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THE FAILURE OF RESPIRATION IN DEATH BY ANTICHOLINESTERASE POISONING

BY

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Many organic phosphorus compounds are now known which are potent inhibitors of cholinesterase, and all have high toxicities. A comprehensive list of such compounds has been published by Holmstedt (1951), and from this we can distinguish several substances which have proved to be biologically interesting and important, such as di*iso*propyl phosphofluoridate (DFP), diethyl *p*-nitrophenyl phosphate (E600; "Mintacol"), ethyl NN-dimethylphosphoramidocyanidate ("Tabun"), *iso*propyl methylphosphonofluoridate ("Sarin"), 3 : 3-dimethyl-*n*-butyl 2-methylphosphonofluoridate ("Soman"), and tetraethyl pyrophosphate (TEPP).

All these compounds produce qualitatively similar effects when administered to mammals. A lethal dose produces the following picture in the conscious animal. There is muscular fasciculation, followed by violent incoordinate convulsive movements, prostration, gasping respiratory movements and signs of "air hunger," engorgement of the veins, and often micturition and defaecation. Unconsciousness follows, respiration ceases, the heart slows and the pupils may contract (miosis always occurs early if the eyes are exposed directly to the drug). Then the skin capillaries collapse and finally the heart ceases to beat.

At autopsy the picture is similar whatever the method of administration. The diaphragm is elevated, with the lungs usually collapsed and ischaemic athough occasionally they are congested. There is spasm of the small intestine and the abdominal viscera, with peritoneal effusion, and the spanchnic veins are engorged with dark venous blood. The right heart is distended and the left ventricle is often empty. Apart from the "venous" colour of the arterial blood, the brain is generally normal in appearance, but there are sometimes a few petechiae in the brain substance.

The general picture in all the species studied—mouse, rat, guinea-pig, rabbit, cat, dog, monkey, sheep, and goat—is characteristic of the asphyxial state and it is evident that failure of respiration is the predominant effect produced by intoxication with an anticholinesterase (DFP, E600, tabun, sarin, soman, TEPP).

There is, however, no general agreement as to how the final respiratory failure occurs. Failure of the respiratory control mechanism in the central nervous system has been suggested as the dominant factor (Modell, Krop, Hitchcock, and Riker, 1946; Freedman and Himwich, 1949); others stress the part played by bronchospasm, stating that this by itself can prove fatal (Koppanyi, 1948); others again are of the opinion that neuromuscular paralysis may be a significant factor (Riker and Wescoe, 1949). The evidence for each of these three possible causes will be considered separately.

Whatever the cause of the respiratory failure may be, it usually leads, in absence of treatment, to death from asphyxia.

Treatment is along two lines—application of artificial respiration and administration of atropine. Conjointly, these are more effective than is either course separately. Although atropine is only able to counteract the muscarinic actions of acetylcholine its efficacy in restoring the respiratory centres to an adequate state of activity is unquestionable (Douglas and Matthews, 1952).

METHODS

Experiments were carried out on cats, dogs, rabbits, monkeys, sheep, goats, mice, rats, and guinea-pigs. Eserine, DFP, E600, tabun, sarin, soman, and TEPP were chiefly used. Administration has been most commonly by intravenous injection or by inhalation. For some purposes we have used subcutaneous, intramuscular, intra-arterial, and intracisternal injections;

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injections into special parts of the C.N.S. by microsyringe; instillations into the conjunctival sac, and applications to the clipped or depilated skin.

Phenobarbitone or pentobarbitone intraperitoneally, or urethane intravenously, were the anaesthetics most commonly used. Some cats were decapitated under ether and given artificial respiration.

Respiratory volumes were recorded by a water-floated counterpoised spirometer; diaphragm contractions by the phrenograph described by de Candole, Douglas, and Spencer (1950); intrapleural pressure by an intraoesophageal balloon, or by a pleural cannula; and intra-abdominal pressures by a balloon inserted at the midline. Arterial pressures were recorded from the femoral artery by a Hg manometer. Intravenous injections were made into the femoral vein.

Nerve action potentials were amplified by a five-stage AC coupled amplifier and were photographed from the cathode-ray tube face.

Other methods used are described in the appropriate parts of the text.

Results

The Production of Bronchoconstriction.—One salient feature of anticholinesterase poisoning in experimental animals is a lessened inflatability of the lungs. The effect has been observed in various species with such compounds as DFP (Modell *et al.*, 1946; Heymans and Jacob, 1947), HETP (Dayrit, Manry, and Seevers, 1948), TPP (Verbeke, 1949), and tabun (Holmstedt, 1951), and is often of such severity as to be suggested as the cause of death (Koelle and Gilman, 1949). This lessened distensibility of the lungs is generally attributed to bronchoconstriction.

The occurrence of bronchoconstriction in anticholinesterase poisoning has been demonstrated radiographically. Rabbits were anaesthetized with urethane, 0.5 ml. of lipiodol introduced into the exposed trachea, and its spread watched on a fluorescent screen. With sarin, given intravenously, evidence of narrowing of the respiratory tubes was obtained at all dosage levels. With 100 μg./kg. sarin, narrowing of the bronchi and of all sizes of bronchioles occurred, and this was maximal 1 min. after the injection.

A quantitative evaluation of the degree of bronchoconstriction has also been attempted in rabbits. The animals were anaesthetized with urethane and were maintained on negative pressure ventilation by enclosing them in a Drinker-type machine which permitted a rhythmical reduction of pressure, constant in rate (52/min.) and extent, throughout the experiment. The chest was opened by splitting the sternum in the mid-line and the tidal air was measured by connecting the tracheal cannula to a rebreathing circuit comprising a soda-lime canister, gas circulator, and small recording spirometer. The artificial respiration was adjusted so that spontaneous respiratory movements continued.

After 40 μg./kg. sarin, intravenously, the pattern of response was similar in 12 out of 14 rabbits, the tidal air falling away within half a minute of the injection, reaching an average minimum value of 40% of normal at about 2 min., and thereafter gradually increasing, so that by the third minute the tidal air was 55% of normal. In the other two rabbits the tidal air was only transiently diminished and the minute volume was hardly affected. The reason for this different behaviour was not apparent; both these animals showed other characteristic signs of anticholinesterase poisoning, such as muscular twitching and the cessation of spontaneous respiratory movements.

Bronchoconstriction has been demonstrated in the decapitate cat and in the dog heart-lung preparation. In the latter, however, the addition of acetylcholine to the circulating blood may be required. The explanation of the bronchoconstriction in anticholinesterase poisoning has been disputed. It has been attributed to an action on the vagal ganglion cells (Verbeke, 1949; Heymans, 1949) or to a direct action on the effector cells (Koelle and Gilman, 1949) or to the accumulation of acetylcholine at the vagal postganglionic nerve endings (Koelle and Gilman, 1949).

By the use of twin preparations of guinea-pig trachea (permitting the necessary control observations) it has been shown that sarin, DFP, and TEPP, in high dilution, not only sensitize the isolated muscle to acetylcholine, but throw it into spasm just as eserine does. Their tracheal spasmogenic potency parallels their ability to inhibit cholinesterase (Koppanyi, Karizmar, and King, 1947), and the tracheal contractions induced show features—such as long latency and slow development—which have been held to characterize drugs acting indirectly by permitting the accumulation of acetylcholine (Adrian, Feldberg, and Kilby, 1947).

There is no doubt, therefore, that anticholinesterases can produce bronchoconstriction, but it is doubtful if this is the main, general cause of failure of ventilation. Furthermore, although failure of respiration is the cause of death in all species, the severity of the bronchoconstriction produced by sarin, tabun, E600, DFP, and TEPP seems to vary with the species, being, at the time of acute failure, slight in rabbits, severe in cats, and often insignificant in monkeys. Thus, although in rabbits the degree of bronchoconstriction pro-

duced by sarin reduces the tidal air to 40% of normal 2 min. after poisoning, the bronchoconstriction produced in cats (pentobarbitone anaesthesia) by tabun, sarin, E600, DFP, and TEPP is much more severe. Records of tidal air, intrapleural pressure, and phrenic nerve discharge show that immediately after injecting one of these drugs a marked degree of bronchoconstriction develops. The cat then makes more powerful inspiratory efforts and the tidal air increases again, but then respiration ceases abruptly (Fig. 1). With a large dose of anticholinesterase, bronchoconstriction may be complete, inspiratory efforts continuing without any resulting air intake.

In the monkey anaesthetized with pentobarbitone, the bronchoconstriction produced by the compounds listed develops more slowly than in the cat and does not become so severe. It seems evident, therefore, on the basis of the data presented, that the failure of ventilation after intoxication with an anticholinesterase cannot be attributed solely to loss of distensibility of the lungs from bronchoconstriction. Can it be explained by an insufficiency of the respiratory "bellows" mechanism?

Production of Neuromuscular Block.—The activity of the respiratory muscles during anticholinesterase poisoning has been studied in some detail in the rabbit anaesthetized with urethane. In one series of experiments the phrenic nerve was stimulated supramaximally at 50–70/sec. every other second and the diaphragm contractions were recorded by means of the phrenograph, the rabbit being artificially ventilated with the chest open. Fig. 2 shows that, within 5 seconds from the end of the intravenous injection of 40 μg./kg. sarin, the height of the tetanic response of the diaphragm to stimulation of the phrenic nerve was much reduced. Ten seconds after the injection the diaphragm had ceased to respond tetanically, giving only a single twitch to the first of each train of impulses. A well maintained tetanus could, however, still be obtained by direct stimulation of the diaphragm. As would be expected, the twitch response of the diaphragm to single shock stimulation of the phrenic nerve (one

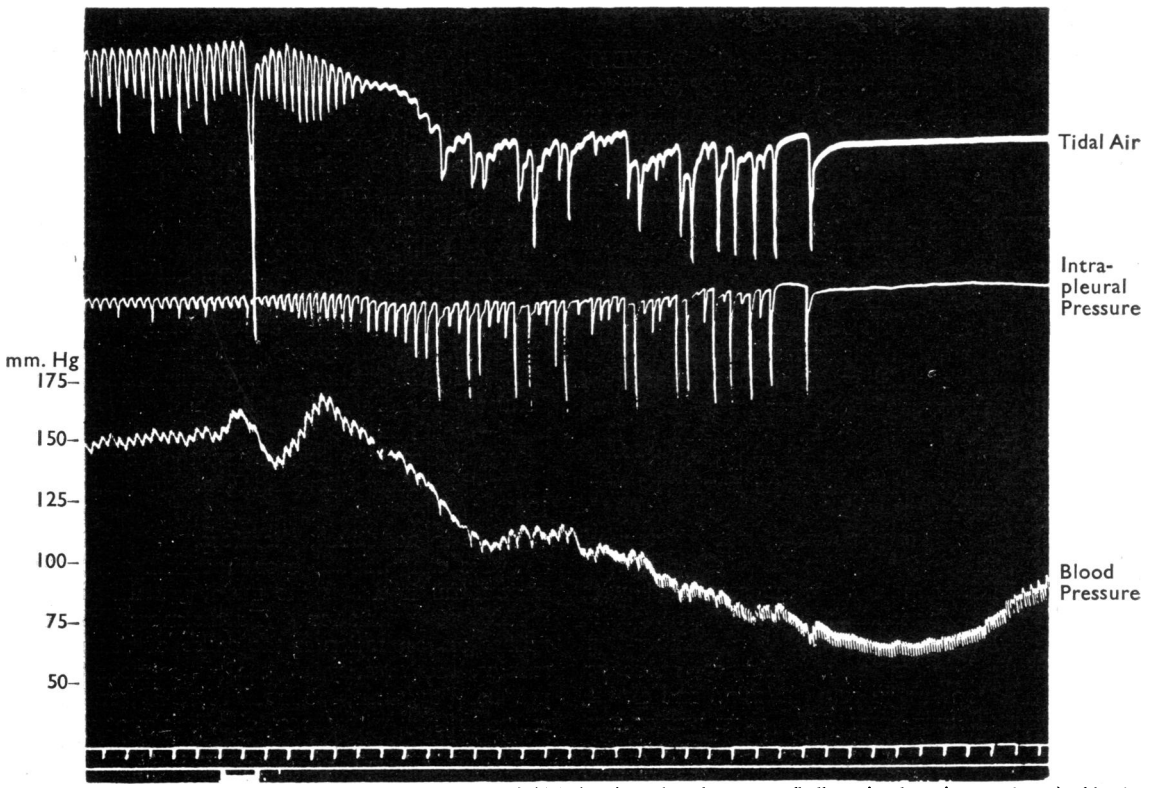

FIG. 1.—Cat, pentobarbitone. Records, from above down, of tidal air; intrapleural pressure (balloon in thoracic oesophagus); blood pressure (femoral artery). E600, 1.5 mg./kg. injected intravenously at signal. Time-marker, 5 sec.

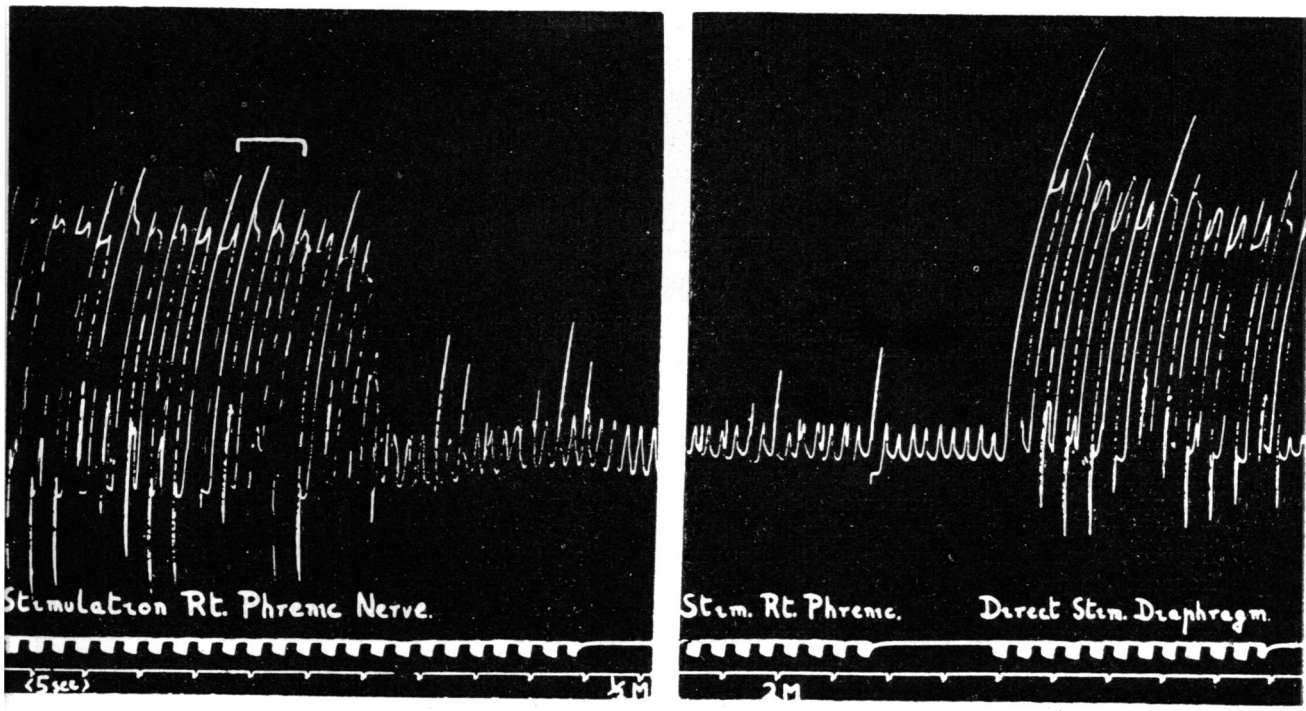

FIG. 2.—Rabbit, urethane, open chest. Contractions of diaphragm (recorded by phrenograph) in response to repetitive stimulation of right phrenic nerve. 40 μg./kg. sarin injected intravenously at upper signal. The effect of direct stimulation of the diaphragm 2 min. 20 sec. from the injection is shown on the right. (The small pointed waves were caused by displacement due to the artificial respiration.)

stimulus every 10 sec.) was not abolished by 40 μg./kg. sarin, being first increased and then only slightly reduced.

The block to rapidly repeated indirect stimulation (an example of Wedensky inhibition; Wedensky, 1885; Adrian, 1913) has also been found to occur in the isolated phrenic-diaphragm preparation of the rat (Bülbring, 1946) with eserine, neostigmine, DFP, TEPP, tabun, sarin, soman, E600, and other anticholinesterases (Evans, 1951). On washing, the inhibition from eserine and E600 was removed easily, from TEPP more slowly, but from DFP only when the concentration was low and the exposure time short.

Thus, undoubtedly, neuromuscular block can and does develop rapidly after sufficiently intense anticholinesterase poisoning, but the results from the isolated diaphragm, and from the stimulation experiments described above, cannot be taken to apply generally to the intact animal breathing spontaneously. Repetitive stimulation of the phrenic nerve for some considerable time before the injection of the drug would result in an abnormally high activity of the acetylcholine neuromuscular transmission mechanism and thus predispose it to block (see, for example, Burns and Paton, 1951). Such stimulation would also be expected to cause vasodilatation in the diaphragm, perhaps resulting in a greater amount of the drug reaching the muscle than would normally be the case. Moreover, if neuromuscular block were the sole cause of respiratory failure, it would be difficult to account for the action of atropine in preventing death from anticholinesterase poisoning, since atropine does not relieve the neuromuscular block caused by anticholinesterase drugs.

It is therefore necessary to study the results of experiments in which the physiological state of the animal was undisturbed until the immediate effects of the drug were over. The right phrenic nerve in the neck of a rabbit was placed on silver-silver chloride stimulating electrodes, *but was not cut.* Sarin, 40 μg./kg., was injected into the femoral vein, and, immediately after spontaneous respiration had ceased, the phrenic nerve was stimulated supramaximally at 30/sec. for periods of 1 second, the diaphragm response being recorded by the phrenograph. Control diaphragm contractions were obtained at least 5 min. before the injection by stimulating the nerve during the apnoea following forced hyperventilation. The stimulus rate was 30/sec., because this is about the

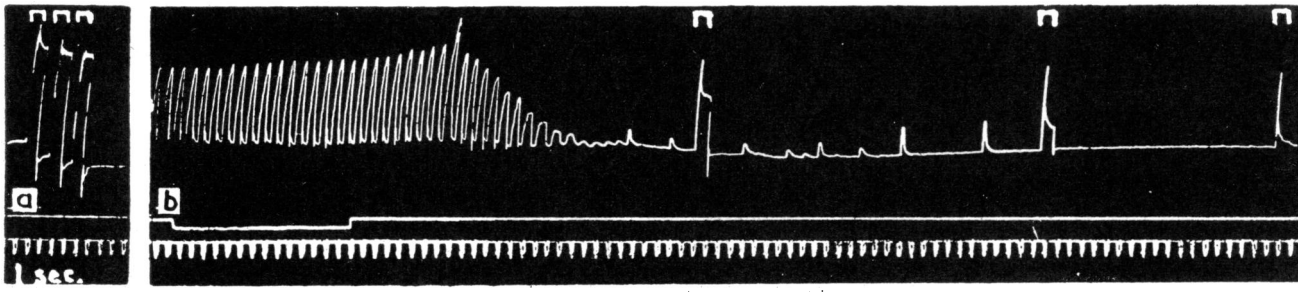

FIG. 3.—Rabbit, urethane. Closed chest, normal respiration. Diaphragm contractions (phrenograph). *a*.—Control response to repetitive stimulation of right phrenic nerve during apnoea after forced hyperventilation. *b*.—Spontaneous diaphragm contractions and responses to stimulation (upper signal) after sarin 40 μg./kg. intravenously at signal. Time, 1 sec.

normal rate of discharge of the spontaneous diaphragm action potentials of an anaesthetized rabbit breathing quietly. In a study of neuromuscular block this would be important, since any developing block at the neuromuscular junction will prevent the transmission of stimuli of higher frequencies while still allowing those of normal frequency to pass.

In rabbits given sarin 40 μg./kg. the development of neuromuscular block varied considerably without parallel variations in the picture of respiratory failure. In some experiments there was little, if any, block at the diaphragm after spontaneous contractions had ceased, whereas in others (Fig. 3) neuromuscular block developed more rapidly but was still not sufficient to account for the initial rapid reduction in diaphragmatic activity.

Production of Central Respiratory Failure.—Since neither neuromuscular block at the diaphragm nor bronchoconstriction appears to be the sole cause of respiratory failure in the rabbit, experiments were done in which the action potentials in the upper root of the right phrenic nerve and the diaphragm contractions of the opposite side were recorded. Figs. 4A and 4B are records of a typical experiment, and show that there is a rapid diminution of the impulse traffic in the phrenic nerve after the injection of sarin, 40 μg./kg., with no further discharge after the diaphragm contractions and resultant air intake have stopped. It would appear from this that the respiratory motor neurones have ceased firing and that the diaphragmatic paralysis results from this and not from a peripheral block.

This central action is also shown with the other anticholinesterases used, although there may be differences in the relative rates at which they stop the central discharge and produce block at the neuromuscular junction. Tabun, 0.15 mg./kg. i.v., resulted in complete neuromuscular block at the rabbit diaphragm 15 sec. after the injection. This led to an *increased* phrenic nerve discharge from central stimulation by asphyxia and by vagal or other afferent nervous discharge (Daly and Wright, 1953). The stimulation, however, was insufficient to overcome the gradual depression of phrenic nerve discharges from the direct effect of the drug on the central respiratory mechanism, which caused the phrenic nerve impulses to cease 25 sec. from the injection. DFP, 4 mg./kg. i.v., stopped the central discharge of a rabbit 14 sec. from the start of the injection, thus resembling sarin (40 μg./kg.), whereas E600 (1.5 mg./kg.) and TEPP (300 μg./kg.) resembled tabun in that neuromuscular block developed rapidly before central failure had occurred.

Apart from any possible variations due to different rates of penetration of the various drugs, the relative rates of development of central inhibition and of neuromuscular block depend on the dose given. Daly and Wright (1953) have shown that with 30 μg./kg. sarin the discharge in a single

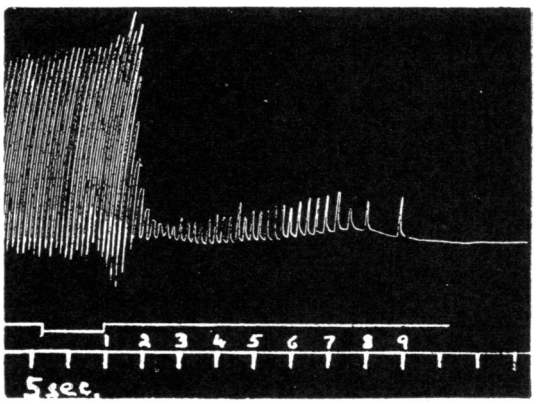

FIG. 4A.—Rabbit, urethane. Closed chest, normal respiration. Diaphragm contractions (phrenograph). Sarin, 40 μg./kg., injected intravenously at signal.

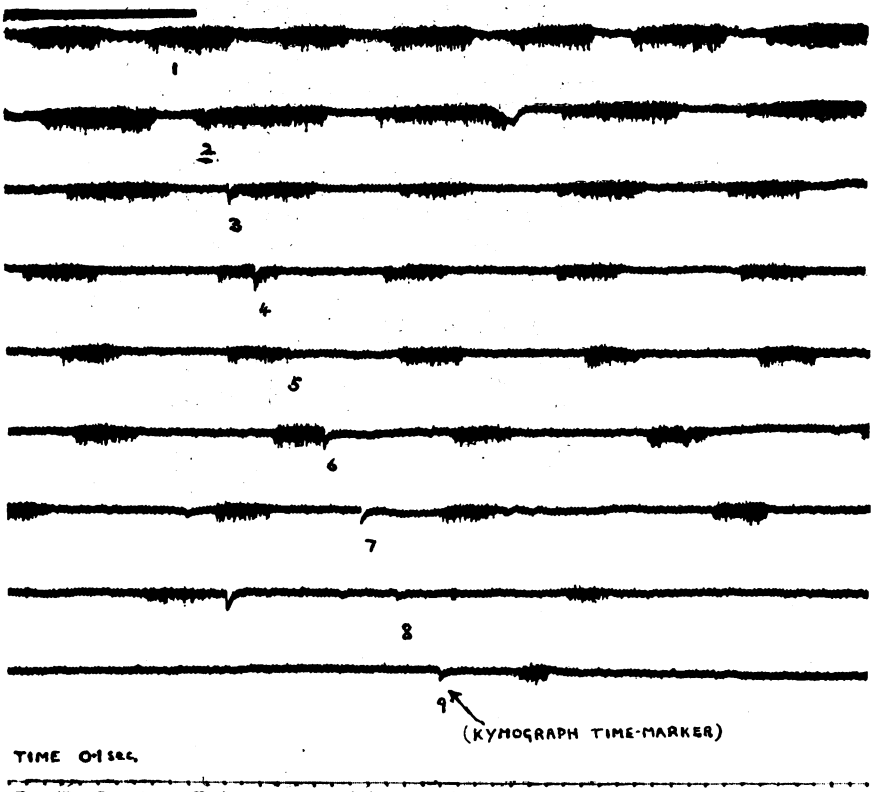

FIG. 4B.—Impulse traffic in upper root of right phrenic nerve associated with phrenogram of Fig. 4A. Numbers correspond to kymograph time-marker in Fig. 4A.

phrenic nerve fibre of a rabbit first increases before it finally fails. This has been confirmed, but with 40 μg./kg. the discharge has been found to fall off immediately without any initial increase. Both effects are shown in Fig. 5.

Species Variations in Response.—From the effects of anticholinesterase drugs on the respiration of rabbits described above, it can be concluded that respiratory failure is due primarily to an action of the drugs on the central respiratory mechanism, often associated with a considerable degree of neuromuscular block at the diaphragm. The chest muscles are less affected, so that chest movements of some magnitude may appear before and until the central inhibition is complete. Bronchoconstriction is variable but not usually severe in rabbits or monkeys.

As indicated above, a similar picture is not seen in other species. The most immediate effect of anticholinesterase poisoning in the cat is a marked bronchoconstriction. The consequent anoxia and hypercapnia cause a stimulation of the respiratory centre, and inspiratory efforts continue until the central discharge ceases abruptly.

According to Douglas and Matthews (1952), the factors responsible for respiratory failure in the cat poisoned with TEPP are paralysis of the respiratory muscles and failure of the respiratory centre, bronchoconstriction playing a secondary role. However, experiments with sarin, tabun, E600, DFP, as well as with TEPP, show that the neuromuscular block is only of secondary importance. Thus (Fig. 1) the large intrapleural pressures which develop after poisoning would not be possible if the respiratory muscles were inactive as a result of neuromuscular block. It was found

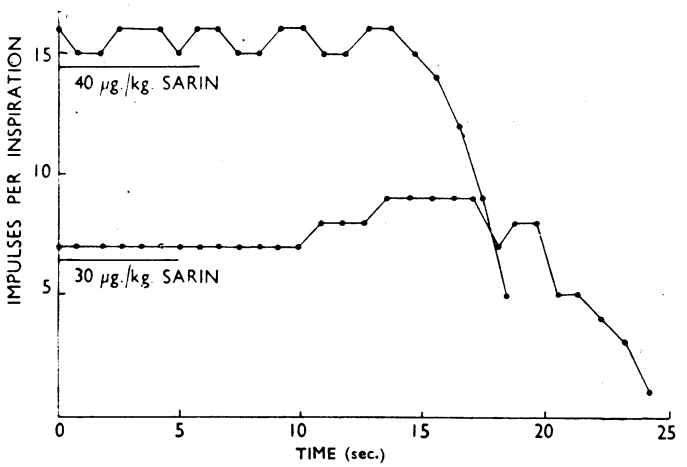

FIG. 5.—Rabbits, urethane. Impulses per inspiration in single phrenic nerve fibres of two rabbits, one given 30 and the other 40 μg./kg. sarin intravenously. The black line under each curve indicates the injection.

in some experiments that neuromuscular block did become complete at the diaphragm, but the picture of respiratory failure was nevertheless not changed, the important factor being that the chest muscles remained active. To demonstrate this, three experiments have been done with TEPP (0.3 mg./kg.) and two with E600 (1.5 mg./kg.) in which both phrenic nerves were cut before poisoning. The diaphragm was thus completely flaccid, but, until after the injection of the drug, adequate ventilation was maintained by the chest muscles alone. All five experiments showed the same result, of which Fig. 6 is an example.

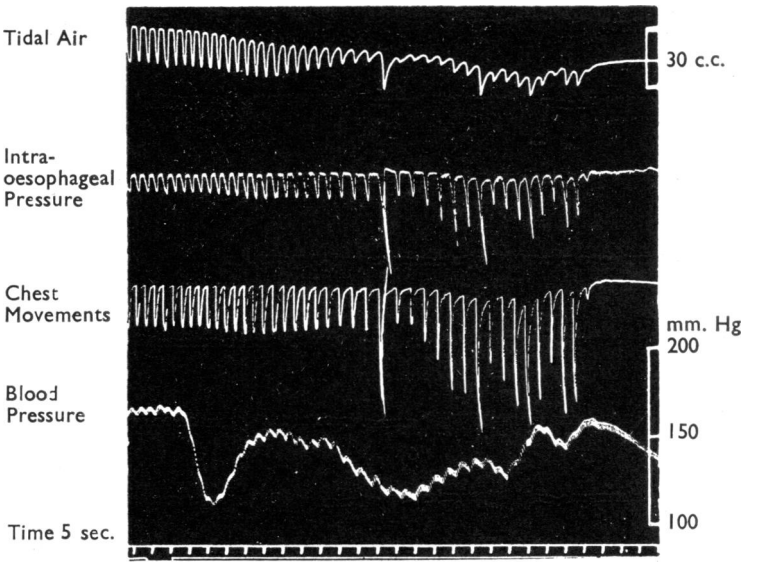

FIG. 6.—Cat, pentobarbitone. Closed chest, spontaneous respiration. Both phrenic nerves cut. Records from above downwards: tidal air, intrapleural pressure (intra-oesophageal balloon), chest movements (stethograph) (inspiration downwards for all three), blood pressure. Time, 5 sec. TEPP 300 μg./kg. intravenously at signal.

Even in this experiment where the chest muscles are more active than normally, there is evidently no significant degree of neuromuscular block; the immediate effect of the TEPP is to cause a marked bronchoconstriction, as shown by the increased intrapleural pressures with reduced air intake.

In monkeys respiratory failure in acute anticholinesterase poisoning, with all drugs used, appears to result entirely from inhibition of the central respiratory mechanism. The failure of respiration is characterized by a gradual reduction in the depth of inspiration, followed by an expiratory tone and forced expirations which pass off into apnoea (Fig. 7).

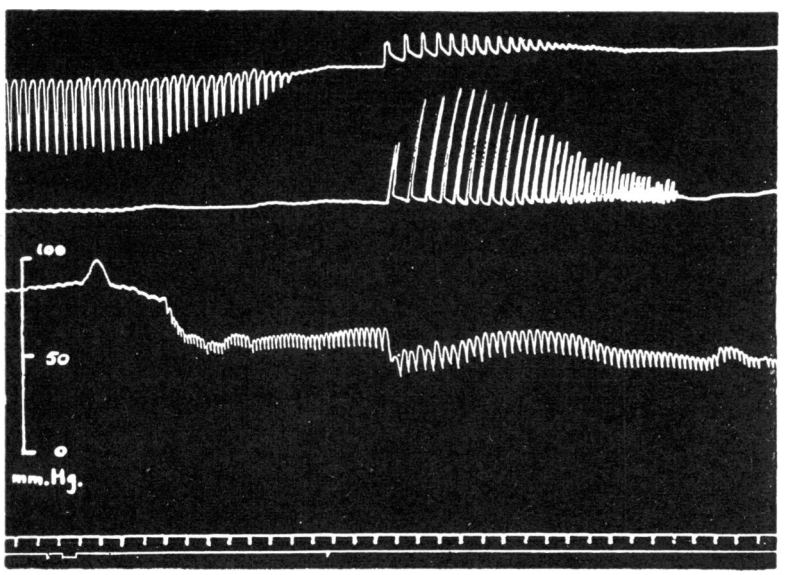

FIG. 7.—Monkey, pentobarbitone. Records from above down: tidal air; intra-abdominal pressure (inspiration downwards in both); blood pressure. Time, 5 sec. TEPP 250 μg./kg. intravenously at signal.

With lower doses of the drugs, the central inhibition is overcome by asphyxial stimuli, and, after periods of apnoea of up to 3¼ min., the apnoea is broken by inspiratory gasps. With sarin the inspiratory rate and depth gradually return to normal, but with E600 and TEPP, although the initial failure of respiration is the same as with sarin, the succeeding gasps are not so deep, and a record of diaphragm action potentials clearly shows some Wedensky block. The gasps were possibly not maintained with these two drugs because the air intake was insufficient to enable the severely strained heart to recover from anoxia.

That the initial inhibition of inspiration results only from a central action of the

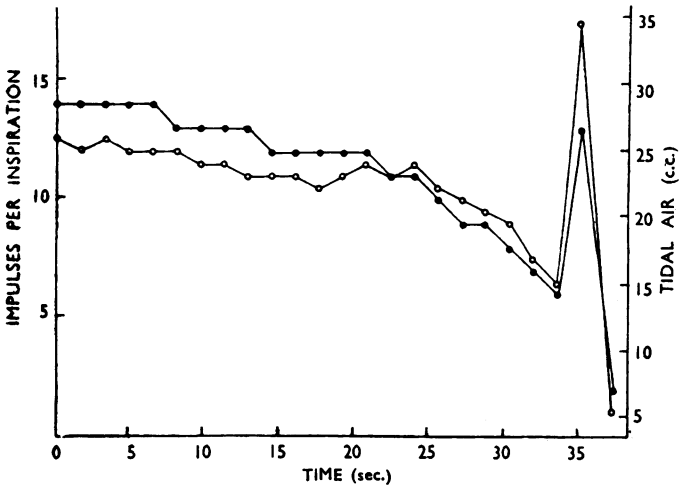

FIG. 8.—Monkey, pentobarbitone. Closed circles: impulses per inspiration in single phrenic nerve fibre (left-hand ordinate). Open circles: associated tidal air (right-hand ordinate). The curves start at the end of the injection of sarin 30 μg./kg. intravenously.

anticholinesterase is shown by the parallel reduction in impulse traffic in the phrenic nerve. If the reduction in air intake were due to bronchoconstriction or neuromuscular block, or both, the phrenic discharge would increase while the tidal air decreased. Fig. 8 shows that the number of impulses per inspiration in a single fibre of the phrenic nerve parallels very closely the air intake for each inspiration in the course of respiratory failure from sarin (30 μg./kg., i.v.).

The action of the anticholinesterase drugs in incapacitating the central respiratory mechanism is probably not due to reflex influences from the periphery, since injection of the drugs into the cisterna magna or into the vertebral artery of the dog also causes respiratory inhibition although the doses were so small (5 μg.) that no peripheral effects occurred. Nor does the respiratory inhibition appear to be due to repetitive excitation of the central vagal neurones (cf. Dirken and Woldring, 1951), since no increase in discharge from the central end of the vagus nerve was found at the time of failure of the phrenic nerve discharge. There were, however, abundant discharges down the vagus after inspiration had stopped, and in the monkey these coincided with the forced expirations (Fig. 7). If the inspiratory centre were inhibited reciprocally by activation of the expiratory centre, the respiration would be expected to change gradually to the forced expiratory type. Some of the kymograph and electrical records suggest, however, that the expiratory activity occurs *after* the inhibition of inspiration, and is therefore the result, not the cause, of the inhibition.

The respiratory inhibition could be explained as being due to direct inhibition of the phrenic motor neurones; but, if this were so, some large-scale inhibitory mechanism must be assumed, since the phrenic discharges, the inspiratory intercostal activity, and the "inspiratory" impulses in the recurrent laryngeal branch of the vagus all run and cease in parallel. The alternative, and more probable, explanation is that the "respiratory centre" itself is inhibited either directly or as a result of inhibitory impulses from some other part of the central nervous system.

Other Possible Factors Affecting Respiration.—There is another possible mechanism of respiratory failure which must be considered. The anticholinesterases may cause a profound fall in blood pressure, and it is conceivable that, with large doses, the blood pressure may be lowered to such a degree that the respiratory centre would fail because its blood supply proved inadequate. Thus, using cats anaesthetized with pentobarbitone, it has been shown repeatedly that 200 μg./kg. sarin intravenously will cause a rapid depression of the blood pressure to about 30 mm. Hg, but that the heart continues to beat, and to maintain circulation, for several minutes after respiration has stopped. On only one occasion was the heart stopped by sarin, and this was only transitory. Then a picture reminiscent of vagal inhibition and escape was seen. In spinal cats it was found that when the animal was maintained on a respiration pump the heart continued to beat after doses of sarin of 2,000 μg./kg.

However, the circulation might be slowed to such an extent that the respiratory centre failed owing to anoxia. The conditions of such anoxic failure of breathing were studied. The circulation in a cat was stopped completely by tightening a loose ligature which had been placed around the pulmonary artery. The last respiration occurred 150 sec. after tightening the ligature, which is about equal to the longest time ever seen for continuation of respiratory efforts following these large doses of sarin.

In the poisoned animals the blood pressure is depressed, but not completely abolished as it is in the control experiment. Therefore, in another experiment, the blood pressure of a cat was lowered by haemorrhage to 30–40 mm. Hg on two occasions, the first time for 180 sec. and, a

few minutes later, for 270 sec., the pressure being restored at the end of each period by re-injecting the blood into the circulation. Respiration continued throughout these periods. Thus it is clear that failure of the circulation is not adequate to explain the failure of respiratory effort. A further indication of this is the fact that, although respiratory arrest occurs in the rat poisoned with an anticholinesterase, the drug causes a large rise in blood pressure in this species.

One of the most striking effects of the anticholinesterase drugs in the conscious animal is the violent convulsions which occur. It was shown by Wescoe, Green, Macnamara, and Krop (1948) that DFP produces convulsive EEG patterns in curarized cats and monkeys, and it might be supposed that such a result might affect the picture of respiratory movements. During anticholinesterase poisoning from intravenous injection the respiration of conscious monkeys has been recorded using a face mask made air-tight with petroleum jelly and connected through valves to a spirometer. Respiratory failure occurred in the same general way as described above for the anaesthetized monkeys, though the picture was complicated by the addition of the convulsive movements.

Another central effect of the anticholinesterase drugs is an action on spinal cord reflexes (for review see Gerard, 1950). Chennells, Floyd, and Wright (1949), using myographic methods, found that TEPP facilitates various reflexes (knee jerk, flexor, peroneal and crossed extensor) and induces convulsions. The effects were due to a direct action of the drug on the central nervous system. The intravenous injection of a large dose of sarin (200 μg./kg.) to cats abolishes, within about 20 sec., the monosynaptic spike of the ventral root response elicited by maximal stimulation of the dorsal root. This is followed by inhibition of the polysynaptic spikes.

Holmstedt and Skoglund (1953) have obtained a similar inhibition of the monosynaptic spike following the intra-arterial injection of small doses of tabun, but find that there is an associated increase in the polysynaptic spikes. With intra-arterial DFP, both the monosynaptic and polysynaptic spikes were facilitated.

Summary

1. The effect of various anticholinesterase drugs in producing respiratory failure in mammals has been analysed.

2. All the drugs studied can impair ventilation in three main ways: by producing (1) bronchoconstriction, (2) neuromuscular block, and (3) central respiratory failure.

3. The central failure seems to be the predominant factor in most instances, but the detailed picture varies with the species studied, the drug used, and the dosage administered. Thus, in the rabbit, bronchoconstriction is slight and develops slowly, while neuromuscular block may be severe at the diaphragm but is less marked at the chest muscles. In the cat, bronchoconstriction may be early and severe, and again, although neuromuscular block may occur at the diaphragm, the chest muscles retain their activity until central failure occurs. In the monkey, central failure appears to be the sole cause of cessation of ventilation, the bronchoconstriction and neuromuscular block being insignificant at the time of respiratory failure.

4. The depression of the activity of the respiratory centre is apparently due to an action of the anticholinesterase within the central nervous system.

5. Atropine will protect against the central inhibition and the bronchoconstriction, and artificial ventilation will maintain life in the presence of neuromuscular block.

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