

**SYMPOSIA OF THE
SOCIETY FOR EXPERIMENTAL BIOLOGY**

NUMBER III

**SELECTIVE TOXICITY
AND
ANTIBIOTICS**

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PREFACE

This number contains most of the papers read at a Symposium of the Society for Experimental Biology, which was held at Edinburgh in July 1948. It is the third of an annual series of symposium reports.

The Symposium for 1949 will be on 'Physiological Mechanisms in Animal Behaviour'. It will be held at Cambridge.

The Society is deeply indebted to Imperial Chemical Industries Ltd., for a grant in aid of publication. We are also most appreciative of the facilities and help made available to us by members of Edinburgh University.

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J. F. DANIELLI

R. BROWN

*Honorary Secretaries
Society for Experimental Biology*

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THE ORGANIC CHEMIST'S APPROACH TO CHEMOTHERAPY

By W. A. SEXTON

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The invention of a new chemotherapeutic agent involves a search for a compound which combines in the best possible manner a number of essential properties. First, it must possess the requisite type of biological activity, that is to say, it must be capable of attacking the parasite or interfering with the function concerned. Secondly, it must have selective action, at least to the extent that it is not toxic to the treated subject. Thirdly, it must have properties which enable it to be administered in a reasonable dose, capable of being absorbed by the subject, transported to the site of action and able to persist for a sufficient time to produce its characteristic effect. All these properties may be related to the one fundamental subject which is of prime interest to the organic chemist, namely, the relationship between the chemical constitution and the behaviour of a molecule in a living system. It follows that knowledge gained in related fields such as the study of insecticides, or in applied botany, is fully relevant to the subject of chemotherapy.

In this paper, therefore, the interpretation of biological activity and the design of biologically active molecules will be considered as a branch of applied chemistry. Of all the branches of applied chemistry, the synthesis of biologically active substances is perhaps unique in the important respect that it is concerned with dynamic as opposed to static chemical systems. It is necessary at the outset to emphasize this point, for it colours the whole consideration of the subject. Recent metabolic studies using isotopic elements have emphasized the important fact that many of the chemical constituents of living matter are in a constant state of change, in that their synthesis and breakdown occur continually throughout life. It is not known whether this dynamic picture applies to certain structural elements upon which an organism depends for its mechanical strength, and of course materials such as food and vitamins which are provided from external sources are subject only to the processes associated with their utilization and in this sense are not classed as body constituents. With these exceptions, however, it seems that the dynamic conception is a general one. A natural product must be considered therefore not as having a static structure, but

must be regarded in relation to its biogenetic chemical precursors, its chemical reactivity and its degradation products.

In attempting a speculative analysis of the effects of structural variation on the selective toxicity of organic compounds towards living organisms, two postulates will be made. The first postulate is that the biological activity of a substance is due to its combination, whether it is a natural constituent of the organism or whether it is a drug, with some substance or substances in the organism; and that this combination is either responsible for maintaining the normal balance of the dynamic chemical processes of the organism, or in the case of a drug, results in upsetting these processes. The term combination is to be interpreted widely as comprising unions of varying nature and force. At the one extreme there are the powerful unions formed through covalent links which unite the drug molecule with the cell constituent through reactions which are practically irreversible. As an example may be cited the union of a heavy metallic ion with a thiol group. At the other extreme there are the weaker forces which cause loose attachment such as van der Waals forces and those due to polar interaction and which, at least where small molecules containing few such linkages are concerned, are easily broken. In such cases, biological activity is often only of a temporary nature, being lost when the invading molecules are eliminated. This applies, for example, to the narcotic action of certain simple compounds such as ether and chloroform. Between these two extremes lies a gradation of types of combination including the relatively firm unions which result from the combination of macromolecular species in stereochemical juxtaposition, so that the molecules are held firmly together by a multiplicity of points of contact at each one of which the force is only small. It is this complex type of multipoint union which determines the specific properties of proteins and complex carbohydrates and which governs the phenomena of enzymology and immunochemistry. This will be referred to again later.

It is next postulated that the combination of biologically active molecule with cell constituent may be modified to a greater or lesser degree by variation of the physico-chemical properties of the active molecule. This variation may be deliberately brought about by structural alterations and can have two major effects. First, it can modify the chemical reactivity or the capacity for combination with cell constituents quantitatively, and secondly, it can for various reasons either prevent or facilitate access of the molecule to the cell constituent concerned or it may render the access feasible only in such organisms as are possessed of the appropriate chemico-morphological constitution. Thus the variation of physico-chemical properties through structural modifications becomes a basis for the selection of susceptible species, for specificity of action between different organs of the

more complicated biological structures and for the selection of the most potent individual compound within a chemical class. One of the most familiar examples of the effects of physical properties in this respect is the variation of biological activity within members of homologous series, some typical examples of which are given in Table 1. The usual effect in an homologous series is a gradual rise to maximum activity at a certain chain length, followed by a fall as the series is ascended further (curve *A* in Fig. 1). This peak effect is often due to the fact that at a certain point, solubility in water becomes a limiting factor. Sometimes the 'peak' may be as low as one or two carbon atoms (curve *B* in Fig. 1), that is to say, the first part of the curve *A* is missing. A curve such as *A* is perhaps typical of the modification of biological activity through the interaction of two opposing factors, and a similarly shaped curve was obtained by Bell & Roblin (1942), who plotted the *in vitro* bactericidal activity of sulphonamide drugs against their acid dissociation constants.

The variation of activity as an homologous series is ascended may on occasion take on more complex patterns, due to the complicating effect of other factors. Thus Stiles & Rees (1935) observed that the toxicity of *n* fatty acids to potato tuber slices decreased gradually from C_1 to C_6 and then increased rapidly to C_9 . This result was attributed to the additive contributions of two factors to the overall toxic effect, the toxicity of hydrogen ions and the toxicity of the undissociated molecule. In formic acid the effect was mainly due to hydrogen ions, and through the first half-dozen members of the series, this predominance of the hydrogen-ion contribution gradually lessened. After this, the main contribution was from the undissociated molecule, and activity rose with molecular weight to C_9 . Higher acids were not examined, but doubtless a peak would have been reached at a certain chain length (see curve *C* in Fig. 1, the broken part of which is hypothetical).

Another effect in homologous series is what may be termed the odd-even effect, the alternation of activity between successive members of a series. Synerholm & Zimmerman (1947) observed that in the series



auxin-like activity was found only in those compounds in which *n* was an odd number, and it was suggested that this might be explained by the fact that only with odd-numbered compounds could β -oxidation give rise to 2:4-dichlorophenoxyacetic acid, which was believed to be the true active agent in each case. A similar alternation in activity has been observed with certain antimalarial drugs.

Table 1. *Variation of biological activity in homologous series*

General formula ($R=n$ -alkyl)	Biological response	Maximum activity (no. of C atoms)
$R.SCN$	Toxicity to aphids Toxicity to animals	10-14 1
<chem>c1ccc2c(c1)sc(SR)n2</chem> $+ R.NMe_3$	Toxicity to flies Fungistatic activity	2-3 1
RO <chem>c1ccc(cc1)CH(CCl3)c2ccc(OR)cc2</chem>	Bacteriostasis Curare effect (frog)	10-12 2-3
R <chem>c1ccc(O)cc1</chem>	Contact insecticide	1
$RO.CSSNa$	Bactericide ('Phenol coefficient')	5
<chem>c1ccc(NC(=O)OR)cc1</chem>	Fungicide	1
<chem>c1ccc2c(c1)ccc(NC(=O)OR)cc2</chem>	Inhibition of oat-seed germination	2
<chem>c1ccc2c(c1)ccc(NC(=O)OCH2COOR)cc2</chem>	Inhibition of rape-seed germination	3
<chem>Clc1ccc(NC(=O)NC(=O)NC(=O)NR)cc1</chem>	Antimalarial	3
<chem>NC(=N)C(CH2)nC(=N)N</chem>	Trypanocide	$n=10-14$
<chem>RO-P(=O)(F)(OR)</chem>	Inhibition of cholinesterase	Not less than 3

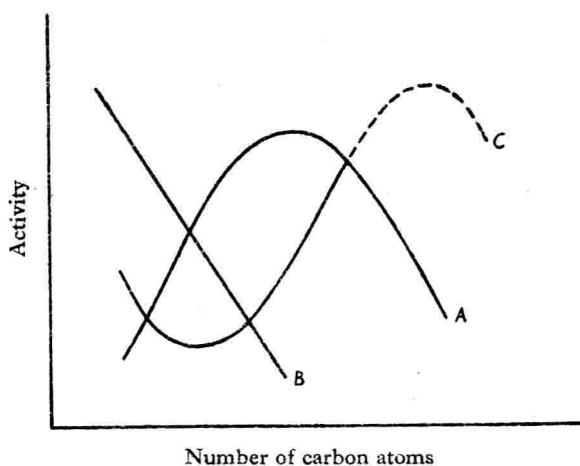
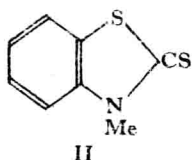
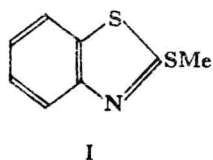


Fig. 1. Figure illustrating types of variation of activity as an homologous series is ascended.

The lesson of this for the organic chemist is that in synthesizing new molecular species for biological evaluation, it is usually not sufficient to examine a single member as representative of a chemical type, for a variation of physical properties might make all the difference between success and failure. This has been well illustrated in various fields, e.g. the thiocyanate insecticides, the phenoxyacetic acid herbicides and the diguanide antimalarials. The other point requiring emphasis is that variation of physical properties can become the basis for selective toxicity. To the examples given in the table may be added a few more in further illustration.



The *S*-methyl derivative of 2-mercaptobenzthiazole (I) is toxic to certain insects but not to others. The isomeric *N*-methyl compound (II) differs from it in physical properties, but in their capacity for combining with cell constituents the two isomers would not be considered to be very different. The susceptibility of insect species is quite different for the two compounds (Davies & Sexton, 1948). The various penicillins differ not so much in their chemical reactivity as in their physical properties, and they are characterized biologically by different bacterial 'spectra'. At a concentration of 0.05%, emulsified hexyl thiocyanate caused 63% mortality of black chrysanthemum aphids, but at this concentration, the mortality of green chrysanthemum aphids or of red spider was very little more than that brought about by the emulsifier (potassium oleate) alone (Bousquet, Salzberg & Dietz, 1935).

We have considered above an analysis of the contributions towards biological activity of 'physical' and 'chemical' factors. This is of course an over-simplification, for the two groups of factors are by no means independent and there is no hard and fast line of demarcation between them. For this reason the terms 'physical' and 'chemical' are given in inverted commas. Nevertheless, it is a convenient conception in quite a large number of instances. Where this type of analysis is applicable, the overall biological effect can be seen to be due to an appropriate balance of 'physical' and 'chemical' effects. There are certain instances, however, in which either the 'chemical' or the 'physical' effect is dominant. If a markedly reactive grouping is contained in a small molecule which is at the same time devoid of other groupings likely to confer distinctive properties in relation to reactions with cell constituents, then biological activity may be expected to be manifested as a general toxic effect. In other words,

dominance of the 'chemical' effect will result in general toxicity. Only when 'physical' effects become significant will marked specificity arise. Three simple examples are the lower alkylmercury salts, methyl thiocyanate and quinone. Methyl thiocyanate is generally toxic, but as the series is ascended one arrives at members in which the physical properties determine the specific toxicity to certain insects and mites. In the same way, quinone is generally toxic, but with the elaboration of the molecule by the introduction of appropriate substituent groups and rings one arrives at substances with characteristic activities such as the K vitamins, echinochrome, selective bactericides and certain anthelmintics. Similarly, there are cases in which 'physical' effects so dominate the situation that the reactivity of the substance with cell constituents is difficult to discern. Again, the 'physical' effects may have such overriding importance that two drugs of appropriate physical properties may produce similar biological effects, even though their chemically reactive groups are of a fundamentally different nature. This may be illustrated by examples. There are certain simple organic molecules, not highly reactive in the conventional chemical sense, but which nevertheless exhibit marked and characteristic biological activity. Such substances as the anaesthetics ethylene, cyclopropane, ether and chloroform come into this category, and it is necessary to consider how they may conform to the first postulate, namely, that they combine with cell constituents. It has been emphasized that combination with cell constituents can include unions of a loose nature, and herein must be found the reconciliation of the biological activity of these substances with this first postulate. The aliphatic hydrocarbon chains, for example, will have a capacity for attachment through van der Waals forces to lipophilic groups in macromolecular species, for example, to certain side-chains of amino-acid components of polypeptides. Similar attachments may be formed by such molecules as ether and chloroform. These attachments may well be sufficient to distort the delicate framework of macromolecular architecture and thus to interfere with dynamic function. In such cases the effects of variation in physical properties will be completely dominant, and it follows that groups of structurally unrelated chemical compounds, provided that they contain no grouping of outstanding chemical reactivity, may produce similar biological effects. Good examples of this phenomenon are provided by Ferguson (1939). Again, in their insecticidal action against blowflies, the *n*-alkyl thiocyanates $R \cdot SCN$ show maximum activity at about $C_{10}-C_{14}$. The 2-alkylthiobenzthiazoles have greatest activity at C_2-C_3 . The characteristic chemical reactivity of the thiocyanates is due to the affinity of the carbon atom for electrons. On the other hand, the 2-alkylthiobenzthiazoles are electron-donating. Thus in the case of the two insecticides, dodecylthiocyanate and

2-ethylthiobenzthiazole, one has a reactive group which is fundamentally acidic in nature and the other has a basic group. What is important, however, is that, given the appropriate physical properties, e.g. fat solubility or fat/water partition, there must also apparently be a group capable of combining to an appropriate degree of firmness with some cell constituent (Davies & Sexton, 1948). If the functional group is not sufficiently reactive, or if it is too reactive, activity will be reduced, e.g. lauronitrile, lauric acid, dodecyl alcohol and dodecyl *isothiocyanate*. Perhaps in the latter instance the reactive NCS group is fixed in a harmless manner before the molecule can reach a site where combination would result in a toxic effect.

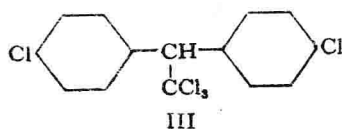
Small molecules of low chemical reactivity, that is to say, small molecules which can become attached to cell constituents by forces less than those of covalence, may be expected to produce general effects, and whether or not activity is exhibited in any particular organism will be more dependent on the precise biochemical characteristics of the organism than is the case with the more reactive molecules. With a highly reactive molecule there are many points in cell constituents for chemical attack. With a less reactive one, the points of attack are less numerous, and significant combination with cell constituents will be to a large extent governed by the details of macromolecular architecture. The effects will be more easily abolished on removal of the drug, and there may be mentioned narcosis and bacteriostasis as easily reversible conditions brought about by simple molecules, such as, for example, ether, urethane and phenol. Specificity of action is here greatly dependent on the physical properties of the molecule, and this is a clear case of the dominance of the 'physical' factor. It might be argued that the characteristic effects of 'physical' dominance, e.g. the homologous series effect coupled with a generalized biological activity (toxicity) could be taken as diagnostic of an interference with macromolecular function.

Generally speaking, the larger or more complex the molecule, the greater is the likelihood of its biological activity being of a highly specific nature. This follows from the general argument that biological activity results from an appropriate combination of physical properties with chemical reactivity. In a complex molecule quite minor structural variations may affect both properties profoundly and thus upset the balance between them. This finds its maximum expression in the highly specific activities of enzymes and other proteins and the phenomena of immunochemistry, but it is also exhibited in molecules of much less than macromolecular complexity. There may be mentioned in this connexion the vitamins and coenzymes in which little structural variation is permissible, the synthetic oestrogens and the insecticide, γ -hexachloro*cyclohexane*, where activity is associated with a

precise stereochemical arrangement, and the highly specific antiprotozoal drugs such as the diguanide and heterocyclic types.

No account of the structural basis of selective toxicity would be complete without at least brief reference to the brilliant work of Landsteiner and of Pauling (see particularly Landsteiner (1936) and Pauling (1940)) on the significance of molecular structure in relation to serological reactions. This properly belongs to the subject of this paper, for the responses of an animal to foreign proteins introduced into the blood either by parenteral injection or formed there as a result of the interactions of a foreign substance of relatively low molecular weight with the body proteins comprise an exhibition of selective toxicity having the highest possible degree of specificity. Here there is a formidable body of evidence to show that the biological activity of a protein is associated primarily with its stereochemical structure, and experimental demonstrations of this have been achieved by modifying proteins through the attachment by means of firm chemical unions, e.g. the azo group and the peptide or ureido groups, of aromatic nuclei bearing chosen substituents. The specificity of action of such modified proteins has been shown to be associated with the nature of their molecular surfaces, and to be in accord with the view that they owe their behaviour to the precise arrangement of the multiple points of attachment to other large molecules. All this work is at present in the stage where a theoretical explanation of serological reactions, based upon considerations of the structure of atoms and molecules, may be advanced with considerable confidence. One cannot help feeling that the further advancement of this subject will eventually provide new principles and new techniques whereby medicinally useful substances can be manufactured in the laboratory without recourse to biological methods of production.

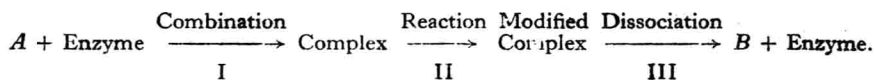
It is not always possible by examining the structure of a biologically active molecule to analyse the contributions made by the component groupings to the 'physical' and 'chemical' aspects of its properties, for it is perhaps the rule rather than the exception that molecular changes may affect both physical properties and the capacity for combining with cell constituents at the same time. Such dual alterations may be mutually complementary or mutually antagonistic in respect of the overall biological effect, and it cannot be too strongly emphasized that the decisive factor is the behaviour of the molecule as a whole. This is well exemplified in the rival views concerning the mode of action of the insecticide D.D.T. (III).



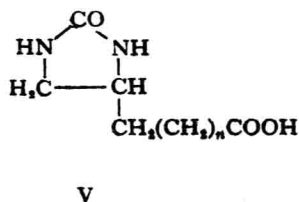
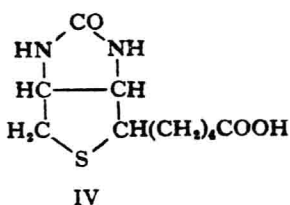
It is generally agreed that in this (and also in certain other contact insecticides) activity is associated with affinity for lipoids combined with a capacity for chemical reactivity. Molecular alteration affects both factors, and neither the highest reactivity nor the highest lipid solubility is always to be associated with maximum insecticidal potency (see, for example, Kirkwood & Phillips (1946), who give references to earlier papers). Reconciliation of the apparently contradictory results can probably be achieved by considering the molecule as a whole, for what is required is probably an appropriate balance of these two properties.

The importance of the effect of structural modifications on physico-chemical properties having been stressed, attention is now directed to other methods of achieving selective toxicity. It is obvious that if an organism is dependent for its functioning on a particular enzyme reaction to the extent that it is to some degree biochemically unique, then this particular enzyme reaction can be made the basis of a specific attack upon the organism or process concerned. The processes of photosynthesis are peculiar to green plants, and plants also have their own characteristic growth-regulatory mechanisms. This knowledge has assisted the synthesis of selective herbicides. Certain metabolite antagonists are only toxic to those bacteria which need to be supplied with the metabolite concerned in the nutrient medium or which can make it only in limiting amounts. This is a line of approach which is particularly attractive to the organic chemist, for it demands a knowledge of the structure of natural substances and of their dynamic function; and it has been the subject of intensive work since the concept of metabolite antagonism was first formally expressed, in particular relation to bacteria, by Fildes (1940). It is desirable to consider, therefore, the position of this concept in the light of the approach to the general question of correlating structures with activity here discussed. In its broadest and simplest form this hypothesis states that interference with the life of a micro-organism, or with a specific process in an organ of a more complicated biological entity, may result from a chemical attack upon an essential metabolite, thereby dislocating the balance of metabolic processes, often with far-reaching consequences. In practice, two general types of metabolite antagonism are recognized, antagonism by neutralization, and antagonism by competition. In the former, an essential metabolite is immobilized by chemical interaction with the drug, and in the latter the place of the metabolite in its next reaction in the sequence of biochemical events comprising the life process is taken by a substance of analogous structure which enters into the reaction concerned to a limited degree only, the subsequent reaction or reactions in the sequence being impossible under natural conditions. The distinction between inhibition by neutralization and competitive inhibition

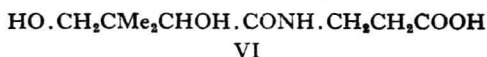
is perhaps artificial, or at least is only a matter of degree. The enzymatic conversion of metabolite *A* to metabolite *B* may be represented by the scheme:



If now a competitive metabolite *A'* enters the system, *A* and *A'* will compete for the enzyme, the degree of competition being determined by the extent of the reversibility of reaction I. Reaction II is possible only with metabolite *A* and cannot proceed with *A'*. Hence, though *A'* is spoken of as competitive antagonist of *A*, it must also be viewed as a neutralizing antagonist for the enzyme; for the enzyme is just as much an essential metabolite as is *A*. Thus it is seen that the phenomenon of competitive metabolite antagonism accords with the first of the two postulates made above, and, indeed, is a special example of a more general phenomenon. The experimental observations available regarding the relationship between structure and the ability of a substance to function as a metabolite antagonist are also in accord with the second postulate, namely, that its efficacy may be very considerably modified by changes, through structural alterations, in its physical properties. An example of the homologous series effect in the field of metabolite antagonism is shown in certain biotin (IV) analogues. Compounds of formula V have been shown by Dittmer & du Vigneaud (1947) to be competitive antagonists of biotin in the metabolism of yeast and *Lactobacillus casei*, and in the series where $n = 3-6$, maximum activity was shown where $n = 4$.

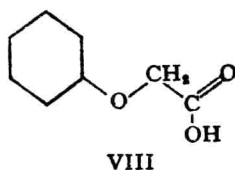
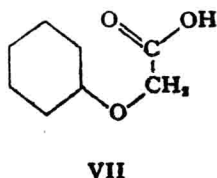


Similar effects are shown in certain analogues of pantothenic acid (VI):

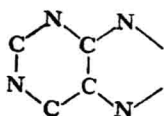


Competitive inhibition usually demands some similarity of structure between the competing molecules. The resemblance may be in the shape of the molecules or, more precisely, in the electrochemical similarity and spatial disposition of these groups which are responsible for the attachment to the relevant cell constituents. The best known examples are the competition of malonic and succinic acids in the succinic dehydrogenase system

and of *p*-aminobenzoic acid and sulphanilamide in the synthesis of pteroyl-glutamic acid. Examples have multiplied greatly in recent years, particularly amongst vitamins, coenzymes and amino-acids, and no doubt more will be heard of this from other speakers in this Symposium. It will suffice here to record a few general remarks upon the subject. First, in regard to molecular shape, the danger of considering two-dimensional formulae as drawn on paper cannot be too strongly emphasized. Molecules are rarely planar, though a good example of an essentially planar molecule of considerable complexity is provided in the porphin ring system. Secondly, the organic chemist in devising new structures, makes use of the fact that freedom of rotation can occur about a single bond. Thus, one may write phenoxyacetic acid as VII or VIII:



How many of the molecules at a given time are in form VII, form VIII or in other forms not depictable on paper is partly a matter for statistical computation, but in living surroundings is perhaps mainly determined by the molecular environment. Thirdly, it is necessary to emphasize the similarity of the valence angles of carbon, oxygen and nitrogen. In consequence of this, similarity of molecular shape is a common phenomenon, but this may have no biochemical significance except to point to the common origin of complex molecules in simple precursors such as the amino-acids and the intermediates of carbohydrate metabolism. There is thus great scope for irrelevant coincidence, and the chemist must be on guard against deceptive structural analogies. To exemplify, the arrangement IX is found in ribo-flavin, the pterins and the purines. This is doubtless one of the reasons



IX

why the synthesis of new biologically active molecules is often achieved as a result of faulty reasoning or why structurally plausible explanations so often follow quickly after empirical discovery.

Although facts are fast accumulating regarding the structural relationship