may be somewhat wider than the actual distribution, due to analytical errors and biological variation in the ratio of single bone to whole skeleton. It is predicted that in 1966 the average young child in the world will have a skeletal concentration of strontium-90 of about 4 μμc of strontium-90 per gram of calcium; that 10 percent may have a concentration of 8 μμc; that 1 percent may have a level of 20 μμc; and that none will have a level exceeding 80 μμc of strontium-90 per gram of calcium.

References and Notes

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2. J. L. Kulp, W. R. Eckelmann, A. R. Schulert, *Science* 125, 219 (1957).
3. W. R. Eckelmann, J. L. Kulp, A. R. Schulert, *ibid.* 127, 266 (1958).
4. The two commercial laboratories were Isotopes, Inc., Westwood, N.J., and Nuclear Science and Engineering Corp., Pittsburgh, Pa.
5. H. L. Volchok, J. L. Kulp, W. R. Eckelmann, J. Gaetjen, *Ann. N.Y. Acad. Sci.* 71, 1, 293 (1957); H. L. Volchok and J. L. Kulp, *Nucleonics* 13, 49 (1955).
6. D. L. Thurber, J. L. Kulp, E. J. Hodges, P. W. Gast, M. Wampler, *Science* 128, 256 (1958).
7. A. R. Schulert, E. A. Peets, D. Laszlo, H. Spencer, M. Charles, J. Samachson, *Intern. J. Appl. Radiation and Isotopes* 4, 144 (1959).
8. A. R. Schulert, E. J. Hodges, E. S. Lenhoff, J. L. Kulp, *Health Phys.*, in press.
9. J. L. Kulp and R. Slakter, in preparation.
10. F. J. Bryant, A. C. Chamberlain, G. S. Spicer, M. S. W. Webb, *Brit. Med. J.* 1, 1371 (1958).
11. *Health and Safety Lab. U.S. Atomic Energy Comm. Publ. No. HASL-42* (16 June 1958).
12. J. L. Kulp and R. Slakter, *Science* 128, 86 (1958).
13. D. V. Booker, F. J. Bryant, A. C. Chamberlain, A. Morgan, G. S. Spicer, *Atomic Energy Research Establ. (G. Brit.) Publ. No. HP/R 2182* (1957); F. J. Bryant, A. C. Chamberlain, A. Morgan, G. S. Spicer, *Atomic Energy Research Establ. (G. Brit.) Publ. No. HP/R 2056* (1957).
14. H. H. Mitchell, T. S. Hamilton, F. R. Steggerda, H. W. Bean, *J. Biol. Chem.* 158, 625 (1945).
15. H. Spencer, D. Laszlo, M. Brothers, *J. Clin. Invest.* 36, 680 (1957); "Deposition and Retention of Ingested Strontium-90 in the Skeleton" (Washington, D.C., 23 Apr. 1957), committee report (official use only).
16. C. L. Comar, R. H. Wasserman, M. M. Nold, *Proc. Soc. Exptl. Biol. Med.* 92, 859 (1956).
17. C. L. Comar, I. B. Whitney, F. W. Lengeman, *ibid.* 88, 232 (1955).
18. *Consumers Repts.* 24, No. 3, 102 (March 1959).
19. J. L. Kulp, A. N. Kaufman, R. S. Slakter, W. R. Eckelmann, in preparation.
20. *Health and Safety Lab. U.S. Atomic Energy Comm. Publ. No. HASL-51* (10 Nov. 1958).
21. L. Machta and R. J. List, "Stratospheric data and meteorological interpretations," paper presented at a meeting on "AEC-sponsored Research and Development Related to the Collection and Classification of Atmospheric Particulates," held in Minneapolis, Minn., 8–9 Oct. 1958.
22. W. F. Libby, *Proceedings symposium on Noxious Effects of Low Level Radiation, Schweizerischen Akademie der Medizinischen Wissenschaften 27–29 Mar. 1958*, p. 309.
23. R. S. Russell, *Nature* 182, 834 (1958).
24. Unpublished data from the Lamont Geological Observatory, Palisades, N.Y.
25. A. M. Brues, *Science* 128, 693 (1958).
26. M. P. Finkel, *ibid.* 128, 637 (1958).
27. E. B. Lewis, *ibid.* 125, 969 (1597).
28. F. J. Bryant, E. H. Henderson, G. S. Spicer, M. S. W. Webb, *Atomic Energy Research Establ. (G. Brit.) Rept. No. C/R 2583* (May 1958).

Isosterism and Competitive Phenomena in Drugs

A study of structure-activity relationships in agents acting upon autonomic effector cells

Daniel Bovet

Making use of the considerable means offered by organic synthesis, many investigators have directed their efforts to the field of therapeutics and have sought to lay the groundwork for a pharmaceutical chemistry or, better, for a chemical pharmacology. If such an ambitious program has not yet been fully realized, nevertheless, during the last five decades, one can notice the emergence of a few basic concepts whose usefulness continues to be confirmed. This is particularly true of the concepts of isosterism and of competition.

Numerous drugs were first derived from products of biological origin, particularly the alkaloids. The elucidation of their structure helped chemists to embark on syntheses of analogous compounds. In this respect cocaine, atropine, and morphine are good illustrative examples. The molecules synthesized according to their models exhibited clinically useful anesthetic properties, spasmolytic activity, or pronounced analgesic effects. In each case, chemical similarity produces in-some-way-related physiological properties.

Analogous observations have subsequently been gathered in many other fields, but it has also become evident that sometimes very different, even antagonistic, pharmacological properties may be found in chemically similar molecules.

Despite the fact that the concept of "antimetabolite" is based on rather old experiments, it was defined essentially in the field of "antivitamins"; the work of Woods (1940) and Fildes (1940) on the antisulfonamide component of yeast and its identification as *p*-aminobenzoic acid found a large acceptance. The idea that a compound structurally similar to one normally present in the organism is able to interfere with the function of this metabolite could be applied in many ways. Its success, especially in enzymology [where, for the first time, it was clearly formulated by Quastel (1925–1928)], in chemotherapy, in vitaminology, and in endocrinology, obviates a detailed discussion of the underlying physicochemical and biological principles. Instead, I would like to draw your attention to the importance of studies of competitive phenomena in pharmacodynamics, especially in the pharmacology of drugs of the autonomic nervous system. I would like to show how a very large part of therapeutical chemistry depends on the relations between many alkaloids or synthetic compounds and a few hormones, chemical transmitters, and products of tissue metabolism of rather simple chemical structure: epinephrine and norepinephrine, acetylcholine and propionylcholine, histamine, and 5-hydroxytryptamine (Table 1).

Dr. Bovet is head of the department of therapeutic chemistry at the Istituto Superiore di Sanità, Rome, Italy. This article is a translation of his Nobel lecture, presented 11 December 1957, when he was awarded the Nobel prize for medicine and physiology for 1957. It is reproduced here with the permission of the Nobel Foundation. We are indebted to Dr. Ernest Schoffeniels of the department of neurology, College of Physicians and Surgeons, Columbia University, for the translation.

Drugs of the Autonomic Nervous System

The history of the research in this field is one of the most spectacular and successful chapters in the chemistry and physiology of the alkaloids and hormones. As far as transmitters of the sympathetic system are concerned, one may recall that the isolation of epinephrine by Takamine (1901) was preceded both by empiric application of ephedrine-rich *mahuang* by the Chinese, and by the fortuitous discovery of the properties of tetrahydronaphthylamine by Bamberger (1888). The exact significance of norepinephrine has been established only recently, by von Euler (1946).

In the field of parasympathomimetic agents, the observation of the properties of muscarine (1811) and the synthesis of acetylcholine (1866) preceded, by a century and a half century, respectively, the discovery of acetylcholine of Loewi (1921) and its isolation from tissues (1931). Histamine was synthesized (1907) shortly before its identification in the products of animal and plant origin and before Dale and Dudley (1910) began their well-known studies of its pharmacological properties.

The recent discovery of 5-hydroxytryptamine (Rapport, 1949) is the culmination of the work of Erspamer on enteramine isolated from enterochromaffin cells (1937–1952) and the work of Rapport, Green, and Page (1947–1948) on the vasoconstrictor factor of serum, serotonin.

The relationship between epinephrine, tissue acetylcholine, and the nervous system was recognized early. In 1904, Elliot, struck by the similarity existing between the pharmacological action of epinephrine and the effect of stimulating the sympathetic system, proposed the hypothesis according to which epinephrine is released from sympathetic nerve endings and transmits the impulse from nerve cell to smooth muscle fiber.

Wieland in 1912 and Le Heux in 1919 tried to demonstrate that choline and acetylcholine were local hormones. Their hypothesis, we know, was successfully developed by Loewi, Dale, Cannon, and Bacq, whose experiments established the concept of chemical transmitters. The hypothesis of chemical transmission by acetylcholine first proposed for viscera innervated by the parasympathetic system was later extended by Dale, Feldberg, and Vogt (1936) to the neuromuscular junction. Recent investigations on the physiology of the end plate have, in sum, confirmed this mechanism. The reaction between acetylcholine and its receptor located at the postsynaptic membrane can now be integrated within the framework of electrophysiological findings, particularly those demonstrating electrical nonexcitability of this membrane and its great sensitivity to the transmitter (Kuffler, 1948; Castillo and Katz, 1956).

To turn now to substances antagonizing these various hormones and transmitters, models for the synthesis of adrenergic and cholinergic blocking agents were furnished by compounds of biological origin, such as ergotoxine, atropine, and curare. The antihistaminics were studied later and represent synthetic products of completely original design.

In practice, these drugs have been widely used in the symptomatic treatment of dysfunction of organs which are dependent on the activity of the autonomic nervous system: heart, blood vessels, bronchi, gastrointestinal tract, and uterus. The antagonists of epinephrine found their major application in the treatment of vascular disorders and hypertension. The antagonists of acetylcholine are used primarily as spasmolytic, mydriatic, and muscle-relaxing

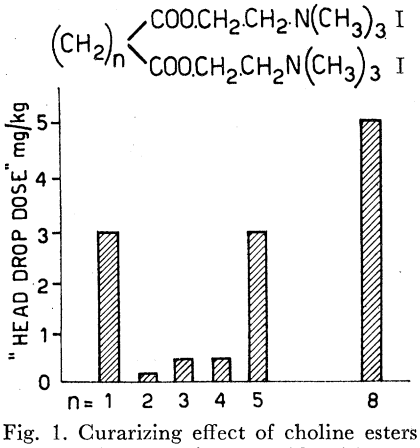


Fig. 1. Curarizing effect of choline esters and dicarboxylic aliphate acids with normal chains. Curarizing activity was established in rabbits by measuring the "head drop" dose of the various compounds given intravenously. Curarizing activity reaches a maximum with succinylcholine and decreases with higher homologues of the series. [Bovet, Bovet-Nitti, Guarino, Longo, and Marotta, 1939]

Table 1. Drugs with a competitive action with respect to epinephrine, acetylcholine, histamine, and 5-hydroxytryptamine.

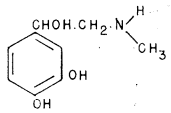
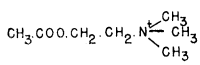
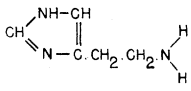
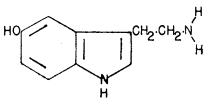
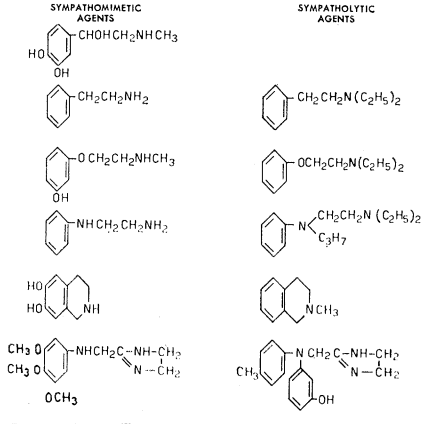
Adrenaline (noradrenaline)	Acetylcholine	Histamine	Hydroxytryptamine
			
Sympatholytic agents:	**Parasympatholytic agents:**	**Antihistaminics:**	**Antihydroxytryptamines**
Ergotamine	Atropine (spasmolytic agents)	929 F	
Yohimbine	Curares:	2339 R.P. (Antergen)	
Benzodioxane (933 F)	*d*-Tubocurarine	Pyrilamine	
Dibenamine	Gallamine	Diphenhydramine	
Phentolamine	Decamethonium	Antazoline	
	Succinylcholine	Promethazine	
	Ganglioplegic agent:		
	Hexamethonium		
	Central ganglioplegic agents:		
	Antiparkinson agents		
	Antiphobic agents		

Table 2. Structural relations between sympathomimetic and sympatholytic agents. [Raymond-Hamet, 1937; Bovet and Simon, 1936; Druey, 1936; Bovet, de Lestrange, and Fourneau, 1942; de Beer and Fassett, 1938; Hartmann and Isler, 1939; Gross, Tripod, and Meier, 1951]



agents. The antihistaminics are most useful in the treatment of urticaria, rhinitis, asthma, and other allergic diseases.

For specific illustrations, I shall use examples from three different pharmacological groups. For the epinephrine group, I will consider ergotamine; for the antiacetylcholine group, curare; and for histamine, I will consider the synthetic antihistaminics.

Synthetic Sympatholytic and Ergotamine-Like Compounds

Sympatholytic drugs form a group characterized by common pharmacological properties. They act as competitors—or blocking agents, in Anglo-Saxon terminology—by opposing the effects of epinephrine and norepinephrine. Most characteristically, they block the hypertension and vasoconstriction produced by epinephrine.

As is often the case, various drugs of this class were introduced empirically into therapeutics long before their pharmacological actions were established. As long ago as 1909, Froelich noticed that animals pretreated with small doses of the dextrorotatory isomer of epinephrine became resistant to the effects of the natural isomer. Today we explain this observation as resulting from a partial block of the receptors by a pharmacologically much less active enantiomorph of the compound. Later Loewe (1927), Külz (1936), and Raymond-Hamet (1937) described N-alkyl derivatives of phenylethylamine with sympatholytic properties; analogous properties were described in the phenoxyethylamine series (Anan, 1930; Levy and Ditz, 1933; Bovet and Maderni, 1933; Bovet, Simon and Druey, 1937), the phenylethylenediamine series (Bovet, de Lestrange, and J. P. Fourneau, 1942), the isoquinoline series (Hjort, de Beer and Fassett, 1938), and the phenylaminoethylimidazoline series (Meier and Müller, 1939; Hartmann and Isler, 1939). In each of these groups the structural similarities between the antagonistic molecules with either sympathomimetic or sympatholytic properties are evident (Table 2); the degree of substitution on the amine, the suppression or displacement of the phenolic function, the closing of a ring, are sufficient to reverse the pharmacological action. It is very important to notice that while the distance between the amine function and the aromatic ring remains constant in both sympathomimetic and sympatholytic agents, the inhibitory molecule has always, in con-

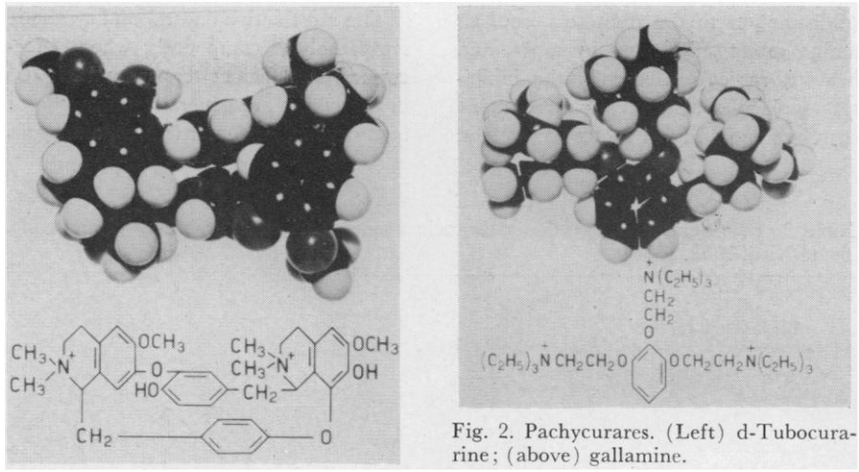


Fig. 2. Pachycurares. (Left) d-Tubocurarine; (above) gallamine.

Table 3. Classification of the main groups of sympathomimetic and sympatholytic agents.

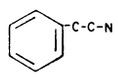
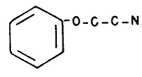
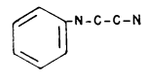
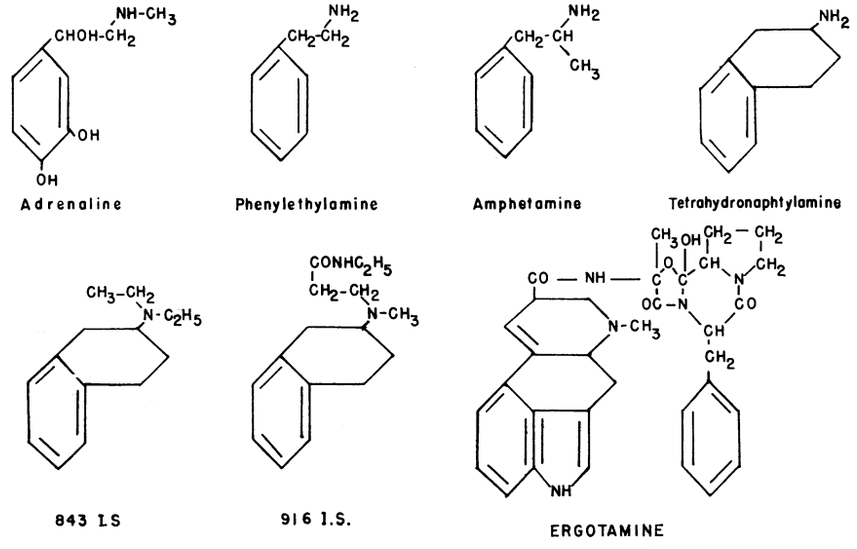
 Phenylethylamines	 Phenoxyethylamines	 Phenylethylene diamines
	Sympathomimetic agents	
Epinephrine Phenylethylamines and their phenolic derivatives	Phenolic derivatives of phenoxyethylamine	Phenylethylenediamine and its phenolic derivatives
	Sympatholytic agents (aromatic series)	
N-Diethylphenylethylamine	N-Diethylphenoxy-ethylamine	N-Diethyl-N'-propyl-N'-phenylethylenediamine
Dibenamine	Dibenzyline	
Tetrahydronaphthylamines, N-substituted		
	Sympatholytic agents (heterocyclic series)	
N-Methyltetrahydro-isoquinoline	Benzodioxane: Prosympal	Phenylpiperazine Phentolamine
Benzylimidazoline	Piperoxan	
	Sympatholytic alkaloids	
Ergot alkaloids		Yohimbine

Table 4. Structural relations between sympathomimetic and sympatholytic agents: from epinephrine to ergotamine. [Marini-Bettolo, Chiavarelli and Landi, Vittory, 1950–1953; Bovet, Bovet-Nitti, Virno, Longo, Marotta, and Sollero, 1953]



tradistinction to the excitatory one, an amino group substituted by more, and heavier, radicals. Generally the inhibitory molecules also have a more stable structure and a higher molecular weight.

The most active natural and synthetic sympatholytic compounds, whose effectiveness is sufficient to permit their use in the clinic, are generally polycyclic or heterocyclic, with structures analogous to the above-mentioned compounds despite their complexity. Benzylimidazoline (Meier and Müller, 1939) and dibenamine (Nickerson and Goodman, 1947) are related to the phenylethylamines; the aminomethyl-benzodioxanes (Fourneau and Bovet, 1933), to the phenoxyethylamines; and phentolamine (Gross, Tripod, and Meier, 1951) to phenylethylenediamine derivatives (Table 3).

Table 5. Investigations of synthetic oxytocic agents, derived from phenylglycinamide. [Bovet-Nitti, 1952, 1954]

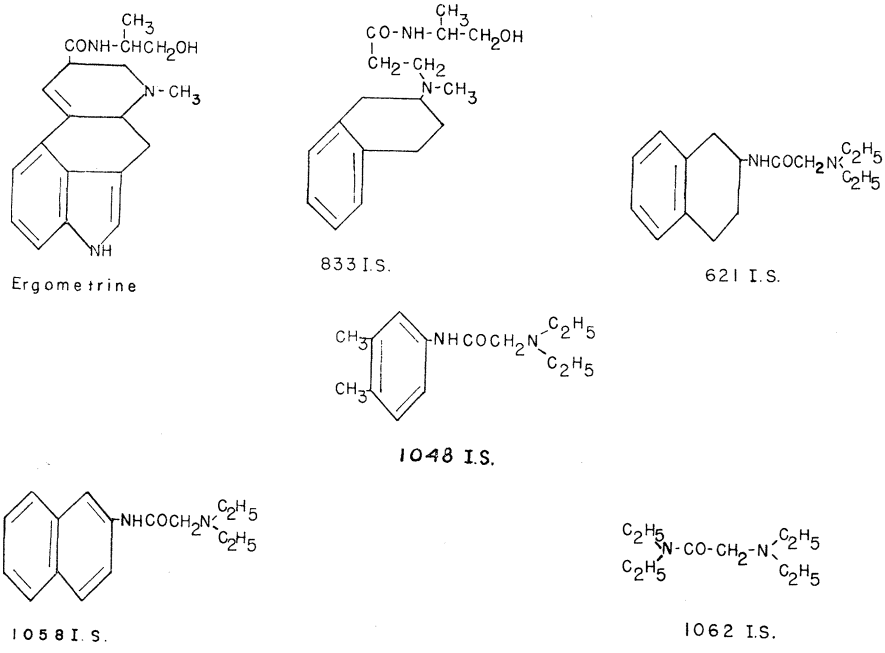


Table 6. Natural and synthetic curares: *d*-tubocurarine (King, 1935; Wintersteiner and Dutcher, 1943); 3381 R.P. (Bovet, Courvoisier, Duclos, and Horclois, 1946); gallamine (Bovet, Depierre, and de Lestrange, 1947); succinylcholine (Bovet, Bovet-Nitti, Longo, and Marotta, 1949; Fusco, Palazzo, Chiavarelli, and Knüsli, 1949).

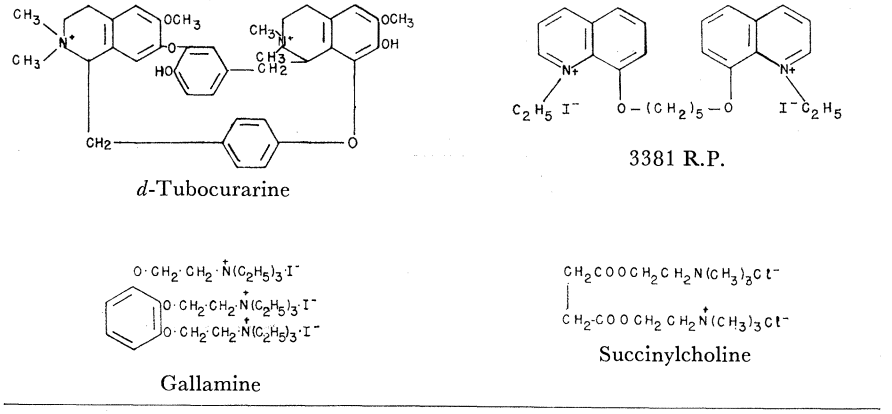


Table 7. Pharmacodynamic properties of synthetic curares.

Subject	Pachycurares (competing agents): tubocurarine, gallamine	Leptocurares (depolarizing agents): succinylcholine, decamethonium
Mammals	Curarization	Curarization (muscular fibrillation)
Birds	Curarization	Contracture followed by curarization
Amphibians (*rectus abdominis*)	Antagonism to acetylcholine	Acetylcholinic contracture

The ergot alkaloids

Studies conducted at the Istituto Superiore di Sanità by Marini-Bettolo and Chiavarelli, on the chemical aspects, and by F. Bovet-Nitti, Longo, Marotta, and Guarino on the pharmacological aspects, illustrate the usefulness of the concepts of isosterism and of competition in this kind of investigation.

When the isolation and structural determination of the ergot alkaloids was achieved—researches for which we are largely indebted to Stoll and Jacobs—much work was done to prepare derivatives by partial or total synthesis; thus, dehydrogenated derivatives (Rothlin, 1947) and oxytocic derivatives closely related to ergometrine (Rothlin, 1947) were prepared, and the diethylamide of lysergic acid with hallucinogenic properties was discovered (Stoll). Since we proposed to investigate the structure-activity relationships of ergotamine, we used as our working hypothesis the concept relating structure to antagonistic action.

At first sight, the structure of the ergot alkaloids seems to be very different from that of epinephrine or of sympathomimetic derivatives of the phenylethylamine series. Nevertheless, since the skeleton of β-tetrahydronaphthylamine (2-aminotetralin) can be recognized in the structure of lysergic acid, we decided to study compounds of this group (Table 4).

Pharmacological tests with derivatives of relatively simple structure demonstrated the sympatholytic activity of 2-diethylaminotetralin (843 I.S.). Studies with more complex molecules, in particular the amide and amine derivatives of 2-tetralin, are a new step in the attempt to reproduce the essential portion of the lysergic acid skeleton. Using molecules of increasing complexity, one may go by successive stages from phenylethylamine to tetrahydronaphthylamine or to N-(2-tetralyl)-N-methyl-N′-ethyl-β-alaninamide (916 I.S.) and the ergot alkaloids, with a resulting progressive diminution at each stage of sympathomimetic properties and the appearance of sympatholytic properties.

Oxytocic activity was observed in a large number of synthetic derivatives,

and this class of compounds seems very broad compared to that of adrenolytic substances (Table 5). In the course of experiments performed on rabbit uterus, isolated or *in situ,* several derivatives of aminotetralin and of aniline and even some aliphatic compounds showed strong activity. We may single out such examples as N,N-diethyl-N′-(2-tetralyl)glycinamide (621 I.S.); N,N-diethyl-N′-3-4-dimethylphenylglycinamide (1048 I.S.); and N,N,N′,N′tetraethylglycinamide (1062 I.S.) (Bovet-Nitti, 1953).

The main difficulty, apparently encountered also by other investigators, was the lack of parallelism between effects observed in laboratory animals and in man. Generally speaking, a satisfactory solution to the problem of synthetic oxytocics has not yet been reached, and the question is still under study.

Antagonists of Acetylcholine: Synthetic Curares

The problem of competitive agents that antagonize acetylcholine activity is rather complex, due to the multiple functions of this transmitter. Acetylcholine is the chemical transmitter in viscera innervated by the parasympathetic system; it has a role at the neuromuscular junction, and it is liberated in ganglia during the passage of a nerve impulse. A surprising fact, which has been profitably exploited in pharmacological investigations of competitive agents, is that compounds antagonizing acetylcholine differ according to the site of action of the local hormone. Thus, atropine and benzoylcholine neutralize the muscarinic effects of acetylcholine on cardiac receptors, on the intestine, or on secretions; tetraethylammonium iodide or hexamethonium block the nicotinic action of acetylcholine on sympathetic and parasympathetic ganglia. Finally, curares are specific antagonists of acetylcholine in striated muscle. With respect to the structure of antagonists, synthetic curares furnish us with a succession of examples comparable to those we have reviewed in the sympatholytic group. These investigations were begun in 1946, after King's elucidation, in 1935, of the structure of one of the physiologically active constituents of Amazonian curares, and after the introduction by Griffith and Cullen in 1942 of the chemically pure alkaloid as an adjuvant in anethesia.

d-Tubocurarine, which is extracted from a menispermum, *Chondodendron tomentosum,* is found in curares prepared by the natives of the Upper Amazon. It is an alkaloid of the group bis(benzyltetrahydroisoquinoline), whose molecule has two quaternary ammonium functions.

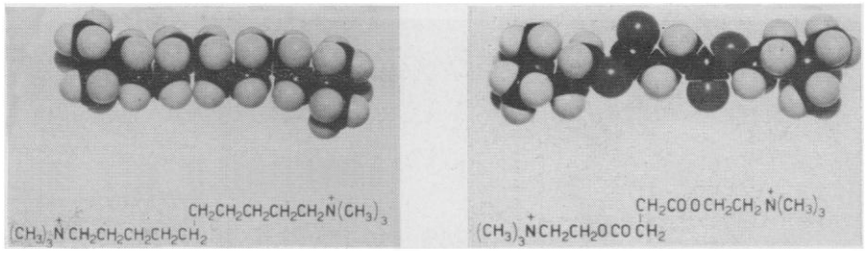


Fig. 3. Leptocurares. (Left) Decamethonium; (right) succinylcholine.

In research done with our colleagues, Viaud, Horclois, and de Lestrange, we first looked for molecules structurally close to the selected model. By successive transformations, we were able to synthesize relatively simple derivatives with analogous properties (Table 6). From a series of new compounds with two quinolinic rings bearing quaternary ammonium functions, we first selected the diiodoethylate of 8′,8″-diquinolyloxy-1,5-pentane (3381 R.P.). This was the first synthetic compound with curare-like action in mammals showing a specificity comparable to that of natural alkaloids isolated from curare (1946).

It was then found that aminophenol derivatives which have neither quinoline nor isoquinoline rings had similar activity, and this was also true for polyphenol ethers and aromatic esters. The latest investigations on the path to ultimate simplification are concerned with the activity of aliphatic derivatives.

In England, Barlow and Ing and Paton and Zaimis (1948) reported extremely interesting observations on the curare-like effect of decamethylene-ω-bis-trimethylammonium hydrate (decamethonium). In our Laboratory of Therapeutical Chemistry at the Istituto Superiore di Sanità, the curare-like action of succinylcholine was first recognized. This compound was synthesized by Hunt in 1911.

The number and variety of compounds with curare-like action, the relative simplicity of their mode of action, and the possibility of precise pharmacological assay permitted a careful study of structure-activity relationships of synthetic curares.

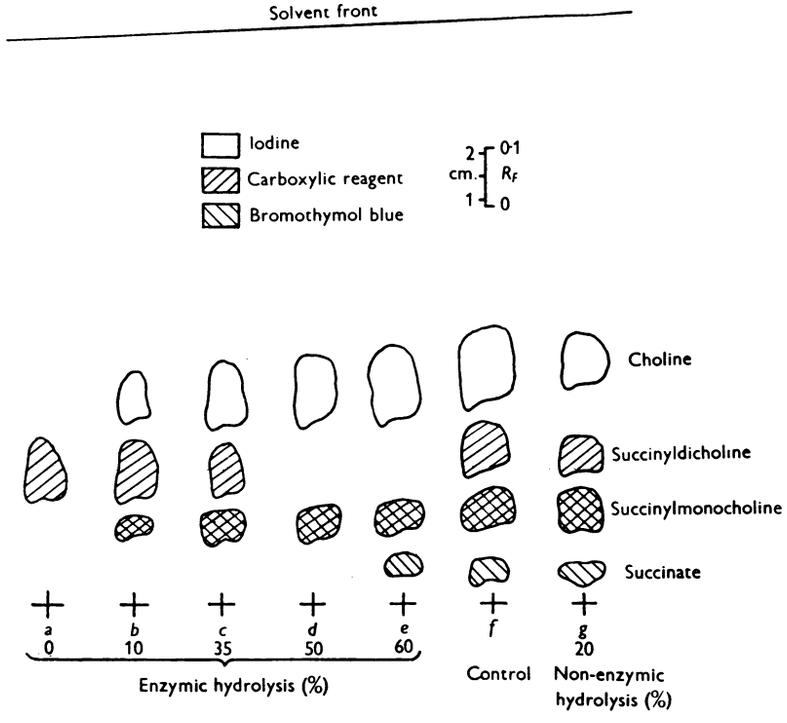


Fig. 4. Chromatograms of (*a* to *e*) succinlycholine at various stages of enzymic hydrolysis; (*f*) a mixture of succinylcholine and its products of hydrolysis; (*g*) 0.1 mg of succinylcholine after nonenzymic hydrolysis. [Whittaker and Wijesundera, 1952]

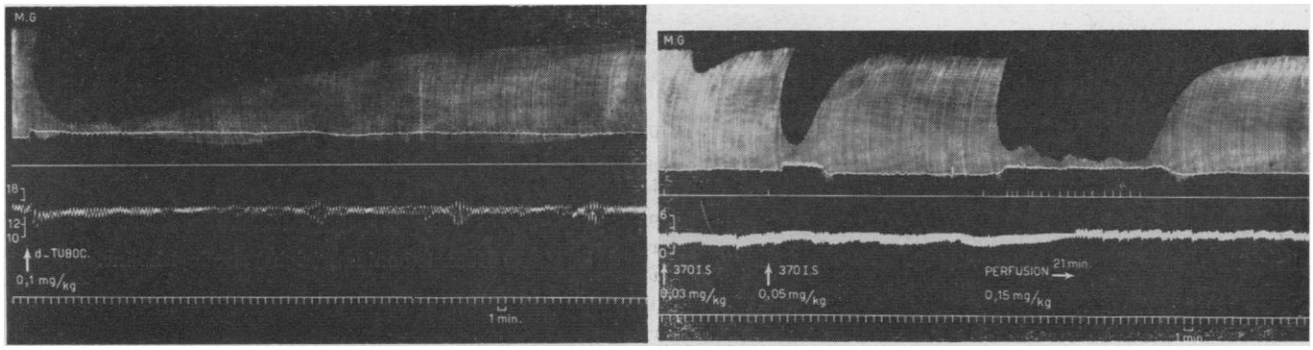


Fig. 5. Comparison between curarizing effects of *d*-tubocurarine (left) and of succinylcholine (right) given intravenously as a single injection or by continuous perfusion on the dog, under chloralose anesthesia. (First line) Contraction of the gastrocnemius muscle following the rhythmic stimulation of the sciatic nerve; (second line) control of the speed of injection; (third line) blood pressure. The record shows clearly the difference between the duration of neuromuscular paralysis following a single injection of succinylcholine (370 I.S., 0.05 mg/kg) and of *d*-tubocurarine (0.1 mg/kg). Also, on comparing the effect of a single injection of *d*-tubocurarine with continuous perfusion of succinylcholine (initial injection of 0.05 mg followed by repeated injection of 0.0062 mg at each signal), one sees that, for the duration of subtotal and reasonably uniform curarization (about 80 percent, for 20 minutes), the reversibility of the effect is quick (about 10 minutes) after infusion of succinylcholine while it is slowly progressive (about 50 minutes) after injection of *d*-tubocurarine. [Reuse, 1953]

I will mention only two important factors which influence the activity of bis-quaternary derivatives: the distance between the quaternary ammonium groups and the massiveness of the molecule.

The first factor is illustrated by comparison of polymethylene-bis-trimethylammonium derivatives (Barlow and Ing; Paton and Zaimis, 1948) as well as of aliphatic diesters of choline (Bovet, Bovet-Nitti, Guarino, Longo and Marotta, 1949) (Fig. 1).

Careful pharmacological study showed that the action of new synthetic derivatives was sometimes quite different from that of the natural alkaloids.

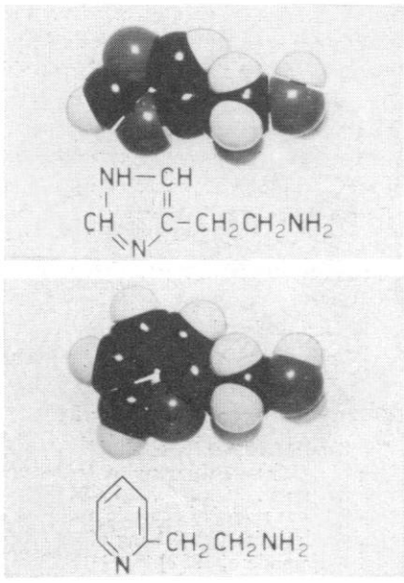
The differences between the action of decamethonium iodide and succinylcholine iodide on the one hand and the action of *d*-tubocurarine and of the triiodethylate of gallamine on the other were carefully studied by Paton and Zaimis, Brown and Dias and in our own laboratory. The British authors have proposed calling these two groups depolarizing agents and competitive curares. We proposed designating decamethonium and succinylcholine as leptocurares, and tubocurarine and gallamine as pachycurares (Figs. 2 and 3; Table 7). The advantage of our nomenclature lies in the fact that it does not presume the mechanism of action. The main difference between the pharmacodynamic effects produced by the two types of curares is determined by the responses of amphibian and bird muscles. In birds, the pachycurares are typical curarizing agents, while leptocurares induce contracture that is followed by curarization.

In mammals the differences between the two groups are less sharp. The responses of muscle from different species or of different muscles from a single species are not always comparable. Also, intermediary steps seem to exist between depolarization and curare competition. The distinction between the groups, though relative with respect to the mechanism of action and the type of preparation used, are, nevertheless, useful if we want to compare relations between chemical structure and pharmacological activity.

Clinically, the most important factor in classification of curares is duration of effect. In this respect, the introduction of a short-acting curare, particularly succinylcholine, is an important step forward. The relative ease with which succinylcholine is hydrolyzed by pseudocholinesterase and the very low toxicity of the products choline and succinic acid account for the brevity of action and the remarkable tolerance of the organism for this curare (Fig. 4; Table 8).

The first clinical observations concerning short-acting curares were published by Valdoni (1949) and Scurr (1951) and deal with suxethonium. The introduction of succinylcholine into anesthesiology was first proposed in Sweden, by Thesleff (1951), Holmberg and Thesleff (1951), Tammelin and Löw (1951), and von Dardel (1951), and in Austria, by Brücke *et al.* (1951), Mayrhofer and Hassfurther (1951), and Holzer (1951).

In the light of these various investigations, one may today recognize two methods of using succinylcholine: single injection when very short action is required (as for endoscopy or electro-



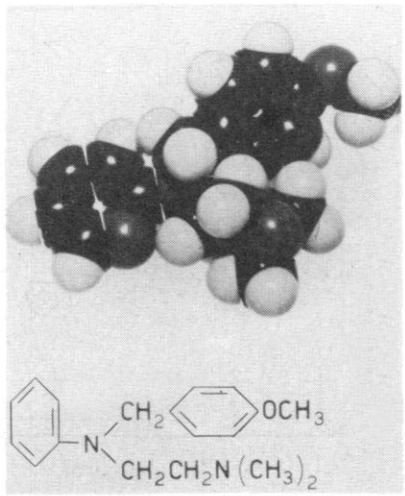
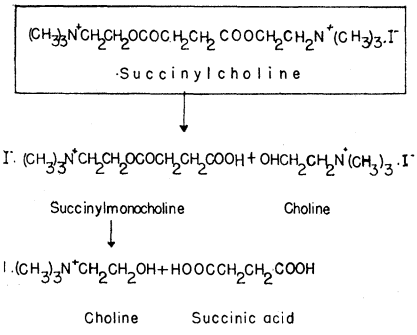


Fig. 6. (Left, top) Histamine; (left, bottom) pyridylethylamine; (above) pyrilamine.

Table 8. Hydrolytic products of succinylcholine.



shock) or continuous infusion in surgical procedures of long duration.

Two recordings from a study in our laboratory demonstrate results obtained with the two types of application. They show the superiority of continuous infusion of short-acting curares over the classical technique (Fig. 5).

Antihistamines

The last example I will use to illustrate the concept of competition is concerned with compounds that antagonize the third local hormone, histamine. This is a particularly rich field since the usefulness of these compounds has stimulated a great many investigations within a very few years. In 1937, in Fourneau's laboratory, we began—A. M. Staub and I—to look for compounds antagonistic to histamine. Considering the number of features that histamine, acetylcholine, and epinephrine have in common, we looked for antagonism comparable to that exhibited by sympatholytic compounds toward epinephrine and by parasympatholytic compounds toward acetylcholine. We obtained the first positive results in 1939 with thymoxyethyldiethylamine (929 F). Our experimental work was then directed toward defining criteria for antihistaminic activity. Staub (1939) extended her observations to phenylethylenediamine derivatives. In 1942, the syntheses by Mosnier, the pharmacodynamic studies of Halpern, and the first therapeutic results of Cuilleret, Thiers, Gaté, Celice, Perrault, Decourt, and Durel with dimethylaminoethylbenzylaniline, or Antergan, definitively established interest in compounds of this group. The role played by histamine in many allergic affections assures a broad area of clinical application of these compounds. After the pioneers (Maderni, de Lestrange, and Benoit in Fourneau's laboratory in Paris; Viaud, Horclois, Mosnier, and Charpentier in French industry; Hartman and Hofman in Switzerland; Rieveschl, Scholz, Huttrer, and Roblin in the United States; Cavallini in Italy), about 500 chemists synthesized, in less than ten years, more than 5000 compounds in the antihistaminic group.

Pharmacologists were easily able to recognize the competitive nature of the antagonism exerted by these antihistaminics toward histamine. Chemists, however, could not perceive any relation between the structure of antihistaminics and histamine which logically might explain such activity, nor could they find a relationship among the various active compounds. It was therefore impossible to escape the conclusion that most of the results were rather empirical.

From the pharmacological viewpoint, it was possible to distinguish three groups of substances (see Table 9) with antihistaminic action and relate them to (i) the sympatholytic group; (ii) the parasympatholytic-sympatholytic group; and (iii) histamine itself.

To the first group belong the phenolic esters (929 F) and the phenylethylenediamine derivatives (1571 F) studied at the Pasteur Institute, Halpern's Antergan, and the antazoline of Meier and Bucher. The compounds of the second group, from a chemical point of view, have more homogeneous structures, in

Table 9. Principal groups of synthetic antihistaminics: 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, Walther, and Fournel, 1944); tripelennamine (Mayer, Huttrer, and Scholz, 1945); thonzylamine (Reinhard and Scudi, 1947).

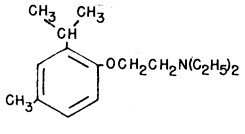
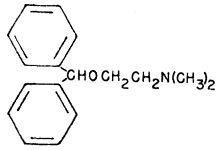
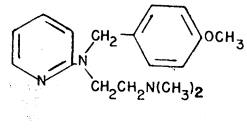
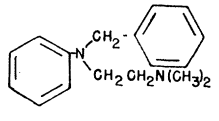
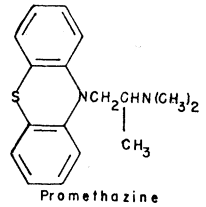
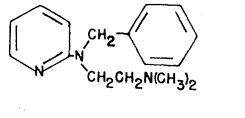
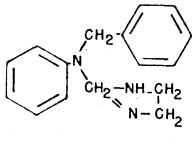
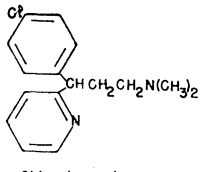
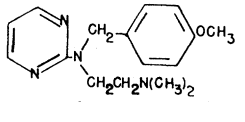
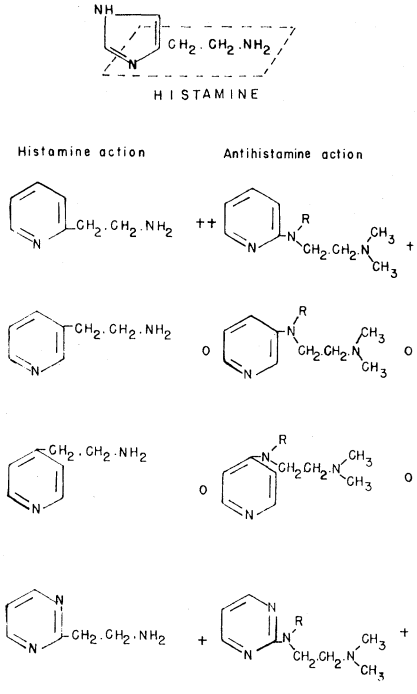
Antihistaminics related to:		
Sympatholytic agents	Spasmolytic agents	Histamine
 929 F	 Diphenhydramine	 Pyrilamine
 Antergan	 Promethazine	 Tripelennamine
 Antazoline	 Chlorphenamine	 Thonzylamine

Table 10. Structural relations between histamine and antihistamines. [Walter, Hunt, and Fosbinder, 1941; Nieman and Hays, 1942; Bovet and Walthert, 1943]



common with atropine-like drugs and other spasmolytics; some of these are, in fact, spasmolytic as well as antihistaminic (diphenhydramine). In derivatives of α-aminopyridine, which form the third group, the antihistaminic action is more specific and almost free of secondary effects. It is interesting to note in this group the isosteric reactions which account for the pharmacological activity. Walter *et al.* (1941) and Niemann and Hays (1942) have shown that α-pyridylethylamine derivatives have histamine-like activity, and that a fundamental difference exists between α-, β-, and γ-substituted pyridines in this respect. In this case, the analogy of structure which is not evident between histamine and pyrilamine (Neo-Antergan) may be seen between the groups α-pyridylethylamine and α-pyridine ethylenediamine (Table 10, Fig. 6). A typical compound from this group is pyrilamine (see Fig. 7), but many other synthetic compounds of similar design have also proved to be active.

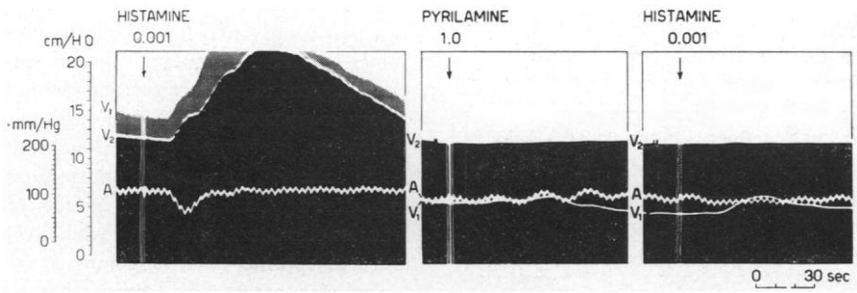


Fig. 7. Antagonistic action of pyrilamine with respect to the vasodilating effects of histamine in cerebral circulation. The subject was a dog under chloralose anesthesia. (*A*) Blood pressure, femoral artery (mm-Hg); (V_1) pressure recorded through a catheter introduced in a centrifugal direction into the external maxillary vein (mm-H_2O); (V_2) pressure in the internal maxillary vein (mm-H_2O). Injection was made into the saphenous vein; dosages are given in milligrams per kilogram. [Virno, Gertner and Bovet, 1956]

Central Action of Transmitters

The compounds considered so far do not exhaust the ranks of competitive agents. Pharmacologists are to some extent *les enfants terribles* of physiology. They did not wait for the battle of the neuromuscular junction to be won before engaging in a more difficult encounter. They proposed that the available evidence suggested the action of a chemical transmitter in the central nervous system, exactly as in the autonomic nervous system.

Analyzing the collective results from various laboratories, Feldberg (1950) concluded that the theory ascribing a transmitter role to acetylcholine in the central nervous system was the only one able to offer convincing and satisfactory interpretations. Even if intervention of noncholinergic chemical transmitters in the central nervous system is not excluded, we must admit that our knowledge about the probable roles of norepinephrine, epinephrine, histamine, and 5-hydroxytryptamine is still quite incomplete.

The physiological role of the reticular formation in the brain stem has been clearly defined by Moruzzi and Magoun (1949). In the last few years, a considerable number of investigations have shown that compounds affecting the autonomic nervous system also affected this formation.

Paradoxically enough, cholinergic as well as adrenergic substances affect the electrical activity of the cortex in the same way that direct electrical stimulation of the reticular formation does. Under well-defined experimental conditions, acetylcholine (Bonnet and Bremer, 1937) and epinephrine itself (Bonvallet, Dell, and Hietzel, 1954) provoke a transient activation in the electroencephalogram. The administration of either an anticholinesterase (eserine, diisopropyl fluorophosphate) or of amphetamine (Bradley and Elkes, 1953) produces an intense and prolonged desynchronization.

From a strictly pharmacological viewpoint, the major interest in this type of investigation stems from the similarity in observed antagonisms between various groups of drugs in the central nervous system and in viscera innervated by the autonomic nervous system.

As early as 1947 we suggested that in extrapyramidal syndromes some relation might exist between the central, "antiparkinson," effect of certain tertiary amines and their ganglioplegic properties in peripheral ganglia (Sigwald and Bovet; Dumont; 1947).

"Antiparkinson" drugs form a relatively homogeneous group comprising diethazine (Diparcol), isothazine (Parsidol), caramiphen (Parpanit), and trihexyphenidyl (Artane), as well as some antihistaminics (diphenhydramine and promethazine).

Electroencephalographic studies (Fig. 8) have shown that three groups of compounds produce an electroencephalogram similar to that recorded during sleep: the parasympatholytics (scopolamine and atropine), the central ganglioplegic or "antiparkinson" drugs (Table 11), and the neuroleptics (chlorproma-

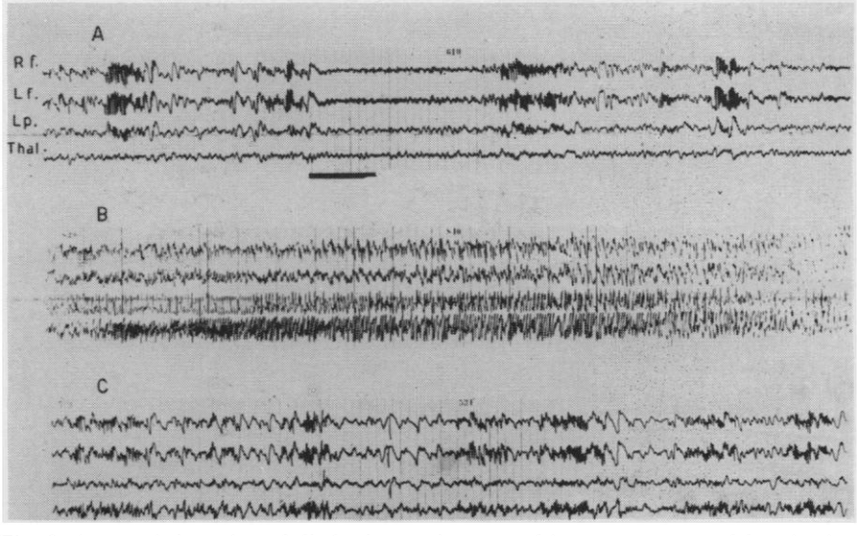


Fig. 8. Antagonistic action of diethazine against convulsive patterns caused by nicotine on the electroencephalogram of curarized rabbit. (A) Blocking reaction after acoustic stimulation (black line). (B) Convulsive seizure by nicotine (2 mg/kg) in normal animal. (C) After injection of diethazine (5 mg/kg) a second injection of nicotine no longer produced the electrical changes observed previously, and the acoustic stimulus fails to produce the blocking reaction. [Longo and Bovet, 1952]

zine, reserpine). These also antagonize the cortical reaction elicited by external stimuli (stress) or by desynchronizing agents (eserine and amphetamine) (Bovet and Longo, 1956). The effect of such synchronizing agents may, as a first approximation, be localized in the reticular formation and thus be comparable to the importance of chemical transmitters at this level.

Many observations suggest that specific receptors for epinephrine, acetylcholine, and histamine are specific proteins with a structural configuration complementary to that of the transmitter. This concept was first proposed by Fischer, who illustrated it with the now famous model of key and lock. This mechanism has been invoked to explain observations in physiological and chemical studies of taste and smell. Recently, Landsteiner and Pauling applied this idea of "complementary configuration" in the field of immunological reactions.

At this point it would not be possible to consider the various aspects of reactions between chemical transmitters, inhibitors, and receptor proteins without taking more space than is available.

The particularly simple case of binding acetylcholine with cholinesterase has been studied by Nachmansohn (1953–1954) and Wilson (1954). They consider acetylcholine to be attached at two points, one electronegative and the other electropositive, and have drawn valid conclusions with respect not only to various anticholinesterases but also to a new group of drugs that reactivate the phosphorylated enzyme.

If I cared to develop the extensive areas covered in this article I could include other topics and point out that different groups of compounds affect the metabolism of mediators because they are precursors or because they inhibit synthesis, slow down or accelerate liberation, or interfere with destruction. In every phase, investigations have been successful and the results appear to be very promising.

Conclusion

The composite picture I have tried to present, at the risk of relating many already well-known facts, appears, despite inevitable gaps, very certain. If, in concluding, we rapidly retrace our path, we will see that in covering the vast field of pharmacology, the structures of a small group of remarkably simple biogenic amines have led us, like the thread of Ariadne, through the labyrinth of very diverse physiological actions and chemical structures.

It has been said that the art of the orator is to speak about what he knows and to hide his ignorance. I do not feel any need to resort to such an artifice in presenting the current picture of the chemical pharmacology, because it is, in final analysis, only a kind of "natural history" and classification of organic molecules.

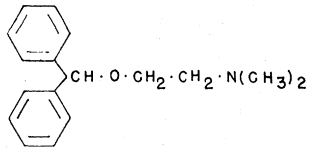
I would say that the results obtained so far give rise to optimism because they let us catch a glimpse of the pharmacology to come as a well-ordered and well-defined science in which foods, drugs, and poisons will be integrated in the metabolism of the simplest constituents of living matter.

Finally, in recalling the great names associated with studies of the pharmacological agents that made it possible for us to reach our present level, I can only speak with emotion of all those who preceded me, particularly of my teacher, Ernest Fourneau, who wrote such a great and glorious chapter of therapeutic chemistry and whose name will forever be written in the history of this science.

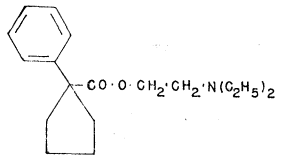
My feelings are sincerely divided between the immense pleasure I feel at the honor which is bestowed on me and my sense of inadequacy at being unable to repay my teachers and colleagues all that I owe them. This feeling is the more vivid because therapeutic chemistry is a very young science that has developed amazingly during the past half century; perhaps in no other domain does the part played by each individual appear so clearly and with such continuity as in our studies, where every formula bears a name always well-known and sometimes very close to us.

The future of pharmacodynamics is, nevertheless, so rich and promising, and it bears so many theoretical and practical possibilities, that I cherish the hope that my future work will justify not only the marvellous distinction I have received today but also the confidence and the friendship of my teachers and colleagues, whose works cannot be separated from those I pursue with confidence, enthusiasm, and love.

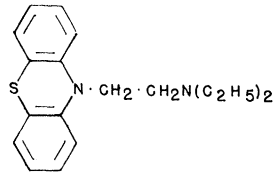
Table 11. Central ganglioplegic agents: diphenhydramine (Loew, Kaiser, and Moore, 1945); diethazine (Sigwald, Bovet, and Dumont, 1946; Bovet, Fournel, and Charpentier, 1947); caramiphen (Domenjoz, 1946; Grünthal, 1946); trihexyphenidyl (Doshay and Constable, 1949).



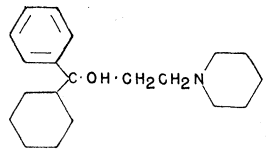
Diphenhydramine (Benadryl)



Caramiphen



Diethazine



Trihexyphenidyl

Bibliography

The following bibliography includes mainly general reviews; concerning studies published prior to 1948, the reader is referred to the work published in collaboration with Mme. F. Bovet-Nitti.

Z. M. Bacq, "La pharmacologie du système nerveux autonome, et particulièrement du sympathique, d'après la théorie neurohumorale," *Ann. physiol. physicochim. biol.* 10, 467 (1934).

D. Bovet, "Introduzione allo studio fisiologico e farmacologico del curaro," *Boll. soc. ital. biol. sper.* 25, 539 (1949).

———, "Introduction to antihistamine agents and Antergan derivatives," *Ann. N.Y. Acad. Sci.* 50, 1089 (1950).

———, "Some aspects of the relationship between chemical constitution and curare-like activity," *ibid.* 54, 407 (1951).

——— and F. Bovet-Nitti, *Structure et Activité pharmacodynamique des Médicaments du système nerveux végétatif* (Basle, 1948).

———, "Curare," *Experientia* 4, 325 (1949).

"Rapports de structure entre sympathomimétiques et sympatholytiques. De l'adrénaline à l'ergotamine," *Actualités pharmacol. No. 6* (1953), p. 21.

———, "Le chlorure de succinylcholine, agent curarisant à brève durée d'action," *Sci. Med. Ital.* 3, 509 (1955).

———, S. Guarino, V. G. Longo, R. Fusco, "Recherches sur les curarisants de synthèse. III, Succinylcholine et dérivés aliphatiques," *Arch. intern. pharmacodynamie* 88, 1 (1951).

D. Bovet and V. G. Longo, "Pharmacologie de la formation réticulée du tronc cérébral," *Compt.-rend. 20ème Congr. intern. physiol. Bruxelles* (1956), pp. 306–329.

D. Bovet and P. Viaud, "Curares synthèse: Chimie et pharmacologie," *Anesthésie et analgésie* 8, 328 (1951).

F. Bovet-Nitti and D. Bovet, "Recherches sur les ocytociques de synthèse: dérivés de la phenylglycinamide," *Arch. intern. pharmacodynamie* 6, 327 (1954).

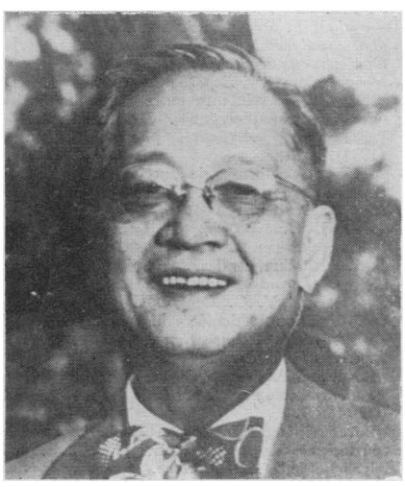
F. Brücke, "Dicholinesters of -dicarboxylic acids

and related substances," *Pharmacol. Revs.* 8, 265 (1956).
W. B. Cannon and A. Rosenblueth, *Autonomic Neuroeffector System* (New York, 1937).
J. Castilljo and B. Katz, "Biophysical aspects of neuro-muscular transmission," *Progr. in Biophys. and Biophys. Chem.* 6, 122 (1956).
H. H. Dale, "Transmission of nervous effects by acetylcholine," *Harvey Lecture Ser.* 32, 229 (1937).
L. Donatelli and U. Serafini, *Gli antistaminici di sintesi* (Naples, 1951).
J. C. Eccles, "The electrophysiological properties of the motoneurone," *Cold Spring Harbor Symposia Quant. Biol.* 17, 175 (1952).
V. Erspamer, "Pharmacology of indolealkylamines," *Pharmacol. Revs.* 6, 425 (1954).
U. S. von Euler, "The nature of adrenergic nerve mediators," *ibid.* 3, 247 (1951).
S. M. Feinberg, S. Malkiel, A. R. Feinberg, *The Antihistamines* (Chicago, Ill., 1950).
W. Feldberg, "The role of acetylcholine in the central nervous system, *Brit. Med. Bull.* 6, 312 (1950).
R. Fusco, G. Palazzo, S. Chiavarelli, D. Bovet, "Ricerche sui curari di sintesi, IV," *Gazz. chim. ital.* 79, 836 (1949).
L. S. Goodman and M. Nickerson, "Clinical application of adrenergic blockade," *Med. Clin. N. Am.* 34, 379 (1950).
H. R. Griffith and G. E. Johnson, "The use of curare in general anesthesia," *Anesthesiology* 3, 418 (1942).
B. N. Halpern, "Les antihistaminiques de synthèse, essais de chimiothérapie des états allergiques," *Arch. intern. pharmacodynamie* 68, 339 (1942).
———, "Sur le mécanisme d'action des antihistaminiques de synthèse," *Presse méd.* 57, 949 (1949).
H. R. Ing, "The curariform action of onium salts," *Physiol. Revs.* 16, 527 (1936).
S. W. Kuffler, "Physiology of neuro-muscular junctions: electrical aspects," *Federation Proc.* 7, 437 (1948).
O. Loewi, "Problems connected with the principle of humoral transmission of nerve impulses," *Proc. Roy. Soc. (London)* 118B, 299 (1936).
G. B. Marini-Bettolo, "Contribution à l'étude des alcaloides des Strychnos du Brésil," *Festschr. Arthur Stoll* (Basel, 1957), pp. 257–280.
———, S. Chiavarelli, D. Bovet, "Ricerche sui simpatolitici di sintesi della serie dell'ergotammina," *Gazz. chim. ital.* 80, 281 (1950).
A. R. McIntyre, *Curare. Its history and clinical use* (Chicago, Ill., 1947).
D. Nachmansohn, "Metabolism and function of the nerve cell," *Harvey Lecture Ser.* 49, 57 (1956).
W. D. M. Paton and E. J. Zaimis, "The methonium compounds," *Pharmacol. Revs.* 4, 219 (1952).
M. Protiva, "Chemie antihistaminových látek a histaminové skupiny," *Nakladatelství Československé Akademie věd* (Prague, 1955).
M. M. Rapport, "Serum vasoconstrictor (serotonin): IV," *J. Biol. Chem.* 180, 961 (1949).
Raymond-Hamet, "Sur un nouveau cas d'inversion des effets adrénaliniques," *Compt. rend. acad. sci.* 180, 2074 (1925).
Rend. ist. super. sanità 12, 1–264 (1949) (numero speciale sui curari di sintesi).
Ibid. 15, 723–1040 (1952) (numero speciale sugli ergotamminici di sintesi).
E. R. Rothlin, "The pharmacology of the natural and dihydrogenated alkaloids of ergot," *Bull. schweiz. Akad. med. Wiss.* 2, 249 (1947).
A. M. Staub, "Recherches sur quelques bases synthétiques antagonistes de l'histamine," *Ann. inst. Pasteur* 63, 400 (1939).
S. Thesleff, "Succinylcholine iodide. Studies on its pharmacological properties and chemical use," *Acta Physiol. Scand. Suppl.* 99, 1 (1952).
D. W. Woolley, *A Study of Antimetabolites* (New York, 1952).

Manuel Luz Roxas, Agricultural Chemist

Manuel Luz Roxas was one of the foremost scientists in the Philippines. His valuable services to the University of the Philippines as a teacher of chemistry in the College of Agriculture and the important role he played in the creation and organization of the National Research Council of the Philippines will be long remembered.

Almost immediately after Dr. Roxas' graduation from the University of the Philippines in 1911, with a B.S. degree in Agriculture, his first research work appeared in the *Philippine Agriculturist and Forester* under the title "The pandan industry in Majayjay." This was soon followed by three other articles in the same journal: "The cultivation of coconut," "The effect of some stimulant upon rice," and "The coffee industry in the island of Luzon." Dr. Roxas pursued further studies in his chosen field and in 1913 obtained his M.S. degree at the University of the Philippines, where he then served as instructor in chemistry until he was appointed a university fellow to the United States. Evidently this appointment was in recognition of his unusual endowment with the "divine spark" to perform research. He enrolled in the University of Wisconsin and received his Ph.D. there in 1916.



Manuel Luz Roxas

On his return to the Philippines, Dr. Roxas resumed his position in the College of Agriculture in the University of the Philippines, where he was later appointed assistant professor, then professor of chemistry, and ultimately, professor emeritus of agricultural organic chemistry. He was also named Distinguished Alumnus of the University of the Philippines in 1932 for achievement in scientific research. All these deserved recognitions were due to his active labor in the field of research, especially in agricultural chemistry and food technology; his 95 scientific papers were published in various journals, including the *Philippine Agriculturist and Forester,* the *Journal of Biological Chemistry, Sugar News,* and the *Journal of the Philippine Islands Medical Association.*

The National Research Council of the Philippines owes its origin to the leadership of Dr. Roxas. He headed a committee that worked continuously in preparing the draft of the bill for its creation which was introduced in the House of Representatives. With the support of Manuel L. Quezon as Senate President and other leaders of the Philippine Legislature, and the cooperation of the then Governor General Frank Murphy, Act 4120 creating a National Research Council for the promotion of research along scientific lines was approved on 8 December 1933. Elected as first chairman of the National Research Council, Dr. Roxas did a great deal in the organization of the different divisions integrating the Executive Committee of the council. For his distinguished and outstanding contributions in scientific research in the Philippines, Dr. Roxas may well be considered the "father of the National Research Council of the Philippines."

Manuel Luz Roxas was a man of sterling character, a good Filipino and patriot, simple and humble; all these qualities enhanced his merit as a true man of science. Our country can never repay what it owes him for his scientific labor and devotion to research.

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