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A Broncho-Constrictor Factor in Cigarette Smoke. (22470)

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Although cigarette smoke is of a very complex chemical nature, the pharmacological effects of the smoke have been largely attributed to the nicotine and tar content. Such studies have been well summarized by Wynder and co-authors(1). The present studies are the result of a lack of published information on acute effects of smoke on the pulmonary airway.

Procedure. Cigarettes used were "king-size" popular brands. Six brands were studied. One was available as plain-tip and filter-tip types. Only the filter tip type of one other brand was available. One brand of "denicotinized" cigarette available with and without filter tip was used. Mature stock guinea pigs were etherized and the cervical spinal cord transected. The upper trachea was cannulated with a Y-cannula, connected to positive pressure artificial respirator. The thoracic cavity was opened by mid-longitudinal section of the sternum, and the cut edges were widely separated by self retaining retractors. The animal was then allowed to recover from the ether. A separate animal was used with each cigarette. The order in which animals received smoke from different brands of cigarettes, as well as lengths of the cigarettes during the test puff was randomly mixed. Four animals were used for each brand and type of cigarette, a total of 48 animals. The positive pressure artificial respirator functioned on the principle of commercially available C. F. Palmer apparatus.* A cigarette could be attached to intake of respirator with the glass adaptor tube, so that a delay of 3 to 4 seconds occurred between drawing of smoke and inflation of lungs with the smoke. The special glass Y-shaped tracheal cannula was constructed with a side arm at the level of entrance of the cannula to the trachea. This side arm was connected to a calibrated rubber membrane manometer for recording directly on the kymograph. A record of the tracheal pressure during each cycle of inflation of lungs was thereby obtained. Emptying of lungs was passive and due only to the elasticity of lungs. The functional dead space in the apparatus was measured directly by filling the apparatus with mercury and found to be 65 ml. All cigarettes were smoked to test lengths by mechanical Robot-Smoker so that each minute it took a single 10 ml puff of 2-second duration on the cigarette.

Results. The nature of the control inflation pressure curve obtained on guinea pigs was very uniform between animals. Fig. 1 shows this typical type of control inflation curve and the effect of a single 10 ml respirator puff of cigarette smoke on the nature of the tracheal pressure curve. The different quantitative responses obtained with the various cigarette lengths studied is also presented in the Figure. The predominant effects of cigarette smoke on pulmonary inflation pressure are a more rapid increase in inflation pressure in the middle of the cycle, and a fall in inflation pressure before the end of inflation cycle. This type of effect is interpreted as being the result of a broncho-constrictor

* Ideal Respirator, available through C. F. Palmer, Ltd., London, England.

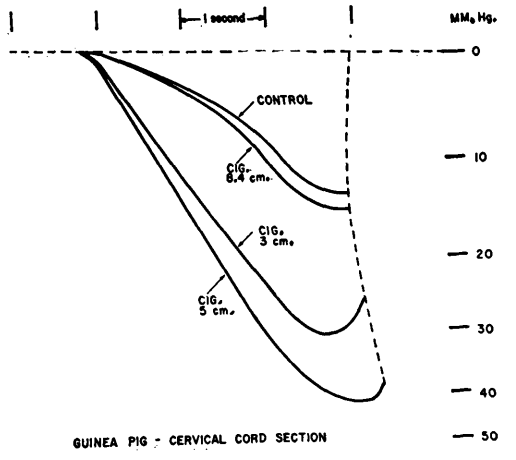

FIG. 1. Tracheal pressure curves during inflation of intact guinea pig lungs before and during response to cigarette smoke.

action of the cigarette smoke. Evidence for this interpretation of the curves is presented in the discussion.

Under conditions of a known pressure and volume of the respirator at beginning and end of each inflation cycle, Boyles Law ($PV = K$) may be used to calculate the actual volume of air from the pump which inflated the lungs, as a result of each pump stroke. This volume is the tidal volume. A standard graph was prepared from which any tracheal pressure value could be recorded as a given tidal volume when the respirator was set to deliver a 10 ml stroke at 9 strokes per minute. Fig. 2 consists of graph which shows maximum effect on tidal air of a single 10 ml puff of smoke from various brands of cigarettes. The least response was obtained when the cigarette length was 8.4 cm, but individual brands varied quantitatively. The greatest response was obtained when the cigarette was 5 cm long except for the "denicotinized" brand which uniformly produced less effect than other brands. Smoke from the 3 cm cigarette showed less effect than that which occurred at 5 cm length of cigarette. The Figure shows that presence of a filter tip did not significantly alter the response in the lung as compared to cigarettes with a plain tip.

Eight additional experiments showed that the lung response to cigarette smoke is not abolished by atropine. Fig. 3 shows atropine blockade of the pulmonary response to both ACh and nicotine, and failure of atropine to block the pulmonary response to cigarette smoke. Four additional experiments uniformly demonstrated that inhalation of amyl nitrite rapidly abolishes the pulmonary response to cigarette smoke.

Discussion. With artificial, positive pressure respiration under conditions of a constant stroke volume and rate, an increase above the control level in inflation pressure, measured at the tracheal level, must be interpreted as the result of a hindrance to inflation of the lung. Hindrance to inflation of lungs could be brought about either by a decrease in the caliber of bronchioles resulting from mucus secretion or bronchiolar constriction or by increase in extrabronchiolar resistance. Enhanced extrabronchiolar resistance will result in a rapid initial increase in tracheal pressure at beginning of the cycle but no decline in tracheal pressure would be expected to occur before the end of the inflation cycle. A decrease in caliber of bronchioles would likewise result in a rapid initial rise in tracheal pressure at the beginning of the inflation cycle and would, in addition, result in a fall in tracheal pressure before the end of the inflation cycle. This terminal fall in inflation pres-

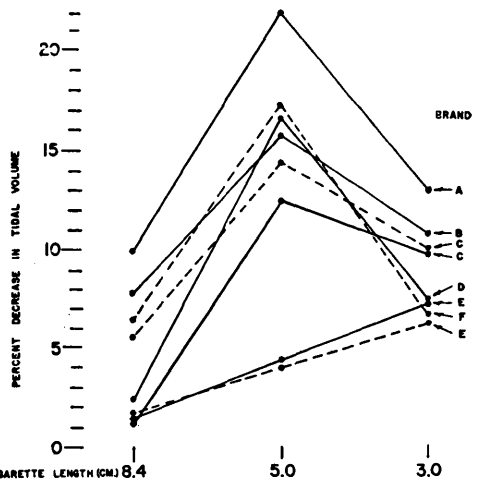

FIG. 2. Influence of cigarette smoke on tidal volume of guinea pig lungs. Each curve represents average effect on 4 guinea pigs. Filter-tip types of cigarettes are indicated by broken lines, and regular tip types of cigarettes are indicated by solid lines. Brand "E" is "denicotinized" brand.

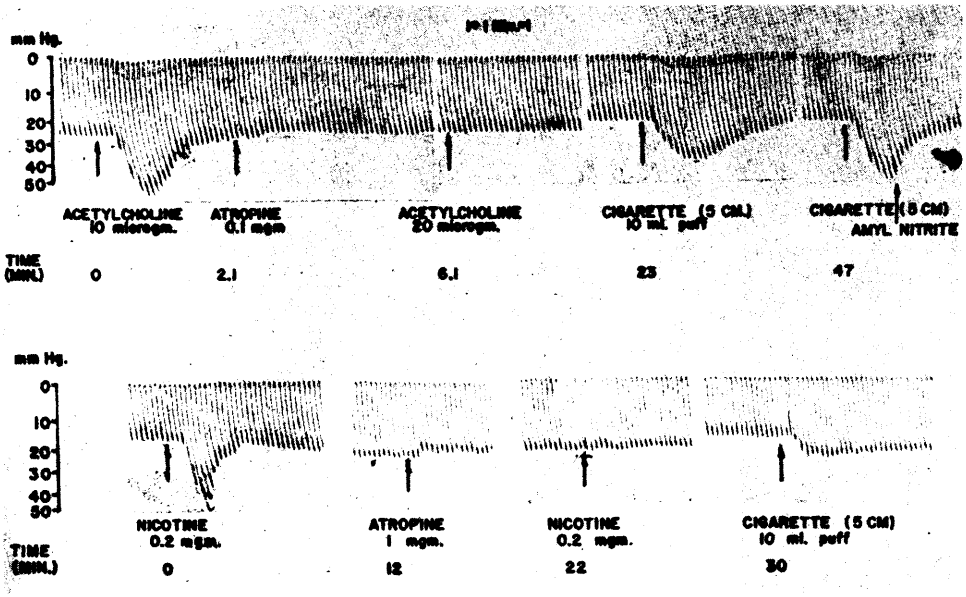

FIG. 3. Two experiments demonstrating influence of atropinization on lung inflation pressure response to acetylcholine, nicotine, cigarette smoke and amyl nitrite. All compounds were given by intracardiac injection (in the right ventricle) except the cigarette smoke and amyl nitrite which were administered by inhalation through artificial respirator.

sure near the end of the cycle would represent a "bleed-off" effect of air passing from trachea through a narrowed bronchiolar airway into the alveoli. Our experiments indicate, therefore, that the response to cigarette smoke is due to a narrowed caliber of the bronchioles. Since response to cigarette smoke appears within 10 to 20 seconds, it is unlikely that this response is due to increased mucous secretions. The rapid response can be accounted for by active bronchiolar constrictor mechanism. The failure to abolish the response to smoke by atropinization as compared to its rapid abolition by amyl nitrite indicates that the response is an atcive broncho-constrictor action which is not due to nicotine.

Reports are available concerning a subjective and edema producing irritant component of cigarette smoke(2). The irritant effects can be only partially accounted for on the basis of nicotine content of smoke. Furthermore, the tars of smoke which have been washed free of water soluble components do not produce acute irritant effects. Effects on the pulmonary airway observed could result from a non-specific irritant in the smoke. The rapid onset of effect from smoke as well as its rapid and complete abolition following inhalation of amyl nitrite indicate that airway edema is not a predominant cause of airway hindrance.

The present experiments indicate that "denicotinized" brand of cigarettes contained less of the agent responsible for the airway hindrance than does the conventional cigarettes. However, the experiments also indicate that the nicotine component is not the active agent. The other alkaloids present in tobacco (primarily nornicotine and anabasine) have some pharmacological properties similar to those of nicotine but have not been extensively studied. Tobacco of "denicotinized" brand of cigarettes may contain only minimal amounts of other constituents besides nicotine.

Our experiments uniformly showed that the greatest effect on the lung of the guinea pig occurred when the cigarette had been "robot smoked" to 5 cm. The least effect occurred when the cigarette was nearly full length (8.4 cm). This indicates that the unsmoked portion of full length cigarette acted in an efficient filtering capacity and withheld the

broncho-constrictor agent from the smoke. As the cigarette became shorter (5 cm), the retained (and possibly concentrated) broncho-constrictor agent may be volatilized by heat of the burning tip of the cigarette so that it is again carried along in the smoke. As the cigarette becomes still shorter (3 ml) an insufficient length of unburned tobacco may remain to act as an efficient filter.

Summary and conclusions. Experiments on intact guinea pigs indicate that cigarette smoke contains a broncho-constrictor agent. The intensity of the broncho-constrictor response is different with different lengths of cigarettes. Evidence is presented which indicates that the active agent in the smoke is not nicotine. Experiments using 2 brands of filter-tipped cigarettes indicated that the filter-tip did not influence the response of the lung to the cigarette smoke. The single brand of "denicotinized" cigarettes showed significantly less total broncho-constrictor effect than did the conventional cigarettes.

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Hypoglycemic Action of Orinase.* Effect on Output of Glucose by Liver. (22471)

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Bondy(1) demonstrated in humans that during postabsorption the output of glucose from the liver into the hepatic vein is in continuous state of flux, its level varying grossly and unpredictably from moment to moment. Bondy employed angio-catheterization of the hepatic vein, a method precluding sufficiently free flow of blood for precise short-interval timing required for methodology presently under consideration. We have explored these aperiodic fluctuations in normal dogs by exposing hepatic veins and directly needling the same for blood-glucose determinations at 1-minute and at 15-second intervals(2). When these readings are plotted, they assume varying configurations by their total irregularity both in rhythm and in magnitude. When similar readings are made on blood from the femoral artery, the same irregular glucose fluctuations are observed peripherally(2). Circulation time from the hepatic vein to the femoral artery was performed with fluorescine under a Wood lamp. Using this determination, one can readily identify the peripheral femoral arterial fluctuations with those emanating from liver. Irregular configuration of the hepatic undulations makes possible this peripheral identification (Fig. 1a). The original hepatic fluctuations are grossly reflected at lower over-all glucose levels throughout the main arterial tree of all 4 extremities in wavelengths of 2 to 7 minutes. When these relatively long "undulations" at both points are broken down into their structural components by taking glucose readings at 15-second intervals, one notes a markedly exaggerated variation from reading to reading, which is registered as a series of sharp flings, up and down (Fig. 1b). These may aptly be designated as "oscillations," each complete "oscillation" taking approximately 30 seconds. The

* Orinase-Upjohn (1 butyl-3p-tolylsulfonylurea) supplied by Upjohn Co. through courtesy of Dr. C. J. O'Donovan. Glucagon supplied by Eli Lilly Co. through courtesy of Drs. F. B. Peck and W. R. Kirtley. The authors are also indebted to Agnes Dann for technical assistance in 2000 glucose determinations.