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THE CLINICAL ASPECTS OF THE TRANSMISSION OF THE EFFECTS OF NERVOUS IMPULSES BY ACETYLCHOLINE*

BY

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LECTURE II

Pharmacology of Carbaminoyl-choline

Carbaminoyl-choline was introduced by Kreitmair (1932), working in the pharmacological laboratories of Merck of Darmstadt. He considered that it excelled acetylcholine in many ways, appearing to be more powerful, and active in doses usually associated with hormones or vitamins. It is much more stable than acetylcholine in solution, withstands boiling, and is active even when administered by the digestive tract.

Simonart and Simonart (1934) showed that it is less active than acetylcholine and that its comparative stability accounted for the apparent greater activity as a parasympathetic stimulant, but that it is stronger in its nicotine-like properties. Kreitmair (1932) worked with dogs, cats, and frogs, and showed that in general it has the same qualitative effects as acetylcholine, acting typically as a mimic of parasympathetic stimulation, and that atropine inhibits its effects. Velten (1933) studied its action on the stomach, noted contraction of the muscle and an increased flow of gastric juice, and found that it induced contractions in the puerperal uterus of cats. He considered that there is no accumulation or habituation in cats with daily doses over long periods, but that injections of subtoxic doses repeated twice daily for several days caused cachexia and death in some cats though not in others, but at necropsy no reason for death was found. In man, however, Starr (1937) has observed evidence of accumulation with subcutaneous injections, and found it necessary to lower the dose. Nöll (1932) studied the effect of subcutaneous injections and of oral and rectal administration in cats following a barium meal, and demonstrated a powerful action on the musculature of the intestines in two and a half hours. He noted great salivation and an increase in the flow of gastric juice. Dautrebande and Maréchal (1933) gave 0.01 mg. per kilogramme of body weight to dogs, and noted tachycardia and a fall in blood pressure followed by bradycardia, and also stimulation of respiration. Dautrebande (1933) gave the same dose to dogs by intracarotid injection, and concluded that the

tachycardia is due to a reflex from the carotid sinus and that the carotid sinus is responsible for the immediate stimulation of respiration and also for a secondary stimulation at the time of the fall in blood pressure. Destrée (1937) gave 0.125 mg. per kilogramme to dogs with Pavlov fistula and found that it produced an increase of total and free acid and of mucus in the gastric secretion. Atropine prevented this action.

In so far, therefore, as its effects on animals are concerned, carbaminoyl-choline differs from acetylcholine mainly in its greater stability, so that prolonged effects can be obtained by subcutaneous injection and even by oral or rectal administration.

Actions of Carbaminoyl-choline in Man

Dautrebande and Maréchal (1933) reported that the administration of 0.1 mg. to man by intravenous injection produced a fall in blood pressure, a feeling of heat, dilatation of superficial vessels, increased activity of movements within the abdomen, salivation, and lacrimation. They also found that the intramuscular injection of 0.2 to 0.3 mg. caused a fall of blood pressure that persisted for twenty to forty minutes.

INTRAVENOUS INJECTION

In 1932 E. A. Carmichael and I began observations on the effects in man of intravenous injections. These preparations were kindly supplied by Merck and Co., and consisted of a solution of carbaminoyl-choline chloride in sterile ampoules (1 c.cm. containing 0.1 mg.) under the name of lentin, and later of ampoules containing 0.25 mg. in 1 c.cm. under the name of doryl. We gave fifty-eight injections to eleven subjects—patients in hospital convalescing from acute infections or admitted for chronic conditions such as osteo-arthritis, tabes dorsalis, etc. Starting with a dose of 0.01 mg., the dose was increased until a definite effect on the pulse rate or blood pressure was obtained. The pulse rate for each three-second period was calculated from a continuous polygraphic record, and blood-pressure readings by the auscultatory method were taken as often as possible. Typically, a fall of both systolic and diastolic blood pressures occurred, accompanied by a rise of pulse rate ten to twenty seconds

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following the injection. Fig. 4 shows the characteristic effect on the pulse rate. The blood-pressure readings are too inaccurate to be worth recording, but falls from a systolic of 130 mm. Hg to 90 mm. Hg and from a diastolic of 80 mm. Hg to 60 mm. Hg were commonly noted. The maximum effect on both blood pressure and pulse rate was reached in from thirty to forty seconds following the injection, and both had returned to the previous level at the end of sixty seconds. These effects appeared with a dose of from 0.03 to 0.05 mg. The previous injection of 1 mg. of atropine sulphate prevented the fall of blood pressure and the rise of pulse rate. In one patient little if any rise of pulse rate was obtained even when other symptoms occurred, and this was noted also following injections in patients who had previously reacted typically to smaller doses. On two occasions only did the pulse rate fall, and in both instances the blood pressures dropped as usual and typical rises of pulse rate occurred in the same patients on other occasions. In neither instance was the fall followed by a rise of pulse rate.

The effect of the intravenous injection of carbaminoylcholine on the pulse rate in producing a rise and only

FIG. 4.

occasionally a fall differs, therefore, from that of acetylcholine, which produced in nearly every instance a fall followed by a rise.

Other symptoms that accompanied the rise of pulse rate were flushing of the head and neck, a feeling of heat throughout the body, a sensation of fullness in the head or headache, coughing, and a feeling of tightness in the throat or upper thorax. These symptoms were transient, variable in degree, and lasted only a few seconds. Less constantly, sweating, salivation, and lacrimation occurred. If the injections were repeated after a few minutes the effects were the same, but after a number of injections had been given a few patients complained of abdominal unrest, and two of them defaecated shortly after the termination of the observations. In four patients effective injections were repeated following the intravenous injection of 1 mg. of atropine sulphate, and in each the symptoms were entirely prevented or very greatly diminished in intensity.

Three patients received doses of 0.02, 0.05, and 0.25 mg. injected into the femoral artery. A slight flush occurred in the distribution of the femoral artery, but no flushing or other symptoms in the rest of the body. In these doses it had much less effect by this route than we had obtained with doses of acetylcholine of 5 to 25 mg., but we hesitated to use larger amounts because of the stability of this ester.

SUBCUTANEOUS AND INTRAMUSCULAR INJECTION

From these results it does not appear that carbaminoylcholine offers any advantages over acetylcholine itself for therapeutic purposes if given by intravenous injection, the effects being extremely transient when safe doses are employed. By subcutaneous or intramuscular injections conspicuous and sustained effects are obtained, and during the past five years I have been able, with the help of

different colleagues, to study the effects on more than twenty-five patients. The results vary considerably from subject to subject, and in the same subject from day to day. They were patients in hospital suffering from chronic illnesses that were unlikely to interfere with the reactions to the drug. An injection of 0.5 mg. will produce definite effects, which, however, are sometimes so pronounced as to be upsetting to the patient; a dose of 0.25 mg. will usually produce some recognizable effects, does not upset the patient, but seldom produces all the typical reactions.

Fig. 5 shows the characteristic response to 0.5 mg. Within a few minutes, usually two, the subject becomes

FIG. 5.

restless, feels hot, flushes on the face, neck, and upper thorax, and swallows because of increased salivation and a vague feeling of constriction in the throat, and tears collect in the conjunctival sac because of increased lacrimation. Throbbing in the head may be complained of early, but may not appear for ten or more minutes. With the onset of the symptoms the pulse rate rises and the blood pressures fall, but after a few minutes, usually five, the pulse rate also falls to below the initial rate. In five to ten minutes after the injection sweating appears all over the body, and in from ten to fifteen minutes borborygmi are audible, the patient is conscious of abdominal unrest, and there may be some nausea. After twenty minutes the symptoms subside, and the pulse rate and blood pressures gradually return to normal, usually regaining the initial levels at the end of forty minutes. The abdominal unrest may continue after the other symptoms have disappeared, and frequently the bed-pan is called for at the end of thirty to forty minutes, when defaecation may occur, or, more often, the bladder only is emptied. This dose produced in one subject an alarmingly rapid fall of blood pressure and of pulse rate, with a feeling of faintness and appearance of collapse; atropine sulphate was accordingly injected intravenously, this being followed by a rapid disappearance of all the symptoms.

If the dose is raised to 1 mg. the effects are increased in intensity, and in different subjects one or other effect attains especial prominence. Fig. 6 shows the result in a patient with muscular dystrophy in whom the most striking effect was the intense pain which he located at the root of the penis. This pain persisted after he emptied his bladder and remained severe at the end of forty minutes, when other symptoms had disappeared or become mild, and he was given atropine, which promptly relieved the pain. Following the injection of 1 mg. in the same subject as in Fig. 5, the slowing of the pulse and the fall of blood pressure were so rapid that atropine was given at the end of six minutes; but the most striking phenomenon was the flow of saliva, which frothed at her mouth in a large ball of fine bubbles. On the other hand, 1 mg. in another patient caused little disturbance apart from the usual effects on pulse rate and blood pressure, and when

FIG. 6.

combined with 1 mg. of atropine sulphate the atropine prevented the effects on the cardiovascular system but not entirely the increased movements of the intestines. The effects in a man with essential hypertension were in no way unusual, 1 mg. producing enough retching and vomiting to necessitate an injection of atropine to relieve his distress, while 0.25 mg. produced mild effects only (Fig. 7). In a woman with exophthalmic goitre the effects of 1 mg. on the cardiovascular system were comparatively mild, the bladder was emptied six minutes after the injection, and abdominal unrest persisted for some hours, even after defaecation occurred at the end of forty minutes.

As a result of their observations on the action in animals, Kreitmair (1932), Nöll (1932), and Velten (1933) stressed the effects on the gastro-intestinal tract. We studied the effects of 0.2 mg. to 0.4 mg. in three human subjects by subcutaneous injections, watching the outlines of the stomach and intestine with the x-ray screen following a barium meal. Fifteen minutes after the injection the movements of the stomach, small intestine, and colon all appeared to increase. The stomach emptied more rapidly than usual, and conspicuous local constrictions appeared in the small intestines and colon, while from time to time a constriction would move vigorously downwards for a short distance. The normal movements seemed to be increased in vigour and frequency, but the most striking

effect was the production of local constrictions. These changes were observable for one hour following the injection. Two patients with colostomy were given 0.2 mg. and 0.4 mg. respectively by subcutaneous injection. Between ten and fifteen minutes later increased movements were observed in the exposed parts of the colon, which pouted and were vigorously contracted and withdrawn while much wind was passed. With the smaller dose no other effects were observed, but with the larger dose there was sweating and abdominal discomfort and the activity of the exposed gut was much more vigorous. The gastric contents were examined following an alcohol test meal in five subjects. At the end of one hour 0.1 mg. or 0.2 mg. of carbaminoyl-choline was injected subcutaneously. No increase of hydrochloric acid occurred, and in three subjects it was diminished, although histamine caused increased acidity in all of them, and following the carbaminoyl-choline injections it sometimes proved diffi-

FIG. 7.

cult to obtain further specimens, possibly because the stomach emptied rapidly.

Starr (1937) reported the effects on twenty-six healthy students of giving 0.1 to 1 mg. by subcutaneous injection and 0.4 to 1 mg. by the mouth. He obtained a fall of blood pressure and a rise of pulse rate followed by a fall, and noted symptoms similar to those found by us. He considered that it is cumulative both by mouth and by subcutaneous injection, and that if repeated injections are given the dose must be reduced, or headache and general malaise result.

Rutenbeck (1935), in a study of ionization as a method of introducing drugs into the body, found that with a solution of 1 mg. per c.cm. of carbaminoyl-choline general effects were obtained from the absorption of the drug. He obtained local vasodilatation that was not so strong as with histamine, and five to ten minutes after the circuit was closed flushing in the head, sweating, abdominal unrest, and increased intestinal peristalsis were experienced. Kramer (1937) also obtained general effects of carbaminoyl-choline by the same method.

Velhagen (1933) observed local effects in the eye following the instillation of a 0.75 per cent. solution into the conjunctival sac. He found that it produced a strong constriction of the pupil and that it lowered the tension

in the eyeball if given two or three times a day. With Dr. Kent Harrison I have tried the effect when given in this way. The ordinary solution for injection (doryl), which contains 0.25 mg. per c.cm., has no effect even when combined with 0.05 per cent. solution of prostigmin, but we found that a 0.75 per cent. solution as used by Velhagen produced a strong constriction of the pupil in two subjects that persisted for six hours, and also engorgement of the conjunctival vessels that passed off somewhat more quickly. In five other subjects we put one drop of a 0.75 per cent. solution with one drop of a 1 per cent. solution of prostigmin into the conjunctival sac and obtained congestion of the conjunctival vessels and constriction of the pupil that persisted for eighteen hours in all of them, and in four a lowering of the intra-ocular tension could be detected with the finger-tips. This lowering of eyeball tension is presumably due to the relaxation of the unstriated muscle fibres of the orbit, and was especially noticeable in a subject with exophthalmic goitre. In no instance could we detect any dilatation of retinal arteries or symptoms of absorption of the choline ester into the general circulation.

These results of the administration of carbaminoylcholine to man show that it has in general the same actions as acetylcholine; but because of its increased stability it is effective by intramuscular and subcutaneous injection, and these actions can be maintained for a much longer time than is possible with acetylcholine. By oral administration its effects appear to be less certain, and when given repeatedly malaise and headache result. It can be administered slowly over long periods by ionization, and local effects in the eye can be obtained by conjunctival instillation. Further, in comparison with acetylcholine the effects on the gastro-intestinal tract and the bladder appear to be greater and those on the cardiovascular system to be less. The rise of pulse rate when a fall might be expected is probably due to a reflex action from the carotid sinus, resulting from the fall of blood pressure, overpowering the direct vagomimetic inhibiting action on the heart as suggested by Dautrebande (1933).

Pharmacology of Acetyl- β -methyl-choline

In 1911 Reid Hunt and Taveau reported the production of an ester of methyl-choline, acetyl- β -methyl-choline, with well-marked parasympathetic and muscarine-like actions as of acetylcholine but feeble nicotine-like effects. They found that it was less readily hydrolysed than acetylcholine. Simonart (1932) confirmed these properties and actions in cats, and found that it was absorbed and active when administered by the gastro-intestinal tract. Comroe and Starr (1933), working with frogs, cats, rabbits, and dogs, found that it has actions similar to those of acetylcholine, less powerful though more prolonged on intravenous injection, and that it is more effective on subcutaneous injection, and active when injected into the lumen of the intestine. In the fully atropinized animal they obtained no rise of blood pressure, pointing to the absence of nicotine-like effects on sympathetic ganglia or adrenal medulla, and the only nicotine-like effects obtained by Simonart were feeble ones on denervated muscle. Schnedorf and Ivy (1937) found that in eight rhesus monkeys, with histamine-resistant achlorhydria but otherwise healthy, acetyl- β -methyl-choline alone by repeated injections caused a flow of acid gastric juice in half of the animals, and that all responded when it was combined with histamine. Flexner, Bruger, and Wright (1938) showed that it caused contraction of the gall-bladder in cats.

Action of Acetyl- β -methyl-choline in Man

Acetyl- β -methyl-choline is usually administered to man as the chloride, which is supplied by Merck under the name of mecholol or mecholyl. Villaret, Justin-Besançon, Cachera, and Said (1932) gave 25 mg. by subcutaneous injection to healthy subjects, and found a fall in blood pressure that lasted for one or two hours, accompanied by vasodilatation and symptoms of vagus stimulation. Villaret, Justin-Besançon, Schiff-Wertheimer, and Gallois (1932) applied it to the eye by instillation of two drops of a 10 per cent. solution into the conjunctival sac and produced powerful miosis and a reduction of ocular tension. They found that it had a powerful effect by subconjunctival injection also. Starr, Elsom, and Reisinger (1933) gave it by subcutaneous injection to normal subjects in doses up to 25 mg., and observed flushing, a feeling of heat, sweating, salivation, lacrimation, increased intestinal peristalsis, epigastric discomfort, increased respiratory excursion, palpitations, and a sense of discomfort in the epigastrium and of constriction under the sternum. The effects appeared in two to three minutes and passed off in twenty to thirty minutes. The pulse rate rose and the blood pressure fell with the onset of symptoms, and a few minutes later the pulse rate fell in some cases to below the original level, an action similar to that of carbaminoylcholine by the same route. They gave it by the mouth also in doses of 100 mg. to 1 gramme, and found that when administered by this route the effects were much the same but less intense, persisted longer, and appeared in thirty to forty minutes. When given orally the rise in pulse rate was not seen.

Fig. 8 shows the action of 25 mg. by intramuscular injection in one of our patients. The symptoms of

FIG. 8.

collapse and the fall of blood pressure appeared so rapidly that 1.2 mg. of atropine sulphate was given by subcutaneous injection at the end of eight minutes. In a second subject 1.2 mg. of atropine sulphate was given twenty-four minutes previously and was not sufficient to prevent the cardiovascular effects of 50 mg.

Abbott (1933) studied especially the actions on the gastro-intestinal tract. When given by subcutaneous injection or by the mouth it caused increased movements

of the stomach, small intestine, and colon, and after oral administration the cardiovascular effects were less intense. He obtained no increase in the amount of gastric juice, but in a few cases of hypochlorhydria there was a slight rise in the concentration of free hydrochloric acid.

Page (1935) observed the usual muscarine-like effects following the subcutaneous injection of 25 mg., but commented on the absence of slowing of the pulse. He found that the T-waves of the electrocardiogram become negative following the injection, and that this effect, in common with the other symptoms, is inhibited by atropine.

Ritvo (1936) observed the effects of 20 to 30 mg. by subcutaneous injection on the stomach and intestines by radiographs following a barium meal. He found an increase of tone in stomach and intestines five to ten minutes after the injection, followed by powerful deep peristaltic waves. In the colon the lumen narrowed and haustrations increased in number and depth. These effects lasted for thirty minutes to several hours, and were accompanied by evidence of parasympathetic stimulation and by headache, sweating, and a fall in blood pressure.

Myerson, Schube, and Ritvo (1937) observed the effects on the colon following a barium enema. They gave 30 mg. by subcutaneous injection, and found increased tone in five minutes, followed by more and more marked haustrations, coming and going for over one hour. The increased tone lasted sometimes for twenty-four hours, and as a rule three or four evacuations occurred. They found that the cardiovascular effects were of short duration in contrast, but considered that they were disadvantageous to the use of the drug in atony of the colon. Atropine sulphate in doses of 1/100 grain by subcutaneous injection inhibited these actions on the colon.

Myerson, Loman, and Dameshek (1937) found that following the subcutaneous injection of 30 mg. the spinal fluid pressure rose by 30 to 140 mm. of water during the lowering of the blood pressure in eighteen psychotic patients.

Myerson, Rinkel, and Dameshek (1936) studied the effect on the gastric juice following the subcutaneous injection of 25 to 40 mg. They concluded that it produces an increased flow of alkaline juice with a high mucus content and that free hydrochloric acid and total acidity are reduced. These effects began to pass off after twenty minutes and had disappeared by forty minutes. Loman, Rinkel, and Myerson (1937) found the same action on the gastric juice when the drug was given by ionization, but the effect was less explosive and the side actions less pronounced; by giving prostigmin in addition they were able to maintain an alkaline juice for two hours or more.

Martin (1937) obtained all the usual actions following absorption by means of ionization, using a 0.25 or 0.5 per cent. solution with a current of 20 to 30 milliamperes for twenty minutes. He observed that the blood sugar fell, but not convincingly, and that there was an increase of gastric juice with a fall in acidity. No case of anacidity developed free acid.

Van Dellen, Bruger, and Wright (1937) put 25 to 250 mg. in a few drops of solution into the anterior nares. Evidence of immediate absorption was seen—hyperaemia and a sensation of warmth in the nose, lacrimation, salivation, flushing of head, neck, and thorax, sweating, and a sharp fall of blood pressure. The symptoms varied greatly from individual to individual, and at times the respirations were accelerated; the effects passed off in four to six minutes.

Myerson and Thau (1937) found the effective dose when given by instillation into the conjunctival sac to be inconstant. A 10 per cent. to 20 per cent. solution usually sufficed to produce a pin-point pupil in twenty minutes. The reaction to light and convergence was retained until miosis was extreme, the palpebral fissures were narrowed, the retinal arteries and veins dilated, and the ocular tension fell 3 to 5 mm. A full effect could be obtained with a 1 per cent. solution containing 1 per cent. prostigmin. General symptoms of absorption did not occur.

From these observations we can conclude that, like carbaminoyl-choline, acetyl- β -methyl-choline has actions similar to those of acetylcholine and is more stable, producing typical effects when given by subcutaneous or intramuscular injection, by the mouth, or by ionization. By injection a dose of 10 to 25 mg. appears to be comparable to 0.25 to 0.5 mg. of carbaminoyl-choline. The effects of both esters are ordinarily of the muscarine-like type, and the only nicotine-like effects observed by us were seen with carbaminoyl-choline, in muscle twitchings and cramps in a patient with muscular dystrophy, and in increased spasticity of muscles in a case of arteriosclerosis of the cerebral vessels. With both esters the results following injection appear in a few minutes, but while the action on the cardiovascular system passes off in from thirty to forty minutes, the action on the gastro-intestinal tract and bladder may persist for several hours. It is generally accepted that the action of carbaminoyl-choline on the gastro-intestinal tract is relatively greater than on the cardiovascular system, and that the reverse is the case with acetyl- β -methyl-choline. With both, local effects can be obtained on the eye and on the nose by instillation into the conjunctival sac or anterior nares.

Therapeutic Uses of Doryl and Mecholin

Both carbaminoyl-choline chloride (doryl) and acetyl- β -methyl-choline chloride (mecholin or mecholyl) have been used in a great variety of diseases to obtain either parasympathetic or vasodilator effects, but the reports in the literature of such uses have, with certain exceptions, consisted of a few case reports, from which it is often difficult to judge conclusively of the value of these substances.

In Ophthalmology.—Miloró (1935) considers that in chronic glaucoma the instillation of doryl is often efficacious when physostigmin and pilocarpine fail. He found that it produced a powerful miosis for two and a half hours and that the ocular pressure was lowered for twenty-four hours.

In Ozaena.—Guns (1934) believes that doryl has a place in the treatment of ozaena, and found that the local application of a 0.04 or 0.05 per cent. solution caused increased secretion.

Contraindicated in Asthma.—Starr, Elsom, and Reisinger (1933) caused an attack of asthma by mecholin in an apparently healthy person who had been subject to asthma; and Villaret, Vallery-Radot, Justin-Besançon, and Claude (1934) reported that, in fifteen persons subject to asthma with various causal factors, attacks were produced by the subcutaneous injection of 0.02 to 0.04 gramme. They suggested that this effect might be used as a diagnostic test. My colleague, Dr. J. G. Scadding, has demonstrated, by means of lipiodol, constriction of the smaller bronchi following 25 mg. of mecholin by intramuscular injection in a woman aged 37 convalescent from pneumonia and with no history of asthma.

IN PAROXYSMAL TACHYCARDIA

Starr (1935, 1936a) found mecholin of value in stopping attacks of paroxysmal tachycardia. It is successful in auricular or supraventricular paroxysmal tachycardia, but fails in paroxysmal tachycardia of ventricular origin and is of no value in other types of tachycardia. Including his own cases he reported that seventy-five attacks in thirty-seven patients were treated and that sixty-six were stopped, there being nine failures. After carotid sinus pressure had failed to stop the attack the drug alone was successful in 58 per cent. of the sixty-six at the first injection; twenty-two per cent. required a second dose, and in 20 per cent. carotid pressure during the action of the drug succeeded. He recommends 10 mg. by subcutaneous or intramuscular injection in young or light subjects and up to 60 mg. for larger persons. It may cause stoppage of the heart for a few seconds, but the heart starts to beat again as in any method of vagus stimulation. In one patient a lengthening of the P-R time and ventricular extrasystoles occurred before normal rhythm returned; in another, complete heartblock was seen, but the tachycardia returned and persisted. Mecholin had no permanent effect in auricular fibrillation and no constant effect in auricular flutter. Fig. 9, for which I am indebted to my colleague

FIG. 9.—*Top:* Paroxysmal auricular tachycardia. Carotid sinus pressure failed to alter the rhythm. *Bottom:* Normal rhythm returned five and a half minutes after intramuscular injection of 25 mg. of mecholin. (Dr. Paul Wood's case.)

Dr. Paul Wood, shows the rhythm before and five and a half minutes after the injection of 25 mg. intravenously in a case of auricular paroxysmal tachycardia. In general no action on auriculo-ventricular conduction is observed following the administration of mecholin or doryl in normal hearts, and during the phase of slowing of the heart rate the action is on the pace-maker only. The therapeutic effect in paroxysmal tachycardia occurs a few minutes after the injection, when the action in normal subjects is to produce a rise of heart rate, and is presumably due to a direct vagomimetic inhibitory action which may be masked by the carotid sinus reflex. Nahum and Hoff (1935) found that mecholin converted normal rhythm into auricular fibrillation in four patients with hyperthyroidism. Birk, Lethaus, and Plugge (1936) gave doryl intravenously in doses of 0.05 to 0.12 mg. in eight cases of paroxysmal tachycardia, and were successful in stopping the attacks in seven. They do not differentiate between supraventricular and ventricular tachycardia, and prefer to use digitalis or strophanthin when congestive failure is present, reserving doryl for cases with compensation. Blumberger and Dericks (1937) gave doryl in doses of 0.1 to 0.25 mg. intravenously to a young girl with mitral stenosis and auricular paroxysmal tachycardia, and caused fibrillation of the auricles.

VASODILATOR ACTIONS

Both doryl and mecholin have been employed in various vasospastic conditions. Starr (1937) considered that doryl relieved the pain in intermittent claudication. He (1936b) found that doryl by subcutaneous injection was

more efficient in relieving pain in peripheral vascular disease than mecholin by oral administration in three cases, but was less efficient in one case. Hypertensive headaches were sometimes relieved, but no permanent effect was noted on the blood pressure in hypertension. Kovaks, Saylor, and Wright (1936) gave mecholin by ionization and found it disappointing in hypertension, chronic arthritis, peripheral vascular occlusions, embolism, etc., but more satisfactory in causing healing of varicose ulcers and in cases of Raynaud's syndrome with ulcers, and in scleroderma. Cohn and Benson (1937) considered that mecholin by ionization was of definite value in relieving pain and increasing efficiency in three out of four cases of arteriosclerosis of the peripheral arteries of the leg and in seven of thirteen cases of thrombo-angiitis obliterans. Kramer (1937) obtained similar results in thirty patients with various types of peripheral vascular lesions. Kovaks (1934) treated various forms of chronic arthritis with mecholin by ionization. In addition to slight general effects, he noted local warmth and flushing, increased capillary flow, reduction of swelling, diminished pain, and increased freedom of movement. He considered it an alternative to other forms of physical treatment. Martin and Eaton (1937) obtained similar results. Rutenbeck (1936) gave doryl by ionization to cases of arthritis, muscular rheumatism, neuritis, pleurisy, paralysis, and habitual headaches, and reports favourable effects. Mecholin by ionization has given encouraging results also in thrombophlebitis.

INTESTINAL STASIS

Starr (1937) considered doryl more efficacious in relieving abdominal distension than mecholin. I have not found any satisfactory report of the use of doryl in a series of cases of post-operative intestinal atony and abdominal distension, but it is being used extensively for these conditions, and I know of surgical clinics in which its administration subcutaneously in doses of 0.25 mg. is a routine measure in post-operative distension. It should be followed in one hour by an enema, and if a satisfactory result is not obtained the treatment should be repeated and again followed an hour later by an enema if necessary.

RETENTION OF URINE

Schulze (1935) found the subcutaneous injection of 0.25 mg. of doryl successful in cases of retention of urine in the puerperium and following abdominal operations. As a rule the bladder is emptied twenty or thirty minutes later, and side effects are not troublesome. Moir (1937) reported success in twenty-two out of thirty-eight cases of post-operative and post-partum retention. Maxwell (1937) had successes in fifteen out of seventeen cases of retention following various surgical procedures. Officer and Stewart (1937) observed a considerable rise of intravesical pressure, and thought it useful in post-operative retention and deserving of further trial in retention associated with spinal cord injuries or tumours or diseases. My colleague, Dr. E. P. Sharpey-Schafer, has demonstrated a rise of intravesical pressure ending in extrusion of the catheter following the intramuscular injection of 0.5 mg. of doryl in a case of hysterical retention. Gernon, Ewert, and Herrold (1935) gave daily doses of 200 mg. of mecholin by the mouth in ten cases of bladder disturbance associated with diseases of the spinal cord, and reported that those with incontinence regained control and those with retention were able to empty the bladder but required continued treatment. They found the method encouraging in retention following resection of the prostate. Schulze (1932)

and Laube (1935) gave doryl by subcutaneous injection followed by oral administration in eclampsia, and considered that the flow of urine was increased and symptoms of eclampsia relieved.

OTHER SYMPTOMS

Starr (1936b) reported the relief of symptoms by mecholin in five cases of Ménière's disease. Gougerot and Albeaux-Fernet (1936) recorded improvement in alopecia following local injection of mecholin. Dameshek and Feinsilver (1937) consider that the failure of mecholin to produce its usual effects in scopolamine poisoning may be of diagnostic value.

There are two conditions in which these substances with actions imitative of parasympathetic stimulation might be expected to act beneficially—cardiospasm and megacolon, for in each a deficient parasympathetic action has been postulated. Starr (1937) found that doryl increased the oesophageal peristalsis in cardiospasm but did not relax the sphincter. I have been able to try doryl in doses of 0.25 and 0.5 mg. by intramuscular injection in a typical case. The oesophagus was shortened and straightened as from an increase of tone in the muscles and the peristaltic waves were increased in depth, but no relaxation of the sphincter occurred and the contents were not forced into the stomach. I have tried the effects of 0.5 mg. of doryl by intramuscular injection in one case of megacolon. The visible peristalsis was greatly increased, as judged by the appearance of the patterns on the abdominal wall; but no emptying of the colon occurred nor passage of wind, so that presumably the sphincters were not relaxed. No organic obstruction was present. From these observations it would seem that if the difficulty is due to achalasia of the sphincters, as Hurst maintained, and if the failure to relax is due to lack of parasympathetic action, as the work of Knight (1934) on the oesophagus suggests, then there must be some other factor that prevents the relaxation in spite of the powerful parasympathetic-mimetic action of the drug as seen in the increased tone and peristalsis.

SUMMARY

It seems clear that doryl and mecholin may have therapeutic value in a great variety of conditions and that many more observations are required before their uses can be defined. In spite of numerous reports on their administration for their vasodilator properties in various spastic conditions of the peripheral arteries and in chronic rheumatic states, the evidence for their value in these conditions is not convincing, apart from the temporary relief of pain. In chronic glaucoma and spastic conditions of the retinal arteries the reports of their use are more encouraging. In essential hypertension there is general agreement that they are valueless except for the relief they afford in some cases of severe hypertensive headache. At present their value appears to have been established for post-operative intestinal atony, for urine retention following surgical operations and labour and in lesions of the spinal cord, and for supraventricular paroxysmal tachycardia. The evidence so far is in favour of doryl in the first two conditions and of mecholin in the third.

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V. Sultzoff, E. L. Burns, M. Moskop, and L. Loeb (*Amer. J. Cancer*, February, 1938, p. 256) have studied in mice the effects on the vaginal and uterine cervical epithelium of repeated injections of oestrogen with and without anterior pituitary and lutein hormones. With advancing age the average depth of the epithelial processes extending from the surface epithelium of the vagina and cervix into the underlying connective tissue increases, but in only one of 128 control mice did the proliferative change become carcinoma-like. In oestrogen-injected mice the increase in depth of the epithelial processes was greater and occurred at an earlier age than in the control mice, and in twenty-five of 234 injected mice the processes passed through a pre-cancerous to a carcinoma-like growth. Large doses of oestrogenic substance in oil were more effective than smaller ones or than aqueous solutions. It was not certain that ovariectomy or hereditary factors acted as they do in the case of the mammary gland, but there were indications that mechanical factors causing erosions might take part in the development of the carcinoma-like growths. The theoretical implications of the experimental results are discussed.