg k'_1$, the agonistic effect precedes the antagonistic effect and *vice versa*.

Also in case of a non-competitive auto-inhibition (chapter VA3), a differentiation in time for the agonistic and non-competitive antagonistic action is possible. Such time-dependent double actions may be the basis of certain forms of tachyphylaxis.

A differentiation in time for the components of a dualistic action is found for the interaction of decamethonium with striated twitching muscle. The decamethonium type of neuro-muscular blockade gradually changes to another curariform type (149).

VI. UNCOMPETITIVE AUTO-INTERACTION



Besides the non-competitive auto-interaction, the uncompetitive type may be mentioned. In this case the compound A takes part in the formation of the receptor system RA for the auto-interaction of A (11)

$$[R] + [A] \rightleftarrows [RA]$$

$$[RA] + [A] \rightleftarrows [RAA']$$

The effect is represented by:

$$E_{AA'} = \alpha[RA] + \alpha(1 + \alpha')[RAA'] = [r]\,\frac{\alpha\dfrac{[A]}{K_A} + \alpha(1 + \alpha')\dfrac{[A]^2}{K_A K'_A}}{1 + \dfrac{[A]}{K_A} + \dfrac{[A]^2}{K_A K'_A}} \qquad \text{(VIII)}$$

Here also the intrinsic activity α' determines the result of the auto-interaction.

1. *Uncompetitive auto-sensitization.* $\alpha' > 0$. The effect of A increases as a result of the auto-interaction.

2. If $\alpha' = 0$, the compound does not exhibit an auto-interaction. With respect to a compound C ($\gamma' \neq 0$), also interacting with RA, A behaves as a competitive antagonist.

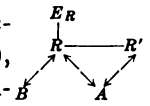
3. *Uncompetitive auto-inhibition.* $-1 < \alpha' < 0$. The effect of A is reduced as a result of the auto-interaction. If $\alpha' = -1$, an equation identical with that for

the "uncompetitive substrate inhibition" is obtained. Hofstee called it competitive substrate inhibition. As indicated by him, it is possible to differentiate between the non-competitive and the "uncompetitive" auto-inhibition (or substrate inhibition) with the aid of a competitive antagonist of A on R (71). In the case of an uncompetitive auto-interaction,

$$[A]_{max} = \sqrt{K_A K'_A} \quad \text{and} \quad E_{AA'max} = \frac{\alpha[r]}{1 + 2\sqrt{K_A/K'_A}}$$

VII. DUALISM IN ANTAGONISM

Suppose a compound A as mentioned under IV has intrinsic activities $\alpha = 0$ and $\alpha' = -1$. With respect to a compound B ($\beta > 0$), which interacts with the receptor system R, A behaves as a competitive (on R) and as a non-competitive antagonist (on R') (8, 9, 11). The equation for this type of interaction is:



$$E_{ABA'} = \left[\frac{\alpha[rr']}{\left(\frac{[B]}{K_B} + 1\right)\frac{K_A}{[A]} + 1} + \frac{\beta[rr']}{\left(\frac{[A]}{K_A} + 1\right)\frac{K_B}{[B]} + 1}\right]\left[1 + \frac{\alpha'}{\frac{K'_A}{[A]} + 1}\right] \qquad \text{(IX)}$$

The dose range, over which the interaction of A with R becomes apparent, is determined by the value of K'_A/K_A.

1. If $K'_A/K_A > 1/\delta$, ($\delta = 0.01$), A mainly acts as a competitive antagonist of B.

2. *Dualism in antagonism.* If $\delta < K'_A/K_A < 1/\delta$, A acts, at the same dose, as competitive and non-competitive antagonist with respect to B. Experimental evidence for the dualism in antagonism is available (8, 11, 27, 79, 101, 128). Drugs exhibiting a dualism in antagonism with respect to a certain agonist are very common.

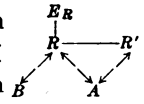
Many parasympatholytics and histaminolytics not only antagonize the contracture of the gut induced by ACh or histamine, but also exhibit a bariolytic action. This implies that besides the specific competitive antagonism, a non-competitive antagonism is present. The quotient of the acetylcholinolytic or histaminolytic and the bariolytic activity is an index for the value of K'_A/K_A.

3. If $K'_A/K_A < \delta$, A acts as a practically pure non-competitive antagonist of B. The experimental evidence produced (8, 11, 101, 128) for the types of non-competitive inhibition mentioned under IIIA3, VA3, and VII3 stresses the reality of this type of inhibition. It cannot be the result of an irreversible binding of the compound with the receptor system on which the agonistic (V,3) or competitive antagonistic action (VII3) has previously been induced. The fact that Dec-N^+-Me_3 is a member of a homologous series of compounds exhibiting an auto-interaction (Figure 1) allows the conclusion that this compound, which behaves as a pure non-competitive antagonist, interacts with its own specific receptor system in a manner which is different from that of the agonist. This is in contrast with the remark of Furchgott (49), that "the only type of antagonism represented by the equation for non-competitive antagonism for which there is

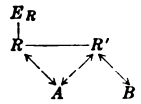
actual experimental evidence, is irreversible competitive inhibition." As a matter of fact, an irreversible interaction between drugs and receptor systems may also take part (16, 34, 48). Experimental evidence for the irreversible competitive type of inhibition of ACh-esterases by di-isopropylfluorophosphate (DFP) is available (16, 34).

VIII. AUTO-INTERACTION COMBINED WITH COMPETITIVE INTERACTION

1. *Combination with a competitive interaction on R.* If in equation (IX) for K_A and K'_A values are substituted, such that $\delta < K'_A/K_A < 1/\delta$, while $\alpha > 0$, $\alpha' = -1$ and $\beta = 0$, it represents the interaction of a compound A, exhibiting an auto-inhibition as mentioned under V, with a competitive antagonist for A on R. The experimental curves obtained for such combinations are in accordance with the theory (8, 11, 16); *e.g.*, Hept-N^+-Me_3 combined with M 130 on the frog rectus abdominis muscle and ACh combined with neostigmine on ACh-esterase from *Electrophorus electricus*.



2. *Combination with a competitive interaction on R'.* This interaction is represented by replacing in equation (VI) the term $\dfrac{\alpha'}{\dfrac{K'_A}{[A]} + 1}$ by its equivalent for the competitive interaction of B and A on R' (see equation II). We get:



$$E_{AA'B'} = \frac{\alpha[rr']}{\dfrac{K_A}{[A]} + 1}\left[1 + \frac{\alpha'}{\left(\dfrac{[B]}{K'_B} + 1\right)\dfrac{K'_A}{[A]} + 1} + \frac{\beta'}{\left(\dfrac{[A]}{K'_A} + 1\right)\dfrac{K'_B}{[B]} + 1}\right] \quad \text{(X)}$$

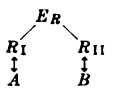
Substituting $\alpha > 0$, $\alpha' = \beta' = -1$ and $K_A/K'_A < 1$, the equation represents the combination of an auto-interaction with a non-competitive antagonist for the interaction of A with R. In fact, on R' there is a competitive synergism or addition. The experimental curves obtained for such combinations are in accordance with the theory (11, 16), *e.g.*, Hex-N^+-Me_3, combined with Dec-N^+-Me_3 on the frog rectus abdominis muscle, and ACh combined with eserine on ACh-esterase from *Electrophorus electricus*.

The dose of A for which the maximum effect is reached, $[A]_{max}$, in the presence of B becomes: $[A]_{max_B} = [A]_{max}\sqrt{1 + [B]/K_B}$ for case 1 and

$$A_{max_{B'}} = [A]_{max}\sqrt{1 + [B]/K'_B} \text{ for case 2.}$$

IX. FUNCTIONAL INTERACTION

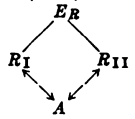
The drugs A and B interact with different independent receptor systems and produce effects by means of a common effector system. Dependent on E_{max}, the maximal effect possible with the effector system, the effects of A and B overlap to a certain degree (12). This type of interaction is represented by:



$$E_{I_A II_B} = E_{I_A} + E_{II_B} - \frac{E_{I_A} \cdot E_{II_B}}{E_{max}} \quad \text{(XI)}$$

in which E_{I_A} and E_{II_B} are the effects of A and B individually (see equation I). Studying the contracture of the rectus abdominis muscle of the frog, induced by combination of quaternary ammonium salts and digitoxin, experimental evidence for this type of interaction could be obtained. From the fact that digitoxin is antagonized neither by dTc, which is a competitive antagonist, nor by Dec-N^+-Me_3, which is a non-competitive antagonist of the quaternary ammonium salts, it may be concluded that digitoxin interacts with a specific independent receptor system. If the compound M 129 is combined with M 115 (Table I) a dualism in action of M 129 is the result. Combining M 129 with digitoxin, M 129 always increases the effect as is to be expected from the theory (5, 10, 12).

It is also possible that one compound interacts with both the receptor systems R_I and R_{II}. This type of interaction is represented by:



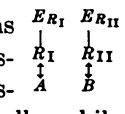
$$E_{I_A II_A} = E_{I_A} + E_{II_A} - \frac{E_{I_A} \cdot E_{II_A}}{E_{max}} \qquad \text{(XII)}$$

The effect is composed of two components. The contribution of the pharmacon-receptor complex with the highest dissociation constant will be masked by that of the one with the lowest dissociation constant. The masked effect can be unmasked by adding a competitive antagonist of the compound, the pharmacon-receptor complex of which has the lowest dissociation constant. Experimental evidence could be produced showing that the contracture of the rectus abdominis muscle, induced by nicotine, is based on such a dualism in action. One of the components of the effect of nicotine could be antagonized by dTc and by Dec-N^+-Me_3 unmasking the other component. The nicotine action was even more complicated, *viz.*, an auto-inhibition existed with respect to the first component of the effect (12).

Functional antagonism also is possible. In that case E_{IA} and E_{IIB} are opposite. The sympathetic and parasympathetic action on smooth muscle is an example.

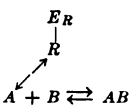
X. PHYSICAL INTERACTION

Drugs A and B interact with different independent receptor systems and produce effects by means of different independent effector systems. As an example gastric juice production may be mentioned. Histamine stimulates production of hydrochloric acid by the oxyntic cells, while parasympathetic stimulation mainly results in a production of the other constituents by the chief cells (66). The contribution of various circulatory components to maintenance or alteration of blood pressure (constriction of the vessels, changes in heart rate, contraction of the spleen, *etc.*) may serve as another example.



XI. CHEMICAL INTERACTION

Compound A interacts with receptor system R, while compound B reacts with A, forming the product AB. Neither B nor AB interact with the receptor system (10).



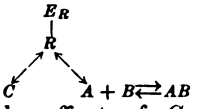
The result of this interaction depends on the intrinsic activity of A, α, and on

the affinity between A and B. The receptor system is not directly concerned in the interaction of B.

1. *Chemical antagonism.* $\alpha > 0$ and $E_{AB} < E_A$. Here, as in competitive inhibition, the dose ratio, $[A]/[B]$, determines the effect. In competitive antagonism the inhibition is determined by the affinity of B for R and is independent of the affinity of A for R. In chemical antagonism the inhibition is determined by the affinity of B for A which varies with the agonist A used (10).

Experimental evidence for this type of interaction was obtained from the study of the contracture of the rectus abdominis muscle of the frog, induced by combinations of quaternary ammonium salts and their chemical antagonist Suramin, B.P. (Germanin) (10, 23, 77).

2. *De-inhibition.* $\alpha = 0$. Compound A is a competitive antagonist of compound $C(\gamma > 0)$, interacting with R. As a result of addition of B, the competitive antagonist of C is withdrawn from the medium, which causes the appearance of the effect of C, formerly antagonized by A.

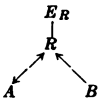


Also for this type of interaction experimental evidence is available (10).

XII. IRREVERSIBLE INTERACTION

The interaction of a drug A and a receptor system is called irreversible if the dissociation constant of the pharmacon-receptor complex is zero (12). The concentration of the pharmacon-receptor complex, $[RB]$, finally equals $[B]$ if $[B] < [r]$. The time necessary to reach this situation depends on the velocity constant of the reaction between B and R. In some cases, *e.g.*, TEPP combined with ACh-esterase, $[RB]$ approaches $[B]$ in a reasonably short time (16). In other cases, *e.g.*, DFP combined with ACh-esterase, the reaction is rather slow (16). Then a kinetic approach to the problem is necessary. This is also the case if $[B] > [r]$. Although in practice a kinetic approach is seldom avoidable, some information may be obtained from a consideration of the final state.

1. *Irreversible competitive interaction.* The drug $A(\alpha > 0)$ and the irreversibly acting compound B $(\beta > 0)$ interact with the receptor system R. The effect is represented by:



$$E_{AB} = \frac{\alpha[r]}{\frac{K_A}{[A]} + 1}\left[1 - \frac{[RB]}{[r]}\right] + [RB]\beta \qquad \text{(XIII)}$$

in which $[RB] = [B]$ and $[r] > [B]$. Compare this equation for the case that B is a competitive antagonist $(\beta = 0)$—the inhibition by B is proportional to $[B]$—with equation (III) for the case that $\beta' = -1$. Experimental evidence for this type of interaction is available (34, 48, 111), *e.g.*, dibenamine combined with sympathomimetics on the rabbit aorta strips.

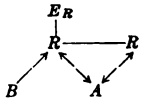
2. *Irreversible non-competitive interaction.* The drug B acts in an irreversible way with R'. The effect of the combination of A and B is represented by:

$$E_{AB'} = \frac{\alpha[rr']}{\frac{K_A}{[A]} + 1}\left(1 + \beta' \frac{[RR'B]}{[rr']}\right) \qquad \text{(XIV)}$$

Compare this equation for the case that B is a non-competitive antagonist ($\beta' = -1$)—the inhibition by B is proportional to $[B]$—with equation (III), for the case that $\beta' = -1$. In case 1 addition of the compound which interacts with R in a reversible way, depending on K_A and k_{1_B}, protects R to a certain degree against the irreversible antagonist (16, 34, 49, 111), *e.g.*, DFP combined with neostigmine or butyryl-choline on ACh-esterase, and dibenamine, combined with sympathomimetics on the rabbit aorta. Little or no protection is obtained in case 2. This also holds if an irreversible antagonist interacts with R and a compound which interacts in a reversible way with R' is added previously (16), *e.g.*, DFP combined with eserine on ACh-esterase from *Electrophorus electricus*.

In case of non-competitive interaction, as mentioned in chapter IIIB, depending on $\kappa_{AB'}$, there may be some protection.

3. *Non-competitive auto-interaction combined with an irreversible interaction.* This interaction is represented by:

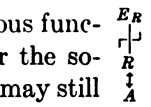


$$E_{ABA'} = \left[\frac{\alpha[rr']}{\frac{K_A}{[A]} + 1}\left(1 - \frac{[RR'B]}{[rr']}\right) + [RR'B]\beta\right]\left(1 + \frac{\alpha'}{\frac{K'_A}{[A]} + 1}\right) \qquad \text{(XV)}$$

In the special case in which $\alpha = 1$, $\alpha' = -1$, $\beta = 0$ and $K_A/K'_A < 1$, experimental evidence for this type of interaction is available (16), *e.g.*, ACh combined with TEPP or DFP and ACh-esterase.

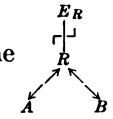
XIII. ALL OR NONE RESPONSE

In the foregoing chapters the effect was supposed to be a continuous function of the number of receptors occupied. This is not the case for the so-called all or none response. Here the relationship between R and A may still obey the mass law or the Michaelis and Menten equation, but the effect E_A is a discontinuous function of the quantity of pharmacon-receptor complex, $[RA]$, or the trigger magnitude T_A, which is $\alpha[RA]/[r]$. In this case the intrinsic activity of A, α, is the contribution to the triggermagnitude per unit of pharmacon-receptor complex. If $T_A > T_r$, $E_A = 0$ and $E_A = 1$, if $T_A \geqslant T_r$. T_r is the value of T_A at which response takes place. The all or none response may be based on some autocatalytic or self-propulsive reaction, initiated if T_A reaches the value T_r. The dose of A for which T_r is reached is called the response dose, $[A]_r$. The all or none response is restricted to a single effector unit. With biological objects composed of many units, *e.g.*, the muscle fibres in a muscle, the S-shape of the dose-action curve may be caused by a biological variance of the fibres with respect to, *e.g.*, T_r (12). Then the slope of the curves depends on the standard deviation, σ (51) and on the intrinsic activity of the drug, while a gradual de-



crease in the intrinsic activity is manifested by a gradual decrease in the slope of the dose-action curves (9a). In measuring T_A or some factor between R and the trigger mechanism a gradual relation may be expected, even if a single unit is studied, *e.g.*, the change in the end-plate potential in case of a twitching muscle fibre.

1. *Competitive interaction in case of all or none response.*



For the combination of compounds A and B interacting with the same receptor system, T_{AB} is represented by:

$$T_{AB} = \frac{[RA]\alpha}{[r]} + \frac{[RB]\beta}{[r]}$$

Suppose the intrinsic activity of A, $\alpha \geqslant T_r$ and of B, $\beta = 0$. B is a competitive antagonist of A. The relation between the response dose in the absence, $[A]_r$, and in the presence of B, $[A]_{r_B}$, is represented by:

$$\frac{[A]_{r_B}}{[A]_r} = \frac{[B]}{K_B} + 1$$

This means that, in case of an all or none response, addition of a competitive antagonist B shifts the dose-action curves for A along the log $[A]$ axis in the same way as if no all or none response were involved (9a). If $\alpha \geqslant T_r$ and $\beta > 0$, the change in the response dose, $[A]_r$, as a result of the addition of B may be obtained from equation (II).

2. *Non-competitive interaction in case of an all or none response.* Combining a compound A with intrinsic activity $\alpha \geqslant T_r$ with a non-competitive antagonist B, for which the point of attack is not located between the trigger mechanism and the effector system, $T_{AB'}$ is represented by:

$$T_{AB'} = \frac{\alpha[RA]}{[r]}\left[1 + \frac{\beta'}{\frac{K'_B}{[B]} + 1}\right] \quad \text{(See equation III.)}$$

If $\beta' = -1$, addition of B causes a decrease in $T_{AB'}$, an increase in $[A]_r$, while finally if $T_{AB'} < T_r$ no response is obtained any more.

The relation between the response dose in the absence, $[A]_r$, and in the presence of B, $[A]_{r_{B'}}$, is represented by:

$$\frac{[A]_{r_{B'}}}{[A]_r} = \frac{\frac{T_{A\max}}{T_r} - 1}{\frac{T_{A\max}}{T_r}\left[\frac{1}{\frac{[B]}{K'_B} + 1}\right] - 1} = \frac{\frac{\alpha}{T_r} - 1}{\frac{\alpha}{T_r}\left[\frac{1}{\frac{[B]}{K'_B} + 1}\right] - 1} \qquad \text{(XVI)}$$

in which $T_{A\max}$ is the maximal value of T_A to be reached with A (compare with $E_{A_{\max}}$). In case of a population of units exhibiting a biological variance for T_r, addition of the non-competitive antagonist B results in a parallel shift of the curves for the agonist A as long as $\alpha K'_B/([B] + K'_B)$ is larger than $(\overline{T_r} + 3\sigma)$. With large doses of B also a decline in the curves becomes manifest. The shift

of the curves is based on a *reserve in receptors*, which is determined by $\alpha K'_B/([B] + K'_B) - (\overline{T_r} + 3\sigma)$; see (9a). The types of interaction mentioned in chapter IV to IX, XI and XII can be introduced in an analogous way.

Experimental evidence for the existence of spare receptors is available (111).

XIV. SHAPE OF THE DOSE-ACTION CURVES

The assumptions on which the equations used in the foregoing chapters are based, are extremely simplified. The equations cannot be regarded as representing reality. In the experimental curves, only in exceptional cases does K approximate a real dissociation constant. In fact this term determines the quantity of pharmacon-receptor complex formed, if a certain concentration of a pharmacon is added to a biological system.

The theory and the equations systematize the various types of action and interaction. If, on the basis of the equations, it is possible to predict certain effects or interactions which can be confirmed experimentally, the system works. In view of the extreme simplifications, one may not expect a perfect fit between theoretical and experimental curves. The main differences are a deviation in the slopes of the curves and the occurrence of asymmetry.

1. *The slope of the curves.* Various investigators obtained experimental curves with slopes deviating from those given by the theory (10, 25, 32, 55, 100, 101). A simple correction for the slopes is obtained if a higher order reaction between pharmacon and receptor is assumed (10, 25, 32, 101). Then in the equations the concentration of the pharmacon, $[A]$, has to be replaced by $[A]^n$. Substitution of various values for n allows any desired slope. Another possibility is to assume a difference between the concentration of A in the bath fluid and that in the biophase (10, 49). In the experimental curve concentrations in the bath fluid are plotted; in fact, the concentrations of the pharmacon in the immediate environment of the receptors should be plotted. As mentioned before, in case of an all or none response, the slope of the curves depends on the biological variance (51). A variation in the slope of the curves within a group of related compounds often has to be attributed to a variation in the intrinsic activity (5, 10, 129).

2. *Symmetry or asymmetry.* Many investigators obtained symmetrical experimental log dose-effect curves (5, 10, 25, 32, 49, 55, 100, 101). For certain biological objects and/or with certain drugs, asymmetrical curves may be obtained. One of the possibilities to introduce asymmetry into the theoretical curves is to put into the equations non-linear functions for the relation between the quantity of pharmacon-receptor complex and the effect (12). Then the effect is not proportional to the number of receptors occupied. The contribution to the effect per unit of pharmacon-receptor complex may vary with the quantity of pharmacon-receptor complex formed or with the effect obtained, *e.g.*,

$$E_A = [RA]\left[1 - \frac{[RA]}{[r]}\right]\alpha \quad \text{or} \quad E_A = [RA]\left[1 - \frac{E_A}{E_{max}}\right]\alpha \qquad \text{(XVII)}$$

Another example is the case of an all or none response in a population of effector units for which $\alpha > (\overline{T_r} + 3\sigma)$. There is a *reserve in receptors*. In order to

obtain a maximal response, only a fraction of the receptors has to be occupied. As a matter of fact, many other possibilities may be suggested. One may introduce asymmetry into the curves in the way mentioned and re-establish symmetry to a certain degree by assuming that the relation between $[RA]$ and $[A]$ is practically linear. This is the case, if only a very small part, $\pm 1\%$ of the receptors, has to be occupied to produce 100% effect (140). Then the intrinsic activity, α, is larger than one.

There may be a difference between E_{max}, the maximal effect possible with the effector system and E_{Amax}, the potential maximal effect to be obtained with a drug. If $E_{max} < E_{Amax}$ there is a reserve in the receptor system (12). Perhaps in very special cases $E_{max} = 0.01\ E_{Amax}$. It is improbable, however, that this is the rule, for then the functional make-up of the body should be for 99% reserve. As a matter of fact, many other functions and constants can be introduced into the equations. The basic assumptions will have to be extended and complicated, possibly in a specific way for each special object. Kinetics will have to be taken into account.

To remain aware of the imperfection of the theory is a good thing. One should not, in order to obtain a perfect fit of theoretical and experimental curves, put into the equations functions or constants, unless they are covered by pharmacological principles and supported by experiments. The equations should be regarded as a kind of shorthand, such that all factors in the equations have a pharmacological meaning.

In summary: On a basis of strongly simplified assumptions, a system describing various types of pharmacological interactions was developed. On many points theory and experiments agree. The main difference between them is found in the slopes of the curves. There are many possibilities of extending the assumptions in such a way, that a perfect fit of theoretical and experimental curves is obtained. We were not able to give experimental evidence for the preference of special ones. On the basis of the theory it was possible to predict a number of interactions which could be confirmed by experiments. A directed synthesis of pharmacologically active compounds was realized. As an example: Theory and experiments (5, 10, 11) made it possible to predict the properties of compounds obtained by replacing, on both the onium groups of decamethonium, one methyl group by an alkyl group of increasing length. As a result of this substitution, a simultaneous decrease in the intrinsic activity and an introduction of a non-competitive auto-inhibition was expected, while the affinity to the receptor system on which the auto-inhibition was induced, was expected to increase. Using the frog rectus abdominis muscle as a test object, starting with methyl groups and ending with decyl groups, compounds with properties as described in the chapters I, II2, VA3, VII and IIIA3 were expected. The experiments which confirmed the expectations are described in a preliminary note (128). As predicted by the theory some series of homologous F2249 compounds exhibited a gradual change from para-sympathomimetic (ACh-like) action via compounds with a dualism in action (chapter II,2) to compounds exhibiting parasympatholytic (atropine-like) action if tested on the rat jejunum (129).

Even the use of an oversimplified theoretical basis has proved to be worthwhile.