

D ANIEL B OVET

The relationships between isosterism and competitive phenomena in the field of drug therapy of the autonomic nervous system and that of the neuromuscular transmission

Nobel Lecture, December 11, 1957

Putting to good use the vast possibilities which organic synthesis offers, a number of workers have directed their efforts towards applying it to therapeutics, and have sought to establish the bases of a science of pharmaceutical chemistry, or, more exactly perhaps, the bases of a science of chemical pharmacology worthy of this name. If such an ambitious programme has not yet been fully realized, we are at least justified in recognizing, in the work which has now been in progress for fifty years, the appearance of a few guiding principles whose value has not ceased to assert itself. This is particularly true, for example, in the case of ideas in isosterism and competition.

The origin of many drugs must be looked for in substances of a biological nature, and in particular in the alkaloids. The elucidation of their structure has been a starting-off point for chemists to synthesize similar compounds. Cocaine, atropine, and morphia are particularly good examples in this respect, since substances which are made like them have shown, clinically, local anaesthetic, antispasmodic, and marked analgesic properties, respectively. In each of these cases the physiological properties of the new compound seem to be similar to the compound to which it is structurally related. This has been verified in many other fields, but it is nevertheless evident that in certain cases, molecules which are chemically closely related have very different and even antagonistic properties.

Although the idea of an "antimetabolite" is based on experiments which are now old, it is chiefly in the field of "antivitamins" that it is most clear: the work of Woods (1940) and of Fildes (1940) on extracts horn yeast which inhibit the bacteriostatic action of sulphonamides, and its identification with p-aminobenzoic acid has had vast repercussions. The concept that a substance whose properties approximate to those of a normal constituent

of the cell can modify the functions normally carried out by that constituent has shown itself capable of a variety of applications. The success which this concept has met with particularly in enzymology - where for the first time it was clearly formulated by Quastel (1925-1928) - in chemotherapy, vitaminology, and in endocrinology, will excuse me from expanding on the physico-chemical and biological bases on which the idea of competition is founded today (Woolley, 1952). I should like, rather, to draw your attention to the importance which the study of competitive phenomena assumes in pharmacodynamics, and in particular in the pharmacology of the autonomic nervous system, showing, in this way, how a vast chapter of Therapeutic Chemistry relates a large number of alkaloids and products of synthesis to a few hormones, chemical transmitters and products of tissue metabolism of a particularly simple nature: adrenaline, noradrenaline, acetylcholine, histamine, and 5-hydroxytryptamine.

Drugs Acting on the Autonomic Nervous System

One of the most brilliant and classical chapters in the chemistry and physiology of alkaloids and hormones is that on the research carried out in this field⁸.

We will recall only how, with regard to transmitter substances of the

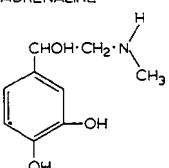
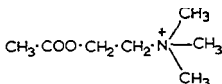
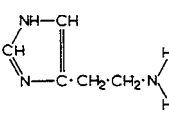
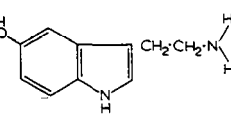
ADRENALINE	ACETYLCHOLINE	HISTAMINE	HYDROXYTRYPTAMINE
			
ANTI-ADRENALINE DRUGS Ergotamine Yohimbine Benzodioxanes (933 F) Dibamine Phentolamine	PARASYMPATHETIC ANTAGONISTS Atropine (Antispasmodics) CURARES α-Tubocurarine Galamine Decamethonium Succinylcholine GANGLION BLOCKING AGENTS Hexamethonium CENTRALLY ACTING GANGLION BLOCKING AGENTS (Antiparkinsonians) (Sedatives)	ANTIHISTAMINICS 929 F 2339 RP (Antergan) Pyriamine Diphenhydramine Antazoline Promethazine	ANTI-HYDROXYTRYPTAMINES

Table 1. Drugs acting in competition with adrenaline, acetylcholine, histamine and 5-hydroxytryptamines.

sympathetic nervous system, the isolation of adrenaline by Takamine (1901) had been anticipated by the empiricism of the Chinese who a thousand years before, used *mahuang* - rich in ephedrine - and by the fortuitous discovery of the properties of tetrahydronaphthylamine by Bamberger (1888). The exact nature of noradrenaline was not discovered until comparatively recently, by von Euler (1946).

In the field of parasympathomimetics, the observation of the properties of muscarine (1811) preceded by a century the discovery of the vagus-stoff by Loewi (1921), and the synthesis of acetylcholine (1866) that of its isolation from the tissues (1931) by fifty years. The synthesis of histamine (1907) shortly preceded its identification in products of animal and vegetable origin, and the names of Dale and Dudley (1910) are associated with this identification and the study of its pharmacological properties.

The latest arrival, 5-hydroxytryptamine (Rappaport, 1949) is the outcome of research by Erspamer on the enteramine first isolated from chromaffine cells (1937-1952), and of Rappaport, Green, and Page (1947-1952) on serotonin, which is considered to be the principle vasoconstrictor in the serum.

The relationships existing between adrenaline, tissue acetylcholine and the nervous system were recognized early on. In 1904, Elliot, struck by the similarity existing between the pharmacological actions of adrenaline and the effects of stimulation of sympathetic nerves, put forward the hypothesis, according to which, adrenaline could be released at the sympathetic nerve endings and transmit the impulse of the nerve cell to the smooth muscle fibre.

In 1912 Wieland, then le Heux in 1919, tried to produce evidence to demonstrate the role of choline and acetylcholine as a local hormone, and their hypothesis was then, later on, developed with success, as we all know, by Loewi, Dale, Cannon, and Bacq, from whose experiments the very idea of chemical transmission grew.

The hypothesis of an acetylcholine-like transmitter, at first formulated for the viscera innervated by the parasympathetic nervous system, was later extended by Dale, Feldberg, and Vogt (1936) to neuromuscular transmission.

Recent research into the physiology of the motor end plate has definitely confirmed the existence of an intermediate acetylcholine-like substance. The reaction between acetylcholine and its receptor, situated at the surface of the postsynaptic membrane, can, perhaps, today be integrated with the mass of electrophysiological data which has, in particular, demonstrated the inex-

citability of the membrane towards electrical impulses and its great sensitivity with respect to the transmitter substance (Kuffler, 1948; del Castillo and Katz, 1956).

In the field of antagonists of these various hormones and chemical transmitters, it is still among the substances of natural origin, ergotoxine, atropine, curare, that the models are found on which antiadrenaline and antiacetylcholine-like drugs have been made, while the antihistamines have only been studied recently and represent the products of completely original synthesis.

In practice, the drugs of this group have found numerous applications in the symptomatic treatment of those organs whose activity is normally under the influence of the autonomic nervous system: heart, vessels, bronchi, alimentary tract and uterus in particular. The adrenaline-antagonists have found their most important use in the treatment of vascular disease and hypertension; the antagonists of acetylcholine are chiefly used for their antispasmodic, mydriatic, and curarizing effects. The antihistamines have found their strongest indications in the therapy of urticaria, rhinitis, asthma, and other allergies.

We shall give three examples taken from different pharmacological groups to illustrate these points. In the group of adrenaline-like substances we shall refer to ergotamine, in that of antiacetylcholine-like substances to curare, and for the third tissue hormone, histamine, we shall take synthetic antihistaminic substances.

Sympatholytic substances – Synthetic ergotamine-like substances

The sympatholytic drugs make up a group of substances characterized by their common pharmacological properties. They act as competitors, or as "blocking agents", according to the terminology generally used by English speaking authors, in opposing the effects of adrenaline and noradrenaline, so that their most characteristic property lies in the fact that they prevent hypertension and sympathetic vasoconstriction.

As often happens, a variety of drugs of this group were introduced into therapeutics empirically, well before the type of pharmacodynamic action which they exercise was established. In 1909 Froelich had already noticed that initial administration of high doses of the dextro-rotatory isomer of adrenaline was likely to make the animal resistant to the natural laevorota-

tory isomer by a mechanism which we interpret today as a partial block of the receptors by a substance optically inverted and pharmacologically much less active. Later on, Loewe (1927), Külz (1936), Raymond-Hamet (1937) described some N-alkyl derivatives of phenylethylamine which showed typical adrenaline inhibition. Analogous properties have been described in the series of phenoxyethylamine (Anan, 1930; Levy and Ditz, 1933; Bovet and Maderni, 1933; Bovet, Simon, and Druey, 1937), of phenylethylene

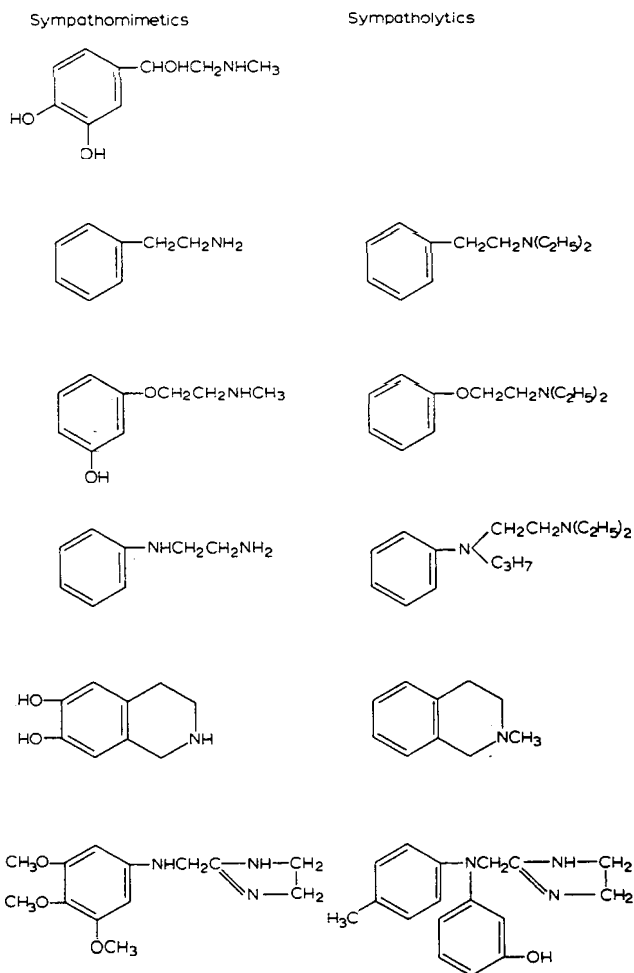


Table II. Similarity in structure between sympathomimetics and sympatholytics⁵. (Raymond-Hamet, 1937; Bovet and Simon, 1936; Druey, 1936; Bovet, de Lestrangé, and Fourneau, 1942; Hjort, de Beer, and Fassett, 1938; Hartmann and Isler, 1939; Gross, Tripod, and Meier, 1951.)

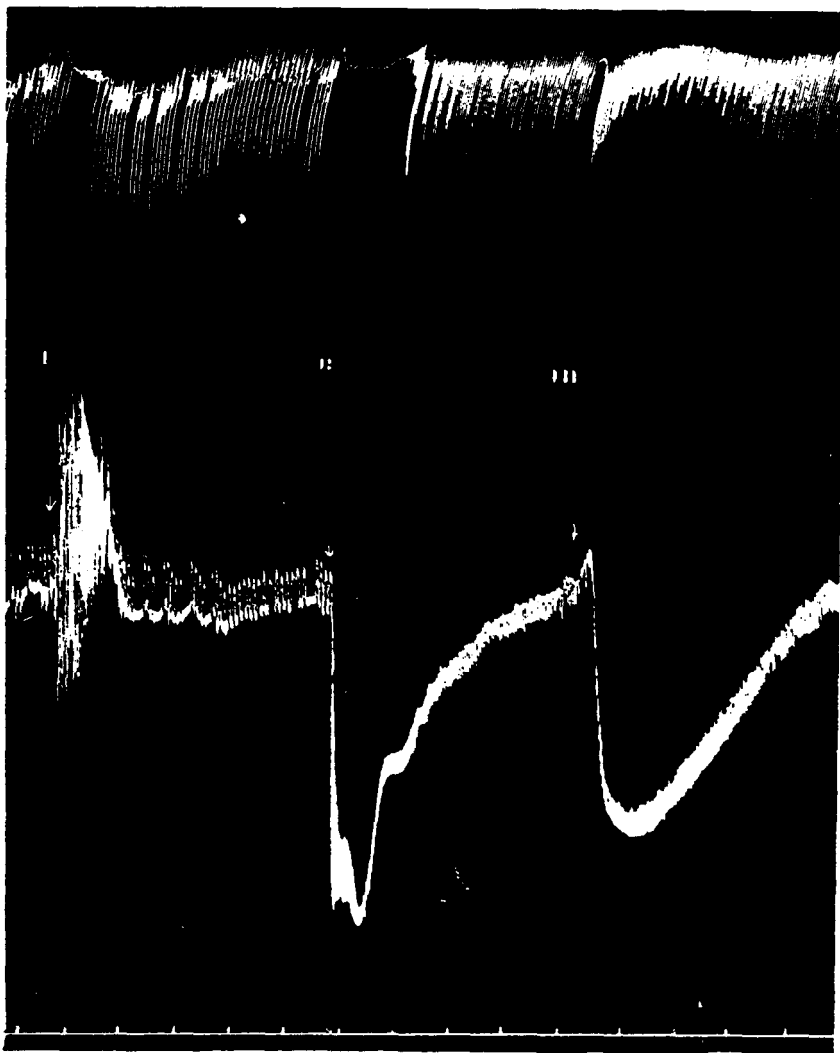
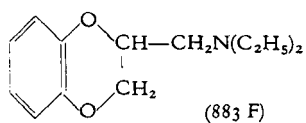


Fig. 1. Anti-adrenaline properties of diethylaminomethyl-2-benzodioxane.



Reversal of the hypertensive action of adrenaline on the blood pressure of a dog. In I and III: injections of adrenaline in the saphenous vein (0.02 mg/kg). In II: injection of 883 F (5 mg/kg) (Foumeau and Bovet' 1933).

	PHENYLETHYLAMINES	PHENOXYLETHYLAMINES	PHENYLETHYLENEDIAMINES
<u>Sympatho-</u> <u>mimetics</u>	Adrenaline Phenylethylamine and its phenol derivatives	Phenol derivatives of phenoxylethylamine	Phenylethylenediamine and its phenol derivatives
<u>Aromatic</u> <u>sympatholytics</u>	N-diethylphenylethylamine Dibenzamine Tetrahydronaphthylamines, N-substituted	N-diethylphenoxylethylamine Dibenzylamine	N-diethyl-N ¹ -propyl- N ¹ -phenylethylenediamine
<u>Heterocyclic</u> <u>sympatholytics</u>	N-methyltetrahydro- isoquinoline Benzylimidazole	Benzodioxans: Prosympal, Piperoxan	Phenyl piperazines Phentolamine
<u>Sympatholytic</u> <u>alkaloids</u>	Ergot alkaloids		Yohimbine

Table III. Classification of the main groups of sympathomimetic and sympatholytic agents⁵.

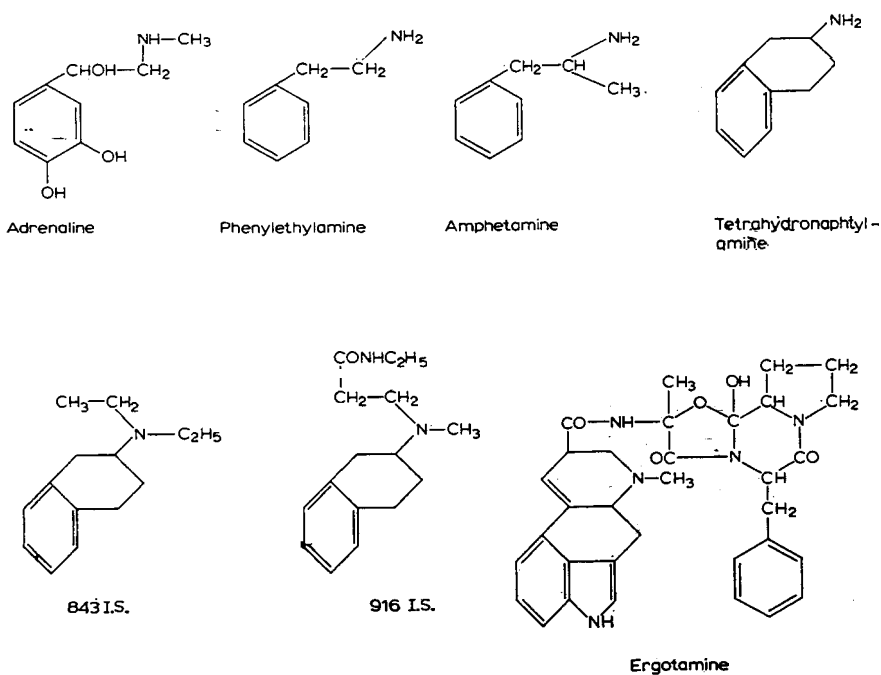


Table IV. Similarities in structure between sympathomimetic and sympatholytic agents from adrenaline to ergotamine⁷ (Marini-Bettolo, Chiavarelli and Landi-Vittory, 1950-1953; Bovet, Bovet-Nitti, Virno, Longo, Marotta, and Sollero, 1952)⁴⁰.

diamine (Bovet, de Lestrangé, and J. P. Fourneau, 1942), of isoquinoleine (Hjort, de Beer, and Fassett, 1938), and of phenylaminoethylimidazoline (Meier and Muller, 1939; Hartman and Isler, 1939). In each of these groups the similarity of structure which exists between antagonistic molecules showing sympathomimetic and sympatholytic properties is clearly shown. The degree of substitution on the amine, the suppression or simple movement of a phenol group, the closing of a chain, is enough to reverse the pharmacological action exercised. It is very significant that while in sympathomimetic and sympatholytic drugs the distance between the amine group and the aromatic nucleus remains constant, the amine group of the inhibitor molecule regularly is substituted for more and heavier radicals, generally appears more stable, and has a higher molecular weight.

The sympatholytics, either natural or synthetic, which are most active and whose usefulness is sufficient to justify their use clinically, tend generally to be poly- or heterocyclic substances whose molecules have, in spite of their complexity, a basic structure in common with those products mentioned above. Benzylimidazoline (Meier and Muller 1939), and dibenamine (Nickerson and Goodman, 1947), resemble the phenylethylamines, the aminoethylbenzodioxanes (Fourneau and Bovet, 1933) resemble the phenoxyethylamines, and phentolamine (Gross, Tripod, and Meier, 1951) resemble the derivatives of phenylethylenediamine.

Work carried out at the Istituto Superiore di Sanità by Marini-Bettólo and Chiavarelli on the chemical side, and by my wife, Longo, Marotta, and Guarino on the pharmacological side⁴⁰, illustrate how the idea of isosterism and competition can help in investigations of this type. Following this work which resulted in the isolation and the determination of the structure of the ergot alkaloids, with which work the names of Stoll and Jacobs are particularly associated, a large amount of work was done with the object of preparing partially or completely synthesized derivatives. This work resulted, in particular, in the preparation of di-hydrogenated derivatives (Rothlin, 1947), new oxytocic compounds closely related to ergometrine (Rothlin, 1947) and the discovery of the hallucinogenic properties of the diethylamide of lysergic acid (Stoll). Having decided to look for the active pharmacological principle of the ergotamine molecule we worked on the idea which we have already illustrated of noting similarities between molecular structure and antagonistic properties, as a working hypothesis.

If we consider the molecule of the ergot alkaloids its structure appears at first sight very different from that of adrenaline or the sympathomimetic

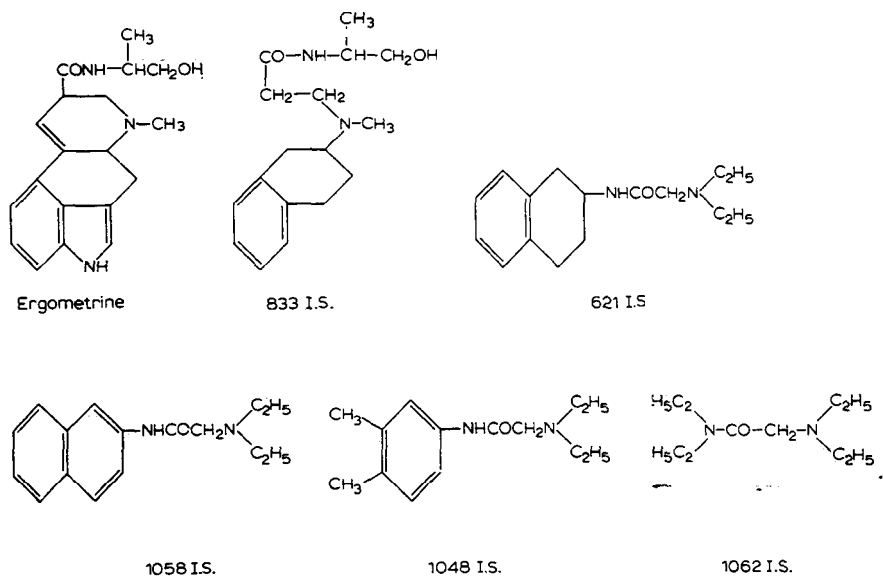


Table V. Synthetic oxytocic agents, derived from phenylglycinamide. (Bovet-Nitti, 1952, 1954)^{12,40}.

derivatives of phenylethylamine. Having noticed, however, the existence of a β -tetrahydronaphthylamine skeleton in the lysergic acid molecule, we decided to resume work on substances in this group.

Pharmacological tests performed on relatively simple derivatives proved the adrenaline antagonist properties of β -tetrahydronaphthylmethylethylamine (843 I.S.S.). The study of more complicated molecules and, in particular, derivatives with amine and amide groups of 2-tetraline represent a new stage in the attempt to reproduce the skeleton of lysergic acid in its essential parts. Progressing through a series of molecules of increasing complexity, one can thus pass through successive stages from phenylethylamine to tetrahydronaphthylamine or to 916 I.S. and to the ergot alkaloids, noting, in each of these stages, a gradual decrease in sympathomimetic properties and the appearance of adrenaline antagonistic properties.

An oxytocic activity has been observed in a large number of derivatives, and the class of substances of this type seems a large one, when compared to the group of adrenaline antagonists.

In the course of laboratory experiments performed on isolated uterus preparations or on the rabbit uterus in situ, several derivatives of aminotetraline and aniline and even some aliphatic compounds showed an intense

activity. We would mention particularly N,N-diethyl-N'(2-tetra-lyl) glycinamide (621 I.S.), N,N-diethyl-N'-3,4-dimethylphenylglycinamide (1048 I.S.) and N,N,N',N'-tetraethylglycinamide (1062 IS.), (Bovet-Nitti, 1952)⁴⁰.

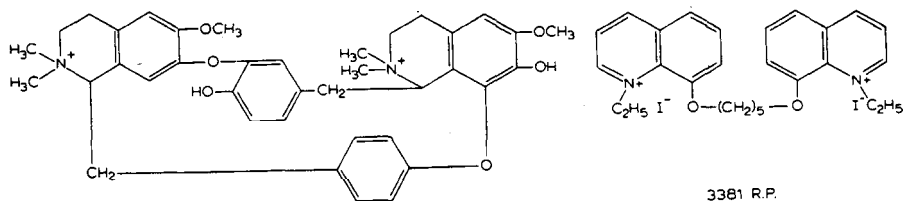
The main difficulty in this work, and that which has struck many workers, is the absence of any close correspondence between the results obtained in small laboratory animals and those seen in man. Generally speaking, the problem of synthetic oxytocic substances would not yet seem to have received any very satisfactory solution and the question is still under investigation.

Acetylcholine antagonists – Synthetic curares

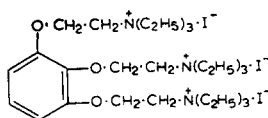
The case of acetylcholine antagonists is a singularly complicated one because of the multiplicity of ways in which the chemical transmitter acts. As well as acting on viscera innervated by the parasympathetic nervous system, it acts at the neuromuscular junction of voluntary muscle and at ganglionic synapses. Great use, in the pharmacology of competitors, has been made of the surprising fact that acetylcholine antagonists differ depending on the site of action of the hormone. This is shown by atropine and benzoylcholine which neutralize the muscarinic actions of acetylcholine on the heart, intestines and secretions, while the iodide of tetraethylammonium or hexamethonium block its nicotinic action on sympathetic or parasympathetic ganglia, and the curares represent the specific antagonists of acetylcholine at the level of voluntary striped muscle.

As for the structural similarities between antagonistic substances the study of synthetic curares will provide us with a succession of examples comparable to those which we have already reviewed in the series of adrenaline antagonists. This work was started in 1946 after King had, in 1935, been the first to identify the structure of one of the physiologically active principles of curare from the Amazon district, to be followed by the introduction, by Griffith and Cullen, in 1942^{2, 5}, of a chemically pure alkaloid as an adjuvant to anaesthesia.

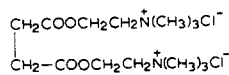
d-Tubocurarine which comes from a Menispermacea - *Chondodendrum tomentosum* - and which comes into the preparation of certain curares by the inhabitants of the Upper Amazon, is an alkaloid of the group bis-(benzyl tetrahydroisoquinoleine) whose molecule carries two quaternary ammonium groups.

*d*-Tubocurarine

3381 R.P.



Gallamine



Succinylcholine

Table VI. Natural and synthetic curares³⁹.

d-Tubocurarine (King, 1935; Wintersteiner and Dutcher, 1943) ; 3381 R.P. (Bovet, Courvoisier, Ducrot, and Horclois, 1946); Gallamine (Bovet, Depierre, and de Lestrang, 1947) ; Succinylcholine (Bovet, Bovet-Nitti, Longo, and Marotta, 1949; Fusco, Pahzzo, and Knüsli, 1949).

Work with our colleagues Viaud, Horclois, and de Lestrang, first directed towards molecules which were chemically related to the chosen model, made it possible to synthesize by successive changes relatively simple derivatives with analogous properties. From one series of derivatives of a new type whose molecules carried two quinoleinic nuclei with a quaternary ammonium group, we first kept the diiodoethylate of 8',8''diquinolyoxy-1,5-pentane (3381 R.P.) which was the first synthetic product whose curarizing activity showed itself in mammals with a selectivity comparable to that of the natural alkaloids isolated from curare (1946).

In the course of investigations it was noticed that the derivatives of aminophenol without quinoleinic or isoquinoleinic nuclei showed an analogous activity, and a curare-like activity was noticed in compounds belonging to the group of ethers of polyphenols and aromatic esters. The latest work for further simplification is concerned with the activity of aliphatic derivatives.

In England, Barlow and Ing, Paton and Zaimis (1948) have produced very interesting data on the curare-like properties of the hydrate of decamethylene-*w*-bis-trimethylammonium (decamethonium). In our Laboratory of Therapeutical Chemistry at the Istituto Superiore di Sanità the curare-

like action of succinylcholine, whose synthesis was first carried out by Hunt as long ago as 1911; has been recognized for the first time.

The number and variety of derivatives which are capable of acting like curare, the relative simplicity of their mode of action, and the possibility of producing accurate pharmacological effects has allowed a close study of structure-activity relationships in the field of synthetic curare-like substances.

I shall only bring attention to two important features which condition the activity of bis-quaternary derivatives: the distance between the two quaternary ammonium groups and the rather large nature of the molecules.

The first factor is illustrated by comparing the derivatives of polymethylene-bis-trimethylammonium (Barlow and Ing, Patton and Zaimis, 1948) and by comparing those of the aliphatic diesters of choline (Bovet, Bovet-Nitti, Guarino, Longo, Marotta, 1949).

A close study of the pharmacology of new syntheses has established that their action is far from being always coincident with those of the natural alkaloids.

The differences which the action of the iodides of decamethonium and succinylcholine present in comparison with that of *d*-tubocurarine and of gallamine triiodoethylate have been particularly studied by Paton and Zaimis, Brown and bias, and in our own laboratories. The English authors

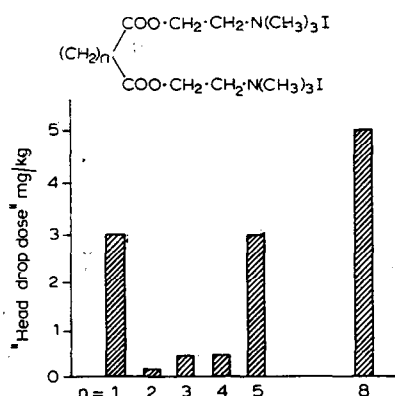


Fig. 2. Curarizing action of choline esters and aliphatic dicarboxylic acids with normal chains.

The curarizing activity has been estimated by determining the "head drop dose", of different products administered intravenously to rabbits. The curarizing activity reaches a maximum for Succinylcholine and decreases in higher homologues of the series (after Bovet, Bovet-Nitti, Guarino, Longo, and Marotta 1939¹⁰.)

	PACHYCURARES (Competitive agents)	LEPTOCURARES (Depolarizing agents)
	Tubocurarine Gallamine	Succinylcholine Decamethonium
Mammals	Curarization	Curarization (Muscular fibrillation)
Birds	Curarization	Contraction followed by curarization
Batrachia (Rectus abdominis)	Antagonism to acetylcholine	Acetylcholine-like contraction

Table VII. Pharmacodynamic properties of synthetic curares^{4,9}.

have suggested that the two groups should be called depolarizing agents and curare competitors. We, ourselves propose to denote decamethonium and succinylcholine by the name of leptocurares, and tubocurarine and gallamine by the title of pachycurares. The advantage of such a nomenclature lies in the fact that it does not prejudice in any way the mode of action of these substances.

The main differences between the pharmacodynamic effects exercised by the two types of curare rest chiefly in their action on Batrachian and bird muscle. In birds the pachycurares are typically curare-like in action while the leptocurares provoke a contraction followed by curarization. In mammals the differences between the two groups of products seem less clear. There are important differences between the reactions of different species, and between those of different muscles in particular, because the reactions of various species and different muscles of the same species are not exactly coincident, and because there seems to be every gradation of action between depolarization and curare competition. The distinction between the two groups, which is only relative as regards the mechanism of action, and whose significance varies according to the neuromuscular preparation under consideration, keeps all its interest in the study of relationships between chemical structure and pharmacological activity.

From the clinical point of view, the main factor in the classification of curares is the duration of action of the different compounds. In this respect, the introduction of short-acting curare-like substances and, in particular, succinylcholine is an important acquisition. The relative ease with which succinylcholine is hydrolysed by the pseudocholinesterases and the very

low toxicity of the choline and the succinic acid which are formed explain the short curare-like action and the remarkable tolerance of the organism towards it (Bovet-Nitti, 1949³⁹).

The first clinical observations regarding the short acting curares were pub-

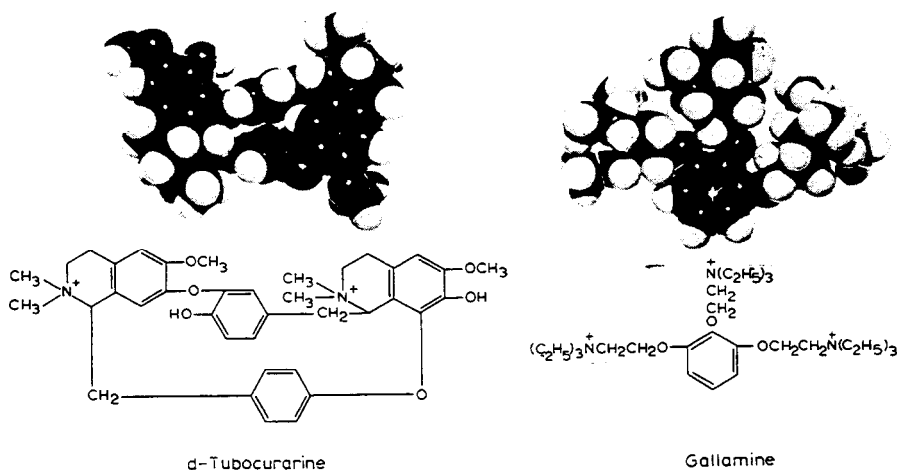


Fig. 3. Pachycurares.

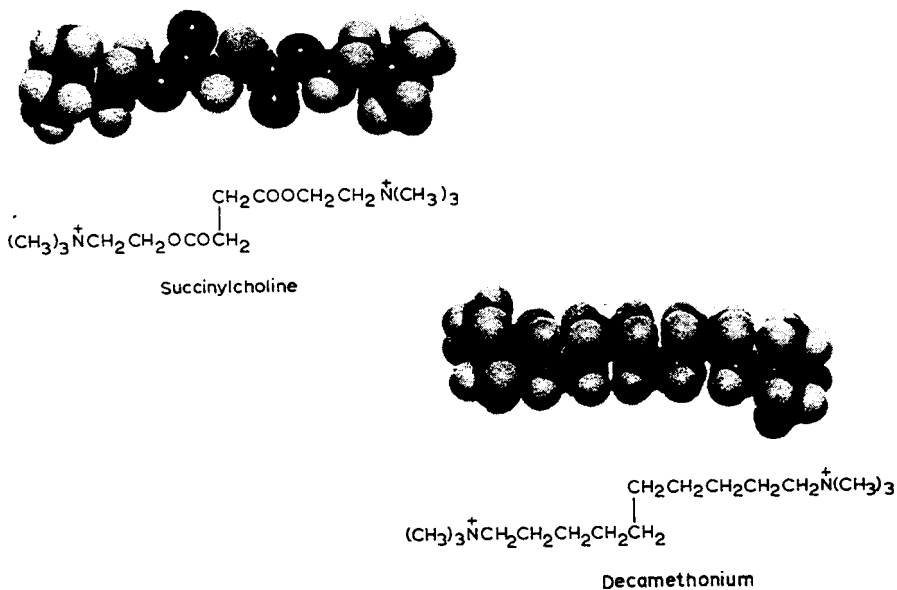


Fig. 4. Leptocurares.

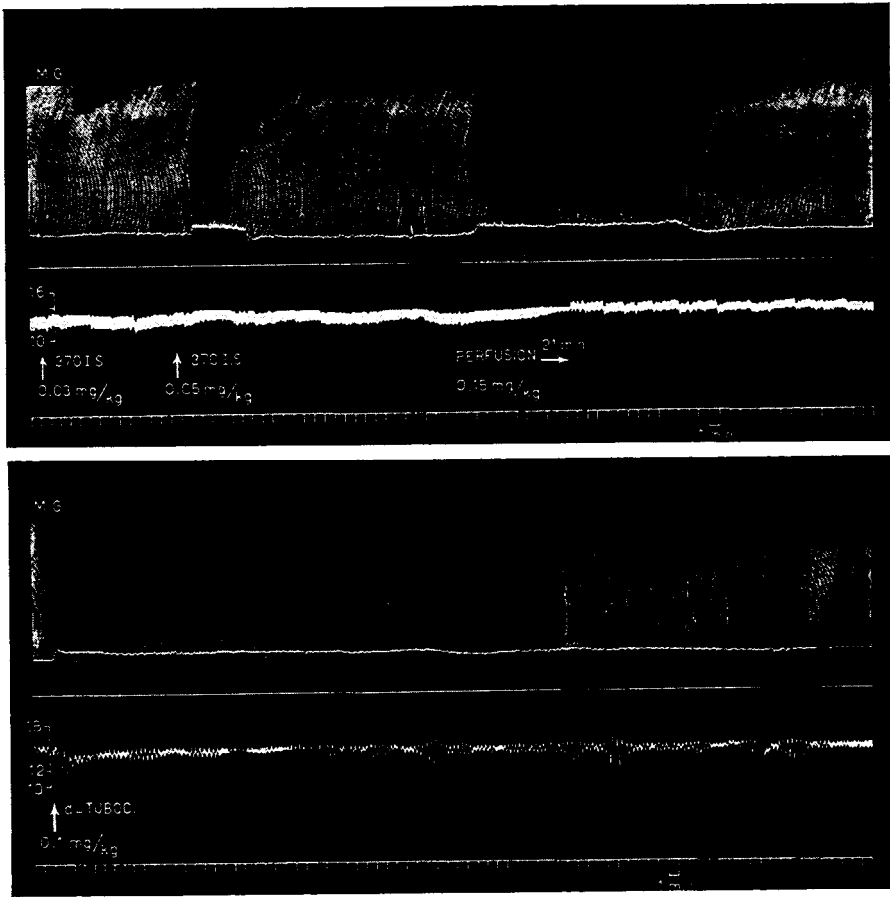


Fig. 6. Comparison between the curarizing action of *d*-tubocurarine and the effects of succinylcholine, given either by single injection or by continuous perfusion.

Dog, under chloralose anaesthesia - (1st line): contraction of gastrocnemius following rhythmic stimulation of the sciatic nerve; (2nd line): control for the speed of injection; (3rd line): blood pressure.

The trace shows, in the first place, the difference between the duration of neuromuscular paralysis following a single injection of succinylcholine (370 I.S., 0.05 mg/kg) and *d*-tubocurarine (0.1 mg/kg). Furthermore, comparing the effect of a single injection of *d*-tubocurarine which corresponds to a continuous perfusion of succinylcholine (initial injection of 0.05 mg followed by injections of 0.0062 mg at each marker) we may state that for practically equal duration of subtotal curarization (about 80% for 20 min) the return to normal is very quick (about 10 min) in the first case and much more gradual (about 50 min) after *d*-tubocurarine.

(After Reuse, 1953.)

indications necessitating a particularly short action (endoscopy, electroconvulsive therapy), and its use as a perfusion for long surgical procedures.

Two tracings taken from a piece of work done in our laboratory illustrate the most significant result of these two types of administration; they show the advantage which curarizing action by perfusion of short-acting curares have over the classical technique (Fig. 6).

Antihistamines

The last of the examples by which we shall illustrate the idea of competition concerns the antagonists of the third local hormone, histamine. This is a particularly rich chapter when we realize that in the course of only a few years interest in this branch of therapeutics has produced a large amount of varied research work. In 1937 in the laboratory of Fourné and in collaboration with Miss Staub, we considered the numerous similarities existing between histamine, adrenaline and acetylcholine, and planned to investigate substances showing a specific antagonism for histamine comparable to the antagonism shown by sympatholytics for adrenaline and parasympatholytics for acetylcholine. The first positive results concerning the specific antagonism of thymoxyethyl-diethylamine (929 F) for histamine dates from 1939. Experimental work on this substance made it possible to make some criteria

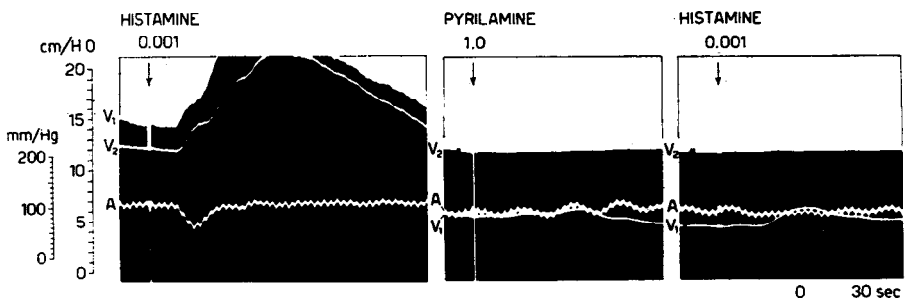


Fig. 7. Antagonistic action of pyrilamine with respect to the vasodilating effects of histamine in cerebral circulation.

Dog, under chloralose anaesthesia - A = femoral artery pressure (mmHg); V_1 = pressure measured in catheter introduced centrifugally in the external jugular vein (nun H_2O); V_2 = pressure in the internal jugular vein (mm H_2O). Injections in the saphenous vein, doses in mg/kg. (After Virno, Gertner, and Bovet, 1956.)

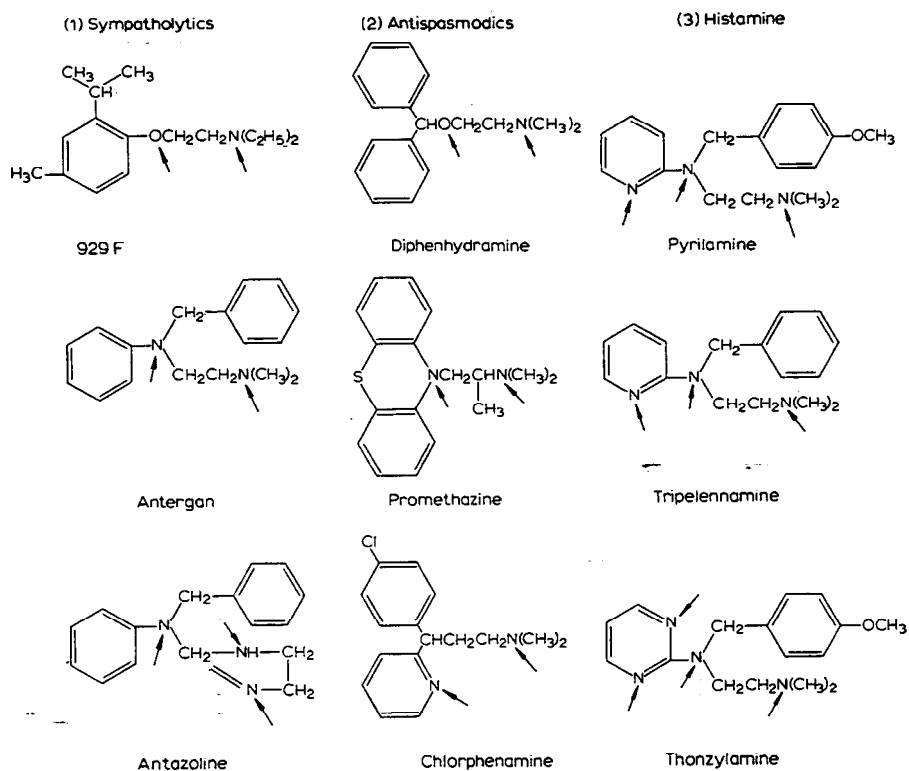


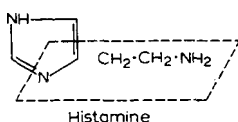
Table IX. Principal groups of synthetic antihistammics, related to (1) sympatholytics, (2) antispasmodics, and (3) histamine.

929 F (Bovet and Staub, 1937); Antergan (Halpern, 1942); Antazoline (Meier and Bucher, 1946); Diphenhydramine (Loew, Kaiser, and Moore, 1945); Promethazine (Halpern and Ducrot, 1946); Chlorphenamine (Tislow, La Belle *et al.*, 1949); Pyrilamine (Bovet, Horclois, Walthert, and Foumel, 1944); Tripeleminamine (Mayer, Huttner, and Scholz, 1945); Thonzylamine (Reinhard and Scudi, 1947).

for histamine antagonists. Staub (1939) herself extended the work to derivatives of phenylethylenediamine. In 1942 the syntheses carried out by Mosnier, the pharmacological analysis of Halpern and the first therapeutic results of Cuilleret, Thiers, Gate, Celice, Perrault, Decourt, and Durel with dimethylaminoethylbenzylaniline (Antergan) definitely established the interest taken in products of this series. The role of histamine in many allergic phenomena was going to guarantee a vast field for clinical application to the products of this group. After the forerunners Maderni, de Lestrangé, and Benoit (in the Laboratory of Fournéau in Paris), Viaud, Horclois, Mosnier,

and Charpentier (in French industry), Hartman and Hofman (in Switzerland), Rieveschl, Scholz, Hutterer, and Roblin (in the U.S.A.), and Cavalini (in Italy), about 500 chemists have in less than ten years performed about 5,000 syntheses in the field of antihistamines.

If the pharmacologists were easily able to recognize the competitive nature of the antagonism exercised by specific antihistamines, neither the similarities in structure between antihistamines and histamines which should logically constitute the first condition of their activity, nor the similarities existing between the different groups of active derivatives, appeared very clearly to the chemists. Whether one likes it or not, in view of the variety of chemical classes to which the active substances belong, it has been necessary to recognize the fact that the majority of results obtained in the laboratory appear rather empirical.



Histaminic action

Antihistaminic action

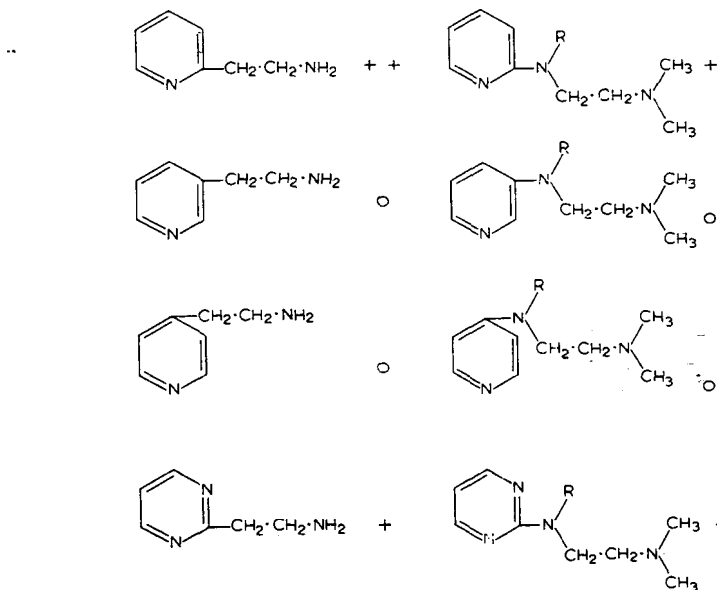


Table X. Similarities in the structure of histamine and antihistamines. (Waker, Hunt, and Fosbinder, 1941; Niemann and Hays, 1942; Bovet and Walthert, 1943.)

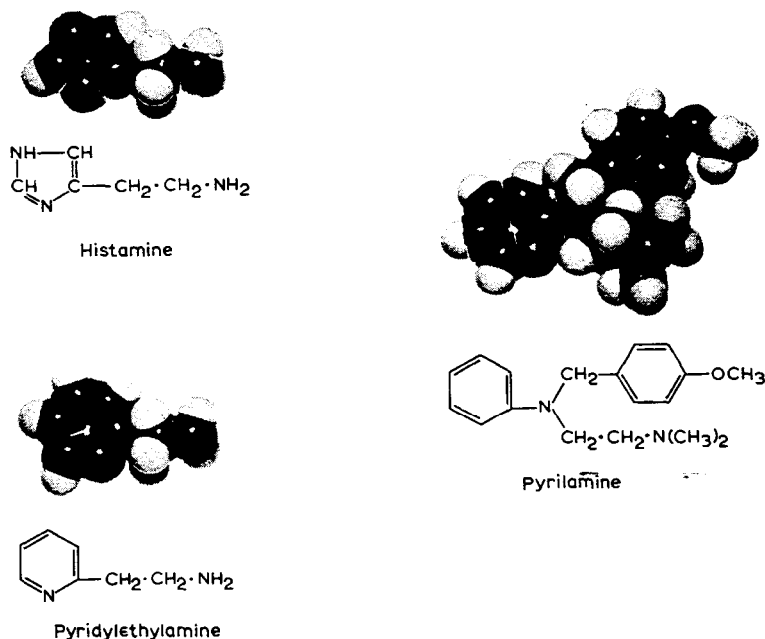


Fig. 8. Histamine, pyridylethylamine, and pylamine.

From the pharmacological point of view the existence has been proved of three groups of antihistamines which resemble (1) sympatholytics, (2) para-sympatholytics and sympatholytics, and (3) histamine itself.

The phenol ethers (929 F) and the derivatives of phenylethylenediamine (157 F) studied at the Pasteur Institute, Halpern's antergan, and Meier and Bucher's antazoline belong to the first group. The substances of the second group are chemically much more homogeneous and possess a structure common to the antispasmodics and atropine-like compounds. They are effective antispasmodics as well as antihistamines (diphenylhydramine, Loew). Because of the absence of any side effects the derivatives of α -aminopyridine which make up the third group, show a higher degree of specificity. It is interesting in the products of this type to remark on the reactions of isosterism which account for the pharmacological activity exercised. Walter *et al.* (1941) and Niemann and Hays (1942) have produced evidence to show that derivatives of α -pyridylethylamine have a typically histaminic activity and that there exists, in this respect, a fundamental difference between the α , β and γ isomer substitutes of pyridine. In this case the similarity in structure which doesn't seem to be very clear between histamine and pylamine (Neo-an-

tergan) on the other hand does appear between the two series of α -pyridyl-ethylamine and α -pyridine-ethylenediamine. The type of products in this group is represented by pyrilamine but many other syntheses made in this way have given active products.

Central action of transmitters

The examples which we have just given certainly do not exhaust the field of competitive agents. The pharmacologists are rather the "enfants terribles" of physiology and have not waited until the battle has been won at the level of the neuromuscular synapses before waging an even greater war by

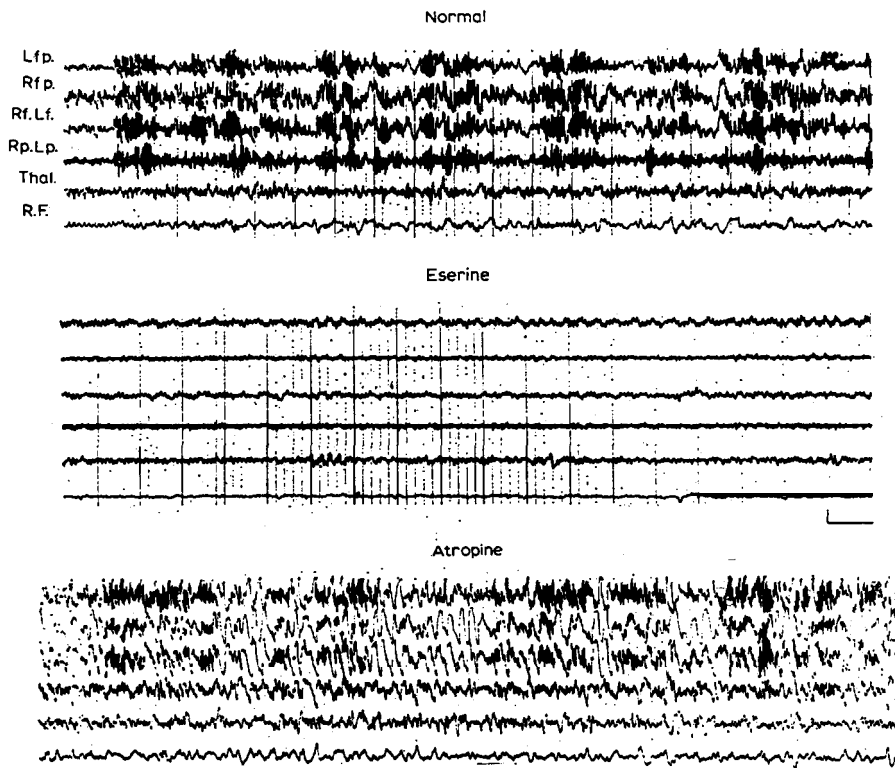


Fig.9. EEG of rabbit, antagonist action of atropine on the desynchronization provoked by eserine.

Injection of eserine (0.1 mg/kg i.v.) provokes desynchronization of the EEG which disappears after administration of atropine (1 mg/kg i.v.) and gives place to a synchronization with many slow waves. (After Longo, von Berger, and Bovet, 1954.)¹⁰

making known experimental results suggesting the intervention of chemical transmitters at central nervous system level whose effects have already been studied on the scale of the autonomic nervous system.

Analysing results collected from different laboratories Feldberg (1950) concluded by saying that the theory of acetylcholine as a transmitter in the central nervous system provided the only convincing and satisfactory explanation. If the intervention of non-cholinergic central nervous system transmitters centrally is not excluded one must recognize that our knowledge of the probable roles of noradrenaline and adrenaline and of histamine and 5-hydroxytryptamine is still very inexact.

In the course of the last few years a considerable amount of research has shown the effect of different types of substances, showing activity on the autonomic nervous system, upon the reticular formation of the brain stem, whose physiological role was clearly shown by Moruzzi and Magoun in 1949.

Rather paradoxically we see that cholinergic substances on one hand and adrenergic substances on the other, show their effects on the electrical activity of the brain which reproduce the action of direct electrical stimulation of the reticular formation. In carefully conducted experimental conditions, acetylcholine (Bonnet and Bremer, 1937) and adrenaline itself (Bonvallet, Dell, and Hiebel, 1954) provoked a transitory stimulation as seen on the electroencephalogram. Administration of anticholinesterases (eserine, DFP and amphetamine [Bradley and Elkes, 1953]) is followed in the two cases by a strong and lasting desynchronization.

From a strictly pharmacological point of view, the chief interest in work in this field is in the fact that one can observe at a central level, between the different groups of drugs, antagonisms comparable to that seen at the level of viscera innervated by the autonomic nervous system.

As early as 1947 we suspected that a connection might exist between the central action - antiparkinsonian - of certain tertiary amines in extrapyramidal lesions and the ganglion-blocking properties which one could recognize in the same substances on the autonomic ganglia (Sigwald and Bove, Dumont, 1947).

The "antiparkinsonian drugs" are a relatively homogeneous group to which belong diethazine (diparcol), isothazine (parsidol), caramiphen (parpanit), and benzhexol (artane) as well as certain antihistamines (diphenhydramine and promethazine).

EEG studies have confirmed that really three groups of products, antiparasymphathetics (scopolamine and atropine), the central ganglion blockers

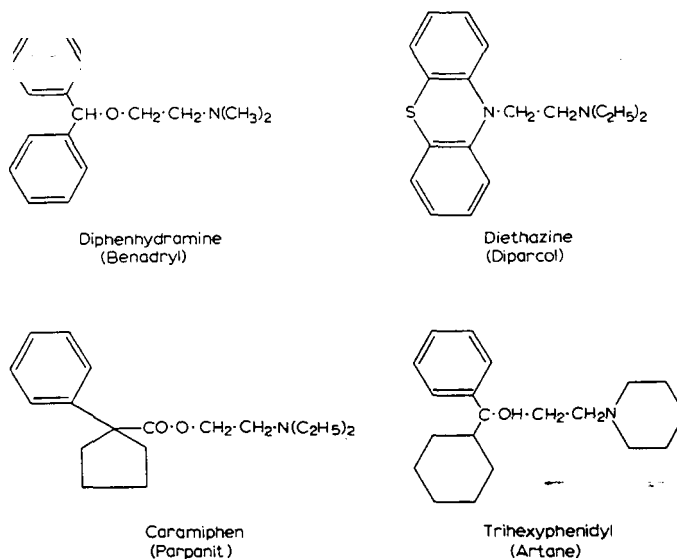


Table XI. Central ganglion blockers (Antiparkinsonics)

Diphenhydramine (Loew, Kaiser, and Moore, 1945); Diethazine (Sigwald, Bovet, and Dumont, 1946; Bovet, Foulon, and Charpentier, 1947); Caramiphen (Domenjoz, 1946; Grünthal, 1946); Trihexyphenidyl (Doshay and Constable, 1949).

or antiparkinsonian drugs and the sedatives (chlorpromazine, reserpine) produce a tracing on the EEG similar to that seen normally during sleep and are at the same time likely to upset the general cortical reaction normally provoked by external stimuli (reaction to alarm) or by desynchronizing substances like eserine and amphetamine (Bovet and Longo, 1956). The action of such synchronizing agents can, at first approximation, be localized in the reticular formation and shows the importance that chemical transmitters seem to exercise at this level.

Many observations today make it seem likely that there are special receptors for adrenaline, acetylcholine and histamine in the organism which might be specific proteins whose configuration is complementary to that of the transmitter itself. Fischer first formulated this concept and illustrated it with his famous example of the lock and key. Physiologists studying taste and smell have looked there for the explication of facts observed in the field of the chemistry of smells and perfumes. Still more recently, following the studies of Landsteiner and Pauling, the hypothesis of these "locks" has found a very suggestive application in immunology.

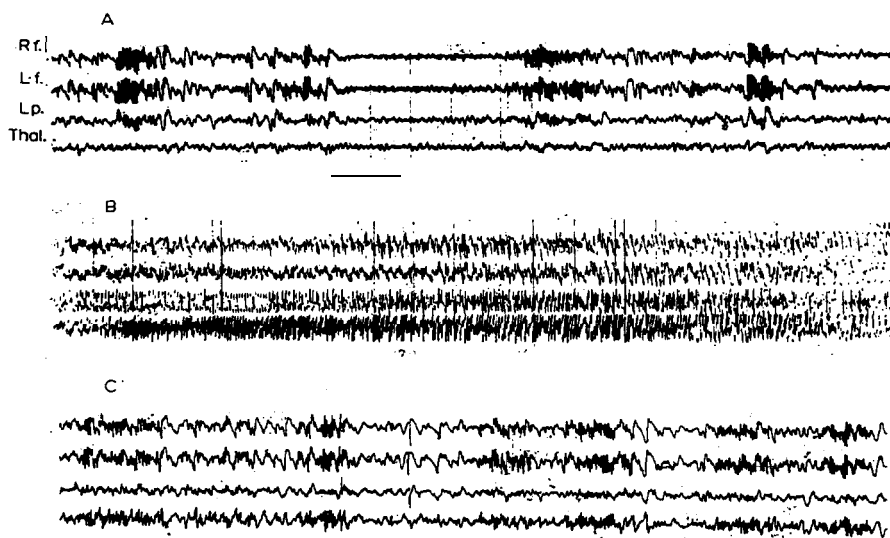


Fig. 10. Antagonistic action of diethazine against convulsive patterns caused by nicotine on the EEG of curarized rabbit. (A) Blocking reaction after acoustic stimulus (black line). (B) Convulsive seizure by 2 mg/kg nicotine in normal animal. (C) After injection of 5 mg/kg diethazine a second injection of nicotine no longer produces the changes observed in (A); the acoustic stimulus fails to produce the blocking action. (Longo and Bovet 1952¹⁰.)

At this stage in my exposition I cannot consider the variety of possible reactions that can take place between chemical transmitters, its inhibitor and its protein base without exceeding the time limit which has been set me.

The particularly simple case of the fixation of acetylcholine by cholinesterase has been examined by Nachmansohn(1953-1954) and Wilson(1954), who think that it is likely that an electropositive and an electronegative group respectively, of the molecule become attached to the acetylcholine molecules and they have drawn valuable conclusions not only in the case of different types of anti-acetylcholinesterases but for the new group of drugs called phosphorylated cholinesterases.

If I wanted to go outside the already stretched framework of this exposition I could introduce other features and recall that different groups of products act on the metabolism of transmitters, whose precursors they represent, or whose syntheses they inhibit, or whose liberation they slow or accelerate, or again whose destruction they modify. On all these counts research has been crowned with success, and the results seem very promising.

Finally the whole picture which we have tried to present here in running the risk of telling you, on many of the points examined, data with which you are already familiar, in spite of some inevitable gaps, appears to be a clearly positive one. If, to conclude we look back, we shall see that in covering the vast field of pharmacology, the structure of a small group of biological amines of a remarkably simple structure, has led us like Ariadne's thread, and has prevented us from becoming lost in a labyrinth of physiological reactions and often diverse chemical structures.

It has been said that the art of a lecturer consists of only speaking about what he knows and hiding what he doesn't. But it didn't seem necessary for me to have recourse to these artifices to present to you the real picture of chemical pharmacology which, in the last analysis, only represents a sort of "natural history" and a system of organic molecules.

I could go so far as to say that the results which we have already, create a good deal of optimism for they allow us to see the pharmacology of the future as an ordered and defined science and in which foods, drugs and poisons will have become integrated with metabolism of the simplest constituents of living matter.

Now I am nearing the end of this exposition and I think of the great names which are associated with the study of pharmacological agents which have allowed us to obtain the results we have today, I cannot evoke, without emotion, all those who preceded me in this path, and particularly my master Ernest Fourneau who has written such a large and glorious chapter in chemical therapeutics and whose name will always be engraved in the history of this science.

And I feel torn between the immense joy I feel again for the honour done me and the feeling of injustice of not being able to repay my masters and colleagues for all that I owe them. This feeling is even stronger seeing that therapeutic chemistry is a very young science whose progress in half a century has been prodigious, and in no other field, perhaps, has the part of each one appeared with such clarity and continuity as in our research where each formula carries a well-known, and sometimes very close, name.

The future of pharmacodynamics is however so rich and promising, it still allows so many theoretical and practical possibilities, that I still have the hope of justifying, by my future work, not only the wonderful distinction paid to me today, but also the trust and friendship of my masters and colleagues whose work could not be separated from that which I now pursue with confidence, enthusiasm, and love.

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