traction of 73% using the guinea pig ileum, acetylcholine and its (RC) analogue require equal doses, but the (RC) analogue requires 250% longer than acetylcholine, and this difference is even more marked at lower dosage levels. In short, although the dose total-response curves are identical within statistical limits, the dose rate-of-response curves are quite different. This brings up the old question: Which—rate of response or final effect—is a more reliable measure of drug receptor fit? Assuming permeabilities and other factors effecting drug transfer to the receptors to be identical for both agents, then acetylcholine appears to "fit" the receptor more readily, as its effect is more prompt. One might, however, argue that the (RC) analogue "fits" just as well, or perhaps better, but it does not so easily gain access to the receptor machinery, thus accounting for the lag in its relative rate of effect. Arguments of this kind, although didactically fruitful, hardly seem profitable at this stage unless operational procedures clarify the questions concerning transfer.

As noted previously (*1*), the reversal of the carboxyl group of acetylcholine, a modification which leaves over-all molecular dimensions unchanged and also introduces little change in the distance relationships of the oxygen groups to the nitrogen head (*5*), effected relatively little apparent change in the drug-muscarinic and nicotinic receptor relationships. Actually, however, a fuller notion of the extent of this change becomes apparent in the study of parallel derivatives in the two series. Further, this study indicates that moieties imbedded within a molecular matrix continue to manifest their presence in a pharmacologic sense, though the quantitative expression of their activity is greatly modified by the impedance of other groups. For example, in the double analogues Nos. 5, 6, and 8, the presence of methylated nitrogen heads held in a given relationship to oxygen groups was manifested through a greater or lesser degree of muscarinic activity, even though these analogues are far removed, in a whole molecule sense, from acetylcholine. At first this might seem to be a mere statement of the "whole-molecule-fit" concept in other terms. Actually it represents a quite different point of emphasis, in which the working unit is a group of chemical constitutional characteristics abstracted from various active molecular species and in which other molecular features are thought of as perturbing factors.

This mode of abstraction is, of course, well recognized in other fields. For example, in chemistry we ascribe certain reactions as typical of aldehyde, hydroxyl, and amino groups which are in given compounds impeded or modified to a greater or lesser extent by the presence of other constitutional features of the molecule. One finds it helpful to approach given cases as deviating from the general for various specific reasons rather than as isolated instances. In a similar manner one may visualize the receptor as an entity which places certain positive requirements upon drugs for activity but places no definite negative requirements other than that the interaction of the moiety not be impeded. Impedance may take many forms, such as steric interference, the presence of other groups exerting electrostatic field effects that prevent the approach of the molecule containing the moiety to the receptor surface, etc. If, on the other hand, one requires the whole molecule to "fit," then all parts of drugs Nos. 5, 6, and 8 must find appropriate places on the receptor, and this would necessarily need to be true for all materials possessing muscarinic activity. What a variety of materials this receptor would have to be able to accommodate totally! Returning to the moiety-fit point of view, in terms of a historic example, a given lock may be opened by many different keys provided the given projections of the key are present to turn the given tumblers of the lock. If extra projections are present, these need not also have tumblers corresponding to them in the lock. They merely must not get in the way of the projections that do correspond to the tumblers.

In the present instance, although chemically parallel derivatives in the acetylcholine series and the (RC) analogue series are frequently parallel in their pharmacologic actions, the occurrence of striking deviations from parallelism indicates that the interchange of the components of the carboxyl group effects an alteration in the drug-receptor relationships.

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A New Versatile Respirator

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The relative merits of the multitude of artificial respirators for animal experimentation may perhaps best be evaluated on the basis of simplicity of construction, ease of control, and versatility of use. The oldest and most widely used design is the electric motor-driven mechanical pump. Only the most complex and expensive custom-built models have any real degree of ease of control and, even then, almost invariably must be stopped to alter the stroke volume which, in turn, is clearly limited by the dimensions of the cylinder. No commercial model has any provision for altering the ratio of time of ventilation to time of exhaust.

In recent years, a number of respirators have been produced which function by opening and closing a valve in an air supply line; these valves, which may be rotary- (*1, 2*), sleeve-, slide-, or piston-type (*3*), are, in some models, activated by air-driven motors (*1, 2*); others are driven by electric motors through

gear trains, double-cone pulleys (*4*), or other speed-reducing and -changing arrangements. This general design affords ease of control in that stroke volume is dependent upon the pressure of the air supply, the size of the leak aperture, and the length of time the valve is open. In this, as in the earlier type, most designs have no means for adjustment of the on–off ratio.

Another design is one in which air is allowed to leak through a small opening, first through a pressure-sensitive switch and then into the animal's trachea. When the intratracheal pressure reaches a predetermined maximum value, the switch, either electrical or mechanical, is thrown, which in turn cuts off the air supply and allows the lungs to exhaust until the pressure reaches another predetermined minimum value, whereupon the cycle repeats. In this type of respirator, tremendous possibilities for variation exist, with all factors interdependent to some extent. Rate is controlled largely by the air supply line pressure and the leak aperture but is generally affected by the characteristics of the animal being treated; stroke volume is dependent upon the pressure-sensitive switches and the animal. The simplest design in this category is the ingenious Burns Pneumatic Balance Resuscitator (*5*); the unit is compact and lightweight, but in its standard form only the input pressure is adjustable.

A series of rather novel respirators has appeared in the literature. One consists of 2 bulbs of the type commonly used to inflate a blood pressure cuff. These bulbs are pressed and released by a motor-driven lever; one pumps air to, the other from, the animal (*6*). Another design uses motor-driven cranks to raise and lower closed reservoirs of mercury to effect pumping action through water valves (*7*).

The new type of respirator herein described fits into the second category but was designed to meet stringent requirements of extreme versatility in volume, rate, and in–out ratio, as well as compactness and simplicity.

A block diagram (Fig. 1) shows the main components and their relation to one another. The timer may be any of the self-cycling designs which range from double clockwork types to electronic condenser discharge circuits or delay-action relay combinations. Fig. 2 shows the self-cycling timing circuit found to be most satisfactory from the standpoints of stability, simplicity, reliability, and cost. It is entirely electronic and depends upon the time required for a condenser

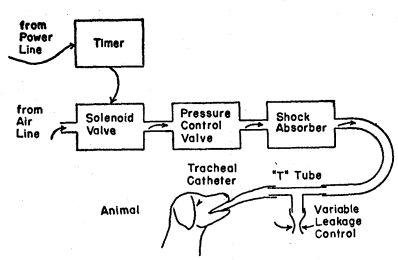

FIG. 1. Block diagram showing main components of the respirator and their relations to one another.

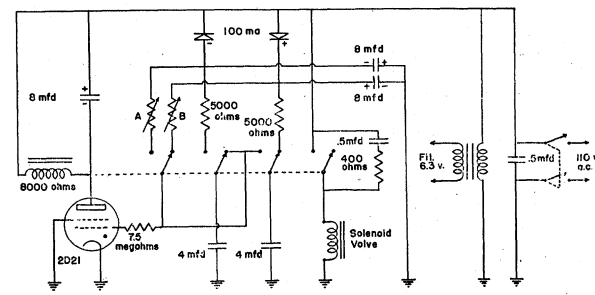

FIG. 2. Electrical circuit of the timer. The relay is a 4-pole double-throw type; all contacts are shown in the deenergized position. Resistor *A* controls the time during which the solenoid valve is open; resistor *B*, the time it is closed. As the accuracy of available components varies ± 20%, values for *A* and *B* are best obtained by cut and try.

to discharge through a variable resistor. The solenoid valve operates directly in the high-pressure air line so that a small orifice valve may be used without interfering with the total volume of air deliverable at the final low pressure. From this valve, the air passes through a pressure-regulating valve and then into a large jar or can, the purpose of which is to smooth out the sudden blast that would otherwise occur when the on–off valve opened. All components were purchased from stock on hand at the local radio parts supply house and refrigeration supply company. In the completed model, timer, valve, pressure control, and shock absorber are housed in a $5'' \times 6'' \times 9''$ box.

In operation, the unit is almost free from sound and, when the case is grounded, causes no artifacts in recording equipment such as an electroencephalograph, even when placed inside the shielded room with the subject. In use, the on–off ratio is set at about 1 : 2, the actual times being governed by the respiratory rate required by the animal. With the leak-off arm of the *T* tube about 70% obstructed (Fig. 1), the tracheal tube is inserted in the anesthetized animal. Following the administration of a curarelike drug, the pressure control is slowly advanced until sufficient air is forced into the lungs to distend them to about two thirds their capacity. Fine adjustments can then be made with the leak valve and the time controls.

If it is desired to use ether, a bubbler bottle may be inserted in the line between the shock absorber and the *T* tube. Simple additions to the equipment allow it to function in closed system anesthesia, as well as in various experimental combinations.

The respirator, working from the standard laboratory air line at 20 lbs pressure has been used for 10 months, and often as long as 24 hr at a time, with complete satisfaction. It has been found to function perfectly with a rat as well as with 2 large dogs simultaneously.

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