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STUDIORUM PROGRESSUS

The Curariform Activity of the Menispermaceous Alkaloids

By DAVID F. MARSH and D. A. HERRING[1]

Types of alkaloids in menispermaceous plants

Interest in agents that produce skeletal muscular paralysis has existed since the sixteenth century writings of P. M. D'ANGHERA[2]. Although extensive pharmacological investigations of crude curare were carried out by BERNARD[3] and some early clinical investigations followed his work, present interest in these agents is the result of the isolation of crystalline *d*-tubocurarine chloride and elucidation of its structure by KING[4], the introduction of large quantities of an authenticated curare from a single menispermaceous plant species (*Chondrodendron tomentosum*) by GILL[5], and the development of a reproducible bioassay by HOLADAY[1]. BOVET and BOVET-NITTI[2] have excellently reviewed the entire field of agents with curariform action including many synthetic substances with this type of activity. Although *d*-tubocurarine chloride is widely used therapeutically to diminish skeletal muscle tone, it does have several minor side-effects that are undesirable[3]. We have investigated the alkaloids of the various menispermaceous plants in order to try to find agents that have lower toxicity, longer duration of action, or more selective effects on given muscular structures.

The menispermaceous plants contain four fundamental types of alkaloids:— (1) The "berberine" type in which a single nitrogen atom is a member of two fused rings and consisting of berberine, columbamine, coptisine, and several similar compounds; (2) The "coclaurine" type which is a derivative of 1-benzyl-1, 2, 3, 4-tetrahydroisoquinoline and consists of coclaurine and isococlaurine; (3) The "biscoclaurine" type or "bisbenzylisoquinoline" type in which two coclaurine type molecules are joined through ether linkages to give tertiary bases of either the curine or oxyacanthine type; and (4) Quarternary bases structurally related to the curine type molecula and consisting predominantly of *d*- and *l*-tubocurarine. See Table I for illustrations of these structural types.

[1] Department of Pharmacology, West Virginia University School of Medicine, Morgantown, W. Va. – This research was supported in part by a grant from S. B. Penick & Co., New York.

[2] PETER MARTYR D'ANGHERA, *De Orbe Novo Decades* (Petri Martyris Anglerii edidit Antonius Nebissensis) 1516 in folio.

[3] C. BERNARD, CR. Acad. Sci. *43*, 825 (1856).

[4] H. KING, J. Chem. Soc. *1935*, 1381 and *1948*, 265.

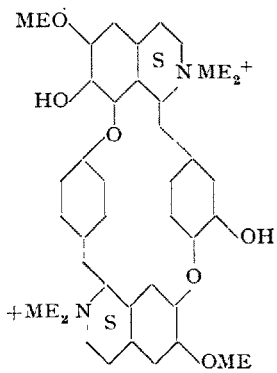
[5] R. C. GILL, Anesthesiology *7*, 14 (1946).

[1] R. F. VARNEY, C. R. LINEGAR, and H. A. HOLADAY, Fed. Proc. *7*, 261 (1948).

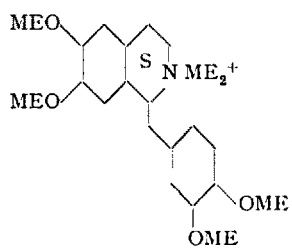
[2] D. BOVET and F. BOVET-NITTI, Exper. *4*, 235 (1928).

[3] E. B. SCHLESINGER, New York State J. Med. *47*, 1689 (1947). – T. C. GRAY and J. HALTON, Brit. Med. J. *1*, 784 (1948).

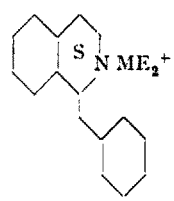
Table I



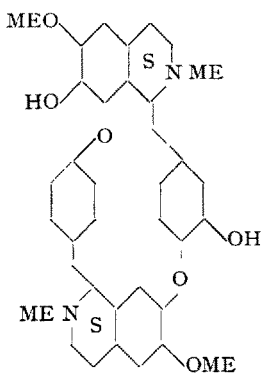
l-dimethylcurine



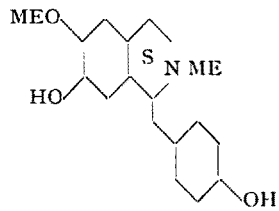
N-dimethyltetrahydropapaverine



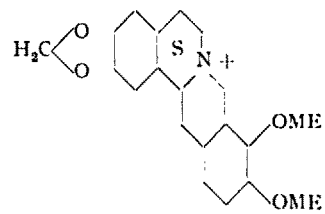
1-benzyl-*N*-dimethyltetrahydroiso-quinoline



l-curine



coclaurine



berberine

Table II
Biscoclaurine tertiary alkaloids ("Type 3")

Plant source	Tertiary base	Formula	Melting point	Optical rotation $[\alpha]_D$
Chondrodendron tomentosum . .	*d*-Chondrocurine	$C_{36}H_{38}O_6N_2$	232—234° C	+ 200 (in HCl at 24°)
Chondrodendron platyphyllum .	*l*-Curine*	$C_{36}H_{38}O_6N_2$	213—215° C	— 190 (in $CHCl_3$ at 24°)
Chondrodendron microphyllum .	*d*-Chondrodendrine	$C_{36}H_{38}O_6N_2$	213—215° C	+ 190 (in $CHCl_3$ at 24°)
	d-Isochondrodendrine	$C_{36}H_{38}O_6N_2$	300—305° C	+ 120 (in HCl at 22°)
Phæanthus ebracteolatus . . .	Phæanthine	$C_{38}H_{42}O_6N_2$	208—210° C	— 263 (in $CHCl_3$ at 24°)
Berberis vulgaris	Oxyacanthine	$C_{37}H_{40}O_6N_2$	215—217° C	+ 280 (in $CHCl_3$ at 24°)
	Berbamine	$C_{37}H_{40}O_6N_2$	170—172° C	+ 106 (in $CHCl_3$ at 25°)
Stephania tetrandra	Tetrandine	$C_{38}H_{42}O_6N_2$	217—219° C	+ 263 (in $CHCl_3$ at 24°)
Cocculus trilobus	Trilobine	$C_{36}H_{36}O_5N_2$	230—235° C	+ 280 (in $CHCl_3$ at 29°)
Menispermum dauricum . . .	Dauricine	$C_{38}H_{44}O_6N_2$	115—118° C	— 139 (in $CHCl_3$ at 11°)
Stephania cepharantha	Cepharanthine	$C_{37}H_{38}O_6N_2$	140—145° C	+ 204 (in $CHCl_3$ at 11°)
	Isotetrandine	$C_{38}H_{42}O_6N_2$	180—182° C	+ 146 (in $CHCl_3$ at 17°)

* Some of these agents are known under various other minor names and are found in several related plant species. The species given are those from which the alkaloids actually used in this study were isolated.

Preparation of curariform active materials

Preliminary experiments with rabbits indicated that no available member of the first three types had any curariform activity at dose levels of 5 mg/kg intravenously. The application of the BROWN-FRASER[1] concept involving conversion of the tertiary nitrogen atoms to the quaternary ammonium derivatives was obviously desirable. The type-1 compounds are not readily converted to such derivatives due to the ability of the nitrogen atom to tautomerize with an imino form. The type-2 compound methiodides are barely active at the 5 mg/kg level, but all of the derivatives of the type-3 alkaloids are highly active.

In many instances the tertiary bases of the type-3 alkaloids were available[2] in pure form (see Table II). These were dissolved in absolute methanol and refluxed with methyl iodide for two hours. The resultant solution was cooled and the quaternary ammonium compound precipitated with anhydrous ether. The materials were recrystallized from methanol-ethyl ether (see Table III).

[1] A.C. BROWN and T.R. FRASER, Proc. Roy. Soc. Edinburgh *6*, 557 (1869).

[2] We are gratèful to Dr. W.G. BYWATER of S. B. Penick & Co., New York, for generously supplying an authenticated specimen of *Chondrodendron* from which the *d*-chondrodendrine was isolated and for large amounts of *Berberis vulgaris* root from which the oxyacanthine and berbamine were isolated; to Dr. D.L. TABERN of Abbott Laboratories, North Chicago, Illinois, for the *d*-tubocurarine chloride from which the *d*-*O*-methyltubocurarine iodide was prepared; to Drs. JAMES D. DUTCHER and JAMES A. SHANNON of the Squibb Institute for Medical Research, New Brunswick, New Jersey, for the *d*-chondrocurine from which the *d*-chondocurarine iodide was prepared; to Mr. H. KING of the National Institute for Medical Research, London, for *l*-curine from which the *l*-*N*-methylcurine iodide and *l*-*O*,*N*-methylcurine iodide were prepared; to Dr. F. VON BRUCHHAUSEN of the Pharmazeutisch-chemisches Institut der Technischen Hochschule, Braunschweig, Germany, for the *O*,*N*-methylberbamine iodide (*N*-methylisotetrandine iodide); to Dr. A.C. SANTOS of the University of the Phillipines, Manila, P. I., for the bark of *Phæanthus ebracteolatus* from which the phæsanthine was isolated and converted to the *N*-methyl derivative; to Dr. K. K. CHEN of Eli Lilly & Company, Indianapolis, Indiana for dauricine, cepharanthine, and tetrandine; to Dr. D.S. TARBELL of the University of Rochester, Rochester, New York, for 2,2-dimethyl-1-benzyl-1,2,3,4-tetrahydroisoquinolinium iodide; and to Dr. H. KONDO of the University of Tokyo for isotetrandine, trilobine, and additional supplies of cepharanthine. Such other compounds as were used in the investigation were either prepared by the authors or purchased in the open market.

The procedure is essentially that used by DUTCHER[1] for the conversion of *d*-chondrocurine to *d*-chondrocurarine. All of these substances are soluble in water to only a limited extent, but 0·3–1·0% solutions can be prepared which are adequate for testing.

In those instances in which the alkaloids were not available, they were extracted from the original plant substances by modifications of the method of SPAETH and KOLBE[2] and SANTOS[3].

Pharmacology of curariform agents

Although there are many methods of determining curare-like activity, the head-drop cross-over assay of HOLADAY[4] (cf. BOVET and BOVET-NITTI[5]) is rapid and easy to use. The results are precise and reproducible, but the rabbit does not yield much information concerning side-effects of these agents. Additional experiments were carried out in order to determine which of these agents might be clinically useful. *N*-Dimethyltetrahydropapaverine iodide and 2,2-dimethyl-1-benzyl-1,2,3,4-tetrahydroisoquinolinium iodide[6] were also investigated for structural comparative purposes.

Technics of measuring curariform action

Rabbits. Solutions containing 0·25 mg of *d*-tubocurarine chloride pentahydrate per cc., or its approximate equivalent of the other agents, were injected in 15–25 seconds into a marginal ear vein of each of 18 rabbits (1·6–2·6 kg); these were restrained individually in an enclosed box. The doses producing head-drop lasting a minimum of 3 minutes in half a group of 10 animals were determined (see Table IV). The experiments were repeated on the same animals after two to four day rest periods until all the agents had been investigated in the same rabbits. After an individual rest period, the 2-day head-drop cross-over assay of HOLADAY was performed in the eight most uniform rabbits (i.e., those showing

[1] J.D. DUTCHER, J. Amer. Chem. Soc. *68*, 419 (1946).

[2] E. SPAETH and A. KOLBE, Ber. Dtsch. Chem. Soc. *58*, 2280 (1925).

[3] A.C. SANTOS, Rev. Filip. Med. Farm. *22*, 243 (1931).

[4] H.A. HOLADAY, cf. R.F. VARNEY, C.R. LINEGAR, and H.A. HOLADAY, l. c.

[5] D. BOVET and F. BOVET-NITTI, l. c.

[6] The names of these compounds are quite cumbersome and have been simplified wherever possible without producing confusion as to the exact material or compound concerned.

Table III

High curariform activity of quaternary ammonium derivatives

Tertiary base from which prepared	Quaternary derivative	Formula	Melting point
(not known)	*d*-Tubocurarine chloride	$C_{38}H_{44}O_6N_2Cl_2 5H_2O$	268–270° C
	d-*O*-Dimethyltubocurarine iodide	$C_{40}H_{48}O_6N_2I_2$	258–260° C
(not known)	*l*-Tubocurarine chloride	$C_{38}H_{44}O_6N_2Cl_2 5H_2O$	268–270° C
l-Curine	*l*-*N*-Dimethylcurine iodide	$C_{38}H_{44}O_6N_2I_2$	270–272° C
	l-*O*,*N*-Tetramethylcurine iodide	$C_{40}H_{48}O_6N_2I_2$	245–250° C
d-Chondrodendrine	*d*-*N*-Dimethylchondrodendrine iodide	$C_{38}H_{44}O_6N_2I_2$	251–253° C
	d-*O*,*N*-Tetramethylchondrodendrine iodide	$C_{40}H_{48}O_6N_2I_2$	257–258° C
d-Isochondrodendrine	*d*-*N*-Dimethylisochondrodendrine iodide	$C_{38}H_{44}O_6N_2I_2$	280–281° C
	d-*O*,*N*-Tetramethylisochondrodendrine iodide	$C_{40}H_{48}O_6N_2I_2$	300–305° C
d-Chondrocurine	*d*-Chondrocurarine iodide	$C_{38}H_{44}O_6N_2I_2$	272–275° C
Phæanthine	*N*-Dimethylphæanthine iodide	$C_{40}H_{48}O_6N_2I_2$	260–268° C
Oxyacanthine	*N*-Dimethyloxyacanthine iodide	$C_{39}H_{46}O_6N_2I_2$	258–261° C
	O,*N*-Trimethyloxyacanthine iodide	$C_{40}H_{48}O_6N_2I_2$	251–255° C
Berbamine	*N*-Dimethylberbamine iodide	$C_{39}H_{46}O_6N_2I_2$	258–261° C
(Isotetrandine)	*O*,*N*-Trimethylberbamine iodide	$C_{40}H_{48}O_6N_2I_2$	265–268° C
Tetrandine	*N*-Dimethyltetrandine iodide	$C_{40}H_{48}O_6N_2I_2$	260–265° C
Trilobine	*N*-Dimethyltrilobine iodide	$C_{38}H_{42}O_5N_2I_2$	270–272° C
Dauricine	*N*-Dimethyldauricine iodide	$C_{40}H_{50}O_6N_2I_2$	200–208° C
	O,*N*-Trimethyldauricine iodide	$C_{41}H_{52}O_6N_2I_2$	180–190° C
Cepharanthine	*N*-Dimethylcepharanthine iodide	$C_{39}H_{44}O_6N_2I_2$	260–272° C

head-drop by this technique at 0·14–0·16 mg *d*-tubocurarine chloride pentahydrate per kg). In this procedure the rabbits are tied belly down and 0·1 cc. of solution administered intravenously every 15 seconds until the head will not rise when the shaven back is electrically stimulated. Since very limited amounts of some agents were available no toxicity studies were carried out in the rabbits.

Technics of measuring secondary effects

Experiments were designed to establish the secondary or non-curariform effects of these agents in other species of animals.

Rats. The relative toxicity was determined in 460 albino rats (150–260 g). Solutions containing 0·12 mg of curariform agent per cc. were injected intraperitoneally and the lethal doses were determined (see Table I). Four to ten minutes after receiving a lethal dose, the animals became limp and unable to walk, respiration stopped in an additional 3 to 6 minutes, and finally cardiac activity ceased. The rats did not show any gross signs that these agents had cholinergic activity. They did not sneeze or salivate or evidence chromodachyria or flush as they do with some samples of crude curare.

Cats. Two hundred fifty mg of sodium barbital per kg were administered intraperitoneally 60 minutes prior to operation in 20 cats (2·1–3·6 kg). The femoral and sciatic nerves to one leg were cut. The peripheral end of the cut sciatic nerve was stimulated for one-tenth second with 6 volts 60 cycle half wave every ten seconds by a motor driven interrupter. The contractions of the gastrocnemius muscle were recorded on photographic paper by means of a strain gage (Baldwin-Southwark SR-4 type A-7) mounted on an isometric lever. The blood pressure in the opposite femoral artery was simultaneously recorded with a Lambert-Wood[1] strain gage manometer. The rabbit head drop dose of curariform agent was administered intravenously and after the muscle had returned to normal, 0·125 mg of *d*-tubocurarine chloride pentahydrate per kg was given. If the two effects were not equivalent, the dose of the first agent was increased or decreased as necessary until an effect equal (within ±5%) that produced by the *d*-tubocurarine was obtained. The equivalent doses are given in Table I. No more than four injections were given to any animal and no injections were made less than 15 minutes apart. See Fig. 1 for portions of a typical record.

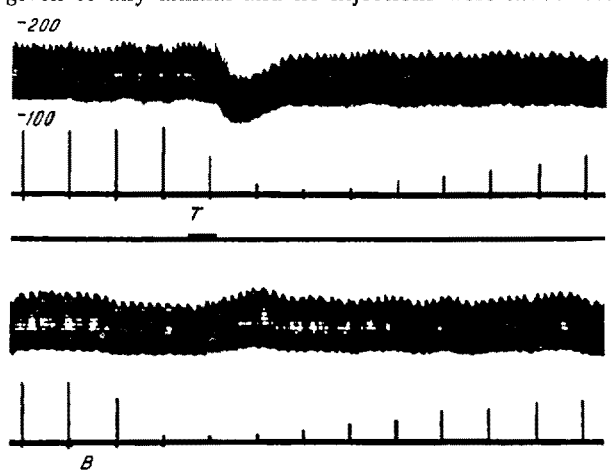


Fig. 1. – Cat (2·1 kg). Blood pressure, in mm Hg, above, and gastrocnemius contractions, below. Peripheral end of cut sciatic nerve stimulated every 10 seconds. Eighteen minutes deleted between portions of record. One hundred twenty five micrograms *d*-tubocurarine chloride pentahydrate per kg given at *T*; 150 micrograms *N*-methylberbamine iodide per kg given at *B*.

In an additional 40 barbitalized cats the cardiovascular response to two micrograms of epinephrine hydrochloride, acetylcholine chloride, and histamine acid phosphate per kg was determined with a Lambert-Wood strain gage in the femoral artery. The equivalent paralysis dose determined above was administered, and the epinephrine, acetylcholine, and histamine injections repeated. Following this, either atropine sulfate (0·69

[1] E. H. Lambert and E. H. Wood, Proc. Soc. Exp. Biol. a. Med. *64*, 186 (1947).

Table IV

	Head drop assay				Muscular paralysis Barbitalized cat equivalent				Secondary effects in unanesthetized dog at head-drop dose					Albino rat LD_{50} intraperitoneal injection mg/kg	Guinea pig tracheal ring	
	Rabbit HD_{50}	Rabbit HOLIDAY	Dog three minutes	Man three minutes	Dose mg/kg	Average change in blood press. mm Hg	Effect on epinephrine response	Antagon. of acet.-choline response	Salivation	Lacrimation	Vomiting	Defecation	Urination		10 μg/ml	Antagon. 0·5 μg acet.-chol. p. ml
d-Tubocurarine chloride	0·125	0·15	0·16	0·15	0·125	–45	+	0	++	+	+	+	+	0·27	++	0
d-*N*-Methylchondrodendrine iodide	0·23	0·27	0·36	0·6	0·5	–40	+	–	+	+	0	+	+	0·55		
l-*N*-Methylcurine iodide	0·20	0·23	0·33		0·2	–25	0	0	++	+	+	0	+	0·48	+	
l-Tubocurarine iodide	5·0*															
d-Chondrocurarine iodide	0·05	0·06	0·08		0·05	–5	0	0	+	0	0	+	+			
d-*O*-Methyltubocurarine iodide	0·016	0·02	0·02	0·03	0·02	–20	0	0	++	++	+	++	++	0·032	++	
d-*O*,*N*-Methylchondrodendrine iodide	0·11	0·13	0·15	0·15	0·10	–30	0	0	++	++	+	+	+	0·37		
l-*O*,*N*-Methylcurine iodide	0·05	0·06	0·08		0·07	–20	0	0	+	+	+	+	+	0·12		
N-Methyloxyacanthine iodide	0·18	0·21	0·28	0·32	0·15	–5	+	+	–	0	0	0	0	0·60	0	+
N-Methylberbamine iodide	0·125	0·15	0·17	0·18	0·125	–5	0	0	0	0	0	0	0	0·40		
O,*N*-Methyloxyacanthine iodide	0·35	0·41	0·44		0·3	–10	+	+	0	0	0	0	0			
N-Methylisotetrandine iodide	0·28	0·35	0·48		0·3	–10	+	0	0	0	0	0	0	0·77		
N-Methyltetrandine iodide	1·2	1·5	1·5		0·8	+20	+	+	+	+	0	+	+		0	+
N-Methylphæanthine iodide	0·61	0·67	1·0		0·3	–10	+	0	0	0	0	0	0	1·65		
N-Methylcepharanthine iodide	0·15	0·18	0·24	0·28	0·15	–5	+	0?	0	0	0	0	0		0	+
d-*N*-Methylisochondrodendrine iodide	2·5	2·9	3·5		2·0	–35	0	0	+	+	+	+	+	5·5		
d-*O*-*N*-Methylisochondrodendrine iodide	0·6	0·7	0·9		0·4	–55	0	0	+	+	+	+	+	3·0		
N-Methyldauricine iodide	0·87	0·95	1·3		0·4	–50	–	+	+++	++	+++	+	+		+++	
O,*N*-Methyldauricine iodide	0·38	0·45	0·6						+++	+	+++	+	+			
N-Methyltrilobine iodide	0·22	2·27	0·33		0·22	0	+?	0	0	0		+	0		0	
Dimethyltetrahydropapaverine iodide	>5·0		5·0		1·0	–10	+	0	++	++	+	++	++		++	
Dimethylbenzyltetrahydroisoquinoline iodide	>5·0				1·0	–20	+	–							++	

mg/kg) or diphenhydramine hydrochloride (2·9 mg/kg) was given and the curariform agent readministered periodically every five minutes until respiratory collapse occurred.

Dogs. Modified head-drop cross-over assays were performed in 6 trained mongrel female dogs (4–8·5 kg). The agents (2·5 mg/cc.) were administered intravenously in 30 seconds or less into the minor saphenous vein while the dog reclined on one side. The animal was allowed to rise, and the time of onset of paralysis (inability to stand) and its duration were recorded with any other objective findings. The head-drop dose was considered to be the dose of an agent that would produce inability to stand for a period of three to five minutes (see Table IV). Doses of agents producing such paralysis could be readministered on the following day and the same duration of action, within ±45 seconds, could be obtained. These assays with unanesthetized dogs were introduced as a preliminary to the investigations in man.

Man. In order to have information concerning possible clinical usefulness of the better agents, experiments were carried out on an 80 kg 29-year old white male, who had been previously standardized to *d*-tubocurarine chloride[1]. The subject was placed in a modified Fowler's position on a treatment table (back elevated about 40° from the horizontal, legs about 120° to trunk). A strap was placed around the lower thighs to prevent the subject from slipping off the table. The rabbit head-drop dose of an agent was given intravenously in 45 seconds and increased as necessary within the next 75 seconds to produce head-drop lasting three to five minutes. The occurrence of apparently maximal ptosis at approximately eighty per cent of the head-drop dose was used as an indication of the total amount of drug that would need to be given. See Fig. 2 for protocol of a typical experiment.

Isolated Tissue Segments. Hearts from four rabbits were prepared for perfusion by the Langendorff technique and varying amounts of the most available compounds added to the Ringer-Locke perfusion fluid. Isolated sections of ileum from 2 rabbits were prepared for recording by the usual Magnus technique in Tyrode solution and the response to acetylcholine chloride and to histamine phosphate were tested before and after addition of the curariform agents. The trachea of five guinea-pigs were prepared by the method of CASTILLO and DE BEER[1]. Ten micrograms of curariform agent were added to each cc. of bath. The larges increase in tone from this concentration by *d*-tubocurarine chloride was equivalent to that produced by 0·02 micrograms

[1] D. F. MARSH, C. K. SLEETH, and E. B. TUCKER, J. Pharmacol. Exp. Therap. *93*, 109 (1948).

[1] J. G. CASTILLO and E. J. DE BEER, J. Pharmacol. Exp. Therap. *90*, 104 (1947).

Fig. 2. – Experiments in man

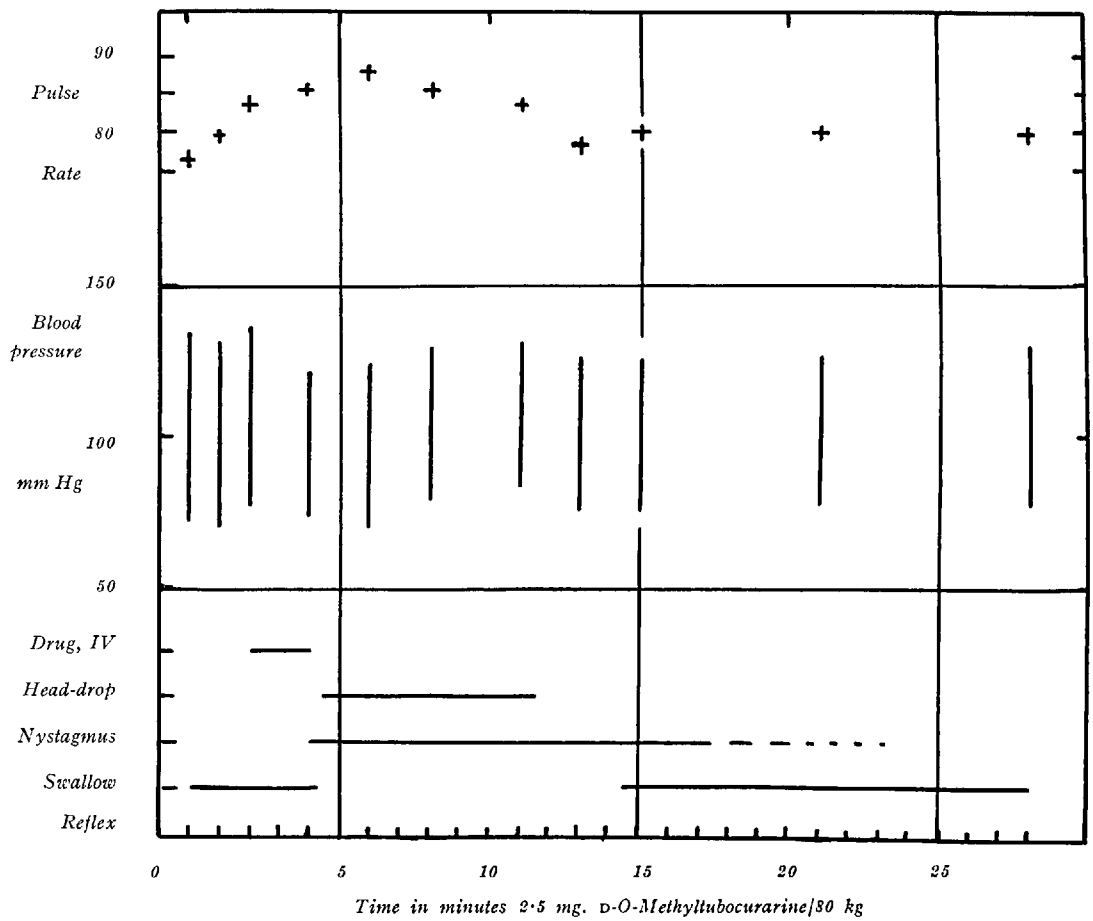


Fig. 2. – Human male (80 kg, 29 years old). D-*O*-Methyltubocurarine iodide (2·5 mg as a 0·125 p. c. solution) was given intravenously at time indicated. Pulse rate, beats per minute, above; systolic and diastolic blood pressure, in mm Hg, between; and presence of miscellaneous effects indicated by solid lines below.

histamine base per cc. Further experiments were carried out to determine the ability of this concentration of the agents to antagonize the contractile effect of 0·5 micrograms of acetylcholine chloride per cc.

Discussion of action

The results are summarized in Table IV. It is not difficult to determine the curariform activity of the highly specific acting agents. It is more difficult with agents that are not particularly active and that also produce cardiac and vasomotor effects. Even with the simple rabbit assay, the poorer compounds yield questionable results; i.e., extensive vasodepression limits the ability of the rabbit to raise its head whether any skeletal muscular depression is present or not. The most difficulty was experienced with the compounds containing only one ammonium ion, and the *N*-methyltetrandine.

It may be noted that the relative effect on skeletal muscle does vary among species and among the various methods of assay although the relative order of compounds remains fairly constant. In general, dogs are less sensitive to the effects of the agent on skeletal muscle than are the rabbits and the particular man used is slightly more tolerant than the dogs. Since the activity of most of these agents that have two ammonium ions is quite high in comparison to those that have only one, the choice of the best agent for some particular clinical use may depend on the presence or absence of undesirable secondary effects.

d-Tubocurarine chloride usually has little action in unanesthetized man other than that related directly to depression of skeletal muscular function[1], although such diverse side-effects as throbbing headache, bronchoconstriction, cold sweat, vertigo, fall in blood pressure, salivation, and flushing of the extremities have been reported[2]. LANDMESSER[3] has established that this agent produces bronchoconstriction in dogs and some similar effect has been observed in man[4]. Unanesthetized dogs that have had paralytic doses of this agent exhibit marked salivation, almost invariably defecation, and often vomiting, lacrimation, and urination[5]. No such side-effects are observed in rats or rabbits.

As indicated in the Table, the *d*-tubocurarine type or group I (see Table V) compounds always produce some fall in blood pressure in the cat even at comparatively low doses. This fall in blood pressure was not prevented by the administration of atropine or diphenhydramine. In general the compounds had very little effect on the

[1] S. M. SMITH, H. O. BROWN, J. E. P. TOMAN, and L. S. GOODMAN, Anesthesiology *8*, 1 (1947).

[2] E. B. SCHLESINGER, l. c., and T. C. GRAY and J. HALTON, l. c.

[3] C. M. LANDMESSER, Anesthesiology *8*, 506 (1947).

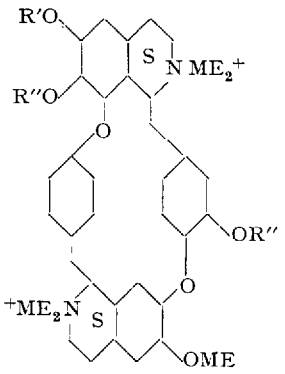
[4] J. H. COMROE and R. D. DRIPPS, Anesthesiology *7*, 260 (1946). – D. F. MARSH, C. K. SLEETH, and E. B. TUCKER, l. c.

[5] G. M. EVERETT, J. Pharmacol. Exp. Therap. *92*, 236 (1948).

Table V

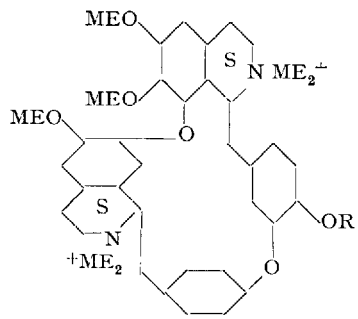
High activity of menispermaceous curariform agents

I



R′ = ME, R″ and R‴ = H
d-tubocurarine
d-*N*-methylchondrodendrine
l-*N*-methylcurine
l-tubocurarine
R″ = ME, R′ and R‴ = H
d-chondrocurarine
R′, R″, and R‴ = ME
d-*O*-methyltubocurarine
d-*O*,*N*-methylchondrodendrine
l-*O*,*N*-methylcurine

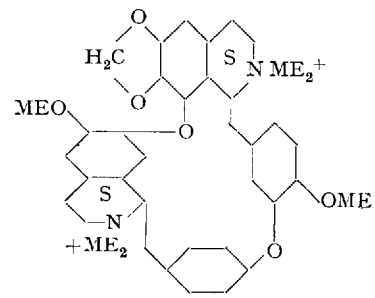
II



R = H
N-methyloxyacanthine
N-methylberbamine

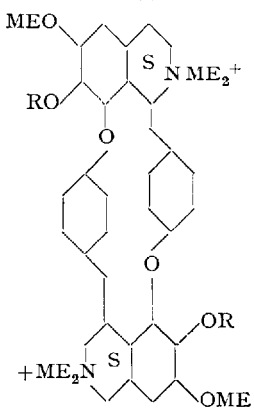
R = ME
O,*N*-methyloxyacanthine
N-methylisotetrandine
N-methyltetrandine
N-methylphæanthine

III



N-methylcepharanthine

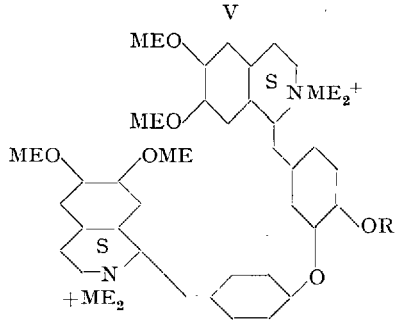
IV



R = H
d-*N*-methylisochondrodendrine

R = ME
d-*O*,*N*-methylisochondrodendrine

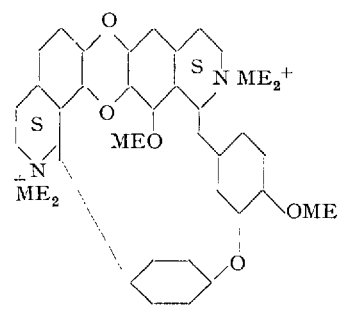
V



R = H
N-methyldauricine

R = ME
O,*N*-methyldauricine

VI



N-methyltrilobine

response to epinephrine, acetylcholine, or histamine, although occasional slight increase in effect by epinephrine and acetylcholine was observed. The group IV and V compounds are so much more vasodepressor than the group I compounds that no experiments were carried out in man with these agents. Most of the vasodepressor effect of *N*-methyldauricine could be antagonized by diphenhydramine. The group II, III, and VI compounds had much less effect on blood pressure and several members of the group had the ability to increase the response to epinephrine approximately twenty per cent and to diminish the response to acetylcholine by as much as thirty per cent.

The side-effects of the group I and V compounds in the unanesthetized dog are very pronounced while they are almost non-existent for group II, III, and VI compounds.

The experiments with isolated rabbit hearts and rabbit ileum indicated that the representative agents *l*-*N*-methylcurine, *N*-methyloxyacanthine, *N*-methyltrilobine, and *d*-tubocurarine had no effect on contractility or rhythmicity at concentrations as high as 50 mg/l (EVERETT[1] found slight increases in rabbit intestinal amplitude with 5–12·5 mg *d*-tubocurarine chloride per liter). *N*-Methyltetrandine and *N*-methyldauricine produced some increase in tone of the isolated intestine at concentrations as low as 1 mg/l. Both *N*-methyloxyacanthine and *N*-methyltrilobine partially antagonized the effects of 1 microgram of simultaneously added acetylcholine chloride per liter of perfusion fluid in the isolated heart and isolated intestine.

The results with the very sensitive guinea-pig tracheal chain are more apparent, but even here *d*-tubocurarine has only 1/500 the activity of histamine. *N*-Methyldauricine had the greatest contractile activity, with

[1] G.M.EVERETT, l. c.

d-tubocurarine and its methyl ether less, *l*-*N*-methylcurine some, and the other agents investigated none. Only *N*-methylcepharanthine, *N*-methyloxyacanthine, and *N*-methyltetrandine had any measurable anticholinergic activity.

Although these various differences in agents are real and measurable in animals, their clinical importance is not so obvious. In the few experiments carried out in man, the differences among compounds were not so great. All the compounds tested produced very transient falls in systolic and diastolic blood pressure of five to ten mm/Hg at the head-drop dose level. Although the *d*-tubocurarine group produced some salivation and the *N*-methyloxyacanthine, *N*-methylberbamine, and *N*-methylcepharanthine did not produce any, this difference would be of no importance in agents used as adjuncts to anesthesia. However, if the agents are to be given repeatedly, or in larger doses or to allergic or vasodepressed individuals, the undesired effects apparent in animals may indicate effects that will be encountered in man.

The conversion of a phenolic OH to a methyl ether in the *d*-tubocurarine type molecule always leads to a marked increase in potency (*d*-*O*-methyltubocurarine eight times as active as *d*-tubocurarine, *l*-*O*,*N*-methylcurine four times as active as *l*-*N*-methylcurine, *d*-*O*,*N*-methylchondrodendrine twice as active as the *d*-*N*-methylchondrodendrine). Conversion of the phenolic OH to a methyl ether in the oxyacanthine type molecule leads to a slight decrease in potency. Since the incidence of side-effects remains almost constant in relation to the curariform activity, such conversion must change the attraction of the agent for non-specific structures that are not involved in neuromuscular transmission.

Although many investigations have been concerned with *d*-tubocurarine[1] and a few with the other members of the group I compounds[2], almost none have been made concerning the group III compounds, and of the group II agents, only *N*-methyltetrandine[3] and *N*-methyloxyacanthine[4] have been investigated. All of the other compounds in group II, and those of group III and VI are pharmacologically new.

Zusammenfassung

Die verschiedenen chemisch charakterisierten Alkaloide, die in Menispermazeen angetroffen werden, sind auf allfällig nützliche Curarewirkung hin untersucht worden. Bloß diejenigen Verbindungen mit Dibenzyltetrahydroisochinolinstruktur, die zwei Stickstoffatome mit je vier Kovalenzen und eine Elektrovalenz besitzen bzw. in solche Verbindungen umgewandelt werden können, besitzen eine nennenswerte Wirkung.

Die zwanzig wirksamen Verbindungen sind auf ihre Fähigkeit, eine Paralyse der Skelettmuskulatur mit minimalen unerwünschten Nebenwirkungen an Ratten, Kaninchen, Katzen, Hunden und Menschen hervorzurufen, untersucht worden. Die *d*-Tubocuraringruppe, einschließlich die Curarin-Chondrodendrin-Chondrocurin-Abkömmlinge, besitzt die wirksamsten Verbindungen, weist aber zahlreiche unerwünschte Nebenwirkungen auf. Die *N*-Methyldauricin-Gruppe, in welcher zwei Benzylisochinolingruppen durch bloß eine Ätherbindung statt zwei verbunden sind, hat die diffuseste cholinergische Histaminwirkung. Die Isochondrodendrinabkömmlinge sind nicht sehr wirksam, haben aber unangenehme Nebenwirkungen. Die Oxyacanthingruppe ist insofern interessant, als alle ihre Glieder, obgleich sie identische Grundformeln besitzen, in ihrer Wirksamkeit und ihren Nebenwirkungen sehr verschieden sind: es gibt hochwirksame Substanzen, die, wie *N*-Methylberbamin, fast keine Nebenwirkungen haben; oder *N*-Methyloxyacanthin, welches curariform und schwach atropinähnlich ist; oder *N*-Methyltetrandrin, welches nikotin- und muscarinähnlich, aber nur schwach curarëähnlich ist. Von den übrigen Gruppen sind die einzig brauchbaren Mitglieder *N*-Methylcepharanthin und *N*-Methyltrilobin, außergewöhnlich, indem sie eine erheblich paralysierende, aber fast keine andere Wirkung zeigen.

[1] A. R. McIntyre, *Curare* (University of Chicago Press, Chicago, 1947). – D. Bovet and F. Bovet-Nitti, *Structure et activité pharmacodynamique des médicaments du système nerveux végétatif* (Karger, Bâle, 1948).

[2] J. D. Dutcher, l. c. – H. O. J. Collier and S. K. Paris, Nature *161*, 817 (1948). – O. V. Brazil, R. A. Seba, and J. S. Campos, Bol. Inst. Vital Brazil *5*, 79 (1945). – D. F. Marsh, C. K. Sleeth, and E. B. Tucker, l. c.

[3] H. M. Lee, A. M. Van Arendonk, and K. K. Chen, J. Pharmacol. Exp. Therap. *56*, 466 (1936).

[4] D. F. Marsh, D. A. Herring, and C. K. Sleeth, J. Pharmacol. Exp. Therap. *95*, 100 (1949).

Bericht über den internationalen Physikerkongreß vom 5. bis 15. September 1949 in Basel und Como

(Schluß)

Beim Durchgang eines sehr schnellen Nukleons durch einen Kern kann dieser zu vielen Teilstücken explodieren; die so entstehenden «Sterne» sind schon vor Jahren mit Hilfe photographischer Emulsionen nachgewiesen worden. Durch die unerhört rasche Entwicklung dieser Technik, die vor einem Jahr in der Herstellung von Platten gipfelte, deren Empfindlichkeitsschwelle unterhalb des Ionisationsminimums liegt, ist es möglich geworden, Teilchen aller Energien und Massen (z. B. schnelle Elektronen) als Spuren festzuhalten. Das Arbeiten mit solchen Platten und insbesondere die Identifikation der Spuren stellt aber große technische Probleme (Referat G. P. S. Occhialini und Kurzreferate seiner Brüsseler Schule).

In den neuen Platten beobachtet man, daß viele Sterne neben den dicken Spuren, die von Kerntrümmern und langsamen Mesonen erzeugt sind, auch dünne Spuren aufweisen, die man Teilchen relativistischer Energie zuschreiben muß. Zumindest ein Teil der letzteren sollen Mesonen sein, womit der Anschluß an die bekannten Schauer hergestellt ist. Die Anzahl solcher Spuren pro Stern, ihre Winkelverteilung usw. bilden das Hauptthema der jüngsten Arbeiten (Referate von C. F. Powell, Bristol, L. Leprince-Ringuet, Paris, u. a.).

Zur Deutung dieser Ereignisse schlagen die Theoretiker zwei Erklärungen vor, die auf entgegengesetzten Standpunkten fußen: 1. in einem Stoß zwischen zwei Nukleonen soll jeweils nur ein Meson erzeugt werden können (Heitler-Jánossy); 2. bei einem Stoß soll zugleich eine Vielzahl von Mesonen entstehen können (Referat W. Heisenberg, Göttingen). Es ist auf Grund des heute vorliegenden Experimentalmaterials noch nicht möglich, eine Entscheidung zu fällen.

Die harten Schauer bilden den Gegenstand vieler Untersuchungen mit Zählrohren (Referat L. Jánossy, Dublin) und Wilsonkammern (Referat P. M. S. Blackett,