THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by J. Paul Quigley for the degree of Doctor of Philosophy. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

_____

Chairman

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E. C. Kendall

The University of Minnesota
The Medical School
Minneapolis

DEPARTMENT OF PHARMACOLOGY

May 28, 1921.

Report of Committee on Written Examination

of

J. Paul Quigley.

The undersigned hereby certify that J. Paul Quigley has satisfactorily passed the examination given in partial fulfillment of the requirements for the degree of Master of Science in Pharmacology.

Earl B. Brown

Arthur D. Hirschfelder.
Chairman.

THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

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Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by J. Paul Quigley for the degree of Master of Science in Pharmacology They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of

Arthur D Hirschfelder
Chairman

Edward C. Kendall.

J Bolmeier.

June 8 1921

The University of Minnesota
The Medical School
Minneapolis

MAY 19 1921

DEPARTMENT OF MEDICINE

May 17, 1921.

Dean Guy Stanton Ford,
The Graduate School.

My dear Dean Ford:-

I have read the thesis of Mr. J. Paul Quigley and am returning same to Dr. A. D. Hirschfelder.

I approve and recommend its acceptance.

Sincerely yours,

J. P. Schneider

The University of Minnesota

The Medical School

Minneapolis

DEPARTMENT OF PHARMACOLOGY

We, the undersigned Committee, have examined J. Paul Quigley and hereby recommend him for the degree of Master of Science in Pharmacology.

J. H. McClendon

E. C. Kendall

Geo B Fraenkel

Arthur D. Hirschfelder.

Chairman.

THE RELATION OF CHEMICAL STRUCTURE TO PHYSIOLOGICAL ACTION OF SOME SUBSTITUTED PHENYL CARBINOLS AND RELATED COMPOUNDS.

J. Paul Quigley.

I N D E X

INTRODUCTION.

The question of exactly to what extent the physiological properties of a compound are dependent on its chemical constitution is one full of fascination and interest. If it were possible to state definitely or even approximately what physiological action on man would be obtained from a certain compound simply from an examination of the structural formula of that substance, a great advance in Pharmacology and its related sciences Physiology, Chemistry, Bacteriology, and Therapeutics would have been attained. Naturally, it is a prerequisite to this condition that we have as a foundation some knowledge regarding the possible values of those several groups which go to make up the completed molecule of the compound considered. The following work was undertaken with the hope of contributing still further to the very valuable accumulation of investigations in this particular field of endeavors which are now at our disposal.

Although the carbinol group occurs free or combined in a large number of compounds which find a more or less extensive application in medicine (e.g. adrenalin, atropine, cocain, stovain, procain, quinine, etc.) the relation of this particular group to the physiological action of the compound in which it occurs, has not, until recent years, received the attention which it might be assumed to deserve. It has therefore, been considered advisable to investigate the physiological properties of some of the more simple carbinols, especially those which

contain the benzene ring.

Considerable work on the phenyl carbinols has already been done in this laboratory by Dr. Arthur D. Hirschfelder and his collaborators. This present work was undertaken with the object of making a further contribution to the investigation of the phenyl carbinol problems.

System of Nomenclature.

In order to distinguish the various isomeric alcohols by names readily expressive of their structure, it has been found convenient to consider them as derivatives of methyl alcohol, (CH_3OH), which for this particular purpose is designated as carbinol.

The essential characteristic of a carbinol is that it possess a $\equiv C(OH)$ group. The three bonds here represented as being free, may be joined to an alkyl or aryl group or to hydrogen or nitrogen or to any combination of these four, and thus form the various carbinols. For example, propyl alcohol ($C_2H_5CH_2OH$) would be designated as "ethyl carbinol".

The compounds with which this research is chiefly concerned may likewise be considered as derivatives of the two compounds benzyl alcohol ($C_6H_5CH_2OH$) and saligenin ($C_6H_4(OH)CH_2OH$). Employing the system as outlined above, benzyl alcohol would be called phenyl carbinol, while saligenin would be designated by the name ortho-oxy-phenyl carbinol.

Earlier Work on Aromatic Carbinols.

Although the actions of the aliphatic carbinols (alcohols) and their relations to chemical constitution has been the subject of a rather complete investigation, a limited search through the earlier literature failed to throw much light on the physiological actions of the phenyl carbinols.

Paul Binet (I) (2) in his investigations of the comparitive toxicity of some phenol derivatives, found that the introduction of an alcohol or aldehyde group in the phenol molecule reduces the toxicity and the convulsant action. However, the excitation from salicyl aldehyde ($C_6H_4(OH)CHO$) is much more pronounced than that obtained from an equivalent amount of saligenin ($C_6H_4(OH)CH_2OH$). Although benzyl alcohol ($C_6H_5CH_2OH$) is isomeric with o-cresol ($C_6H_4(OH)CH_3$), its toxicity and convulsive action is decidedly lower. Binet considers this effect to be especially due to the presence of the carbinol grouping.

Nencki (3) found that saligenin is oxidized in the organism to salicylic acid and excreted as salicyluric acid, while benzyl alcohol is oxidized to benzoic acid provided the reaction continues long enough. This is supported by the findings of Macht (12) that benzyl alcohol is excreted as hippuric acid, probably after being oxidized in the organism to benzoic acid.

Work by Reidel (4) shows that the benzoyl derivatives of some of the more complicated phenyl amino carbinols (tertiary amines) have a low toxicity and also possess marked local anesthetic properties, but no mention is made regarding the properties of the carbinols themselves.

Bechhold and Ehrlich, (5) found that the joining of two phenol molecules by means of a :CHOH group greatly increased the antiseptic action. However, the results were practically the same when the :CH_2, :$CH(OCH_3)$, or :$CH(OC_2H_5)$ group was employed instead of the carbinol linking. Hexabromdioxydiphenyl carbinol ($OHC_6 \cdot HBr_3CHOH \cdot C_6HBr_3OH$), the one investigated was found to be practically non-toxic but to possess a rather high bactericidal value, for some strains being 250 times so active as phenol.

Hoering and Baum (6) consider the use of several oxyphenyl carbinols as internal antiseptics.

In an investigation of some of the tropeins, Cushny (7) arrives at the conclusion that the atropine action of these compounds is greatly intensified by the presence of an asymmetric carbon and a hydroxy group in the side chain. Whether the effect was more dependent on the asymmetric carbon or the carbinol linking, he was unable to ascertain.

Barger and Dale (8) in an investigation of some carbinols related to adrenalin, conclude that when two phenolic hydroxyls are in the benzene ring in the 3:4 position the presence of an alcoholic hydroxyl (carbinol) still further intensifies the sympathomimetic activity of the compound.

Dakin (9) reached a somewhat similar conclusion.

A final consideration of this limited number of articles seems to emphasize the impression that up until recent times the investigation of the physiological properties of the phenyl carbinols has been a somewhat neglected field.

Recent Work on the Aromatic Carbinols.

Recent work by D. I. Macht (10) (11) (12) (13) (14) (15) and A. D. Hirschfelder (16) has shown that a large number of simple synthetic compounds such as benzyl alcohol, saligenin and benzyl benzoate possess properties which are similar to, or in some respects even superior to the complicated substances cocain, atropine, etc.

SCOPE OF PRESENT INVESTIGATION.

Alteration in Chemical Constitution Considered.

In benzyl alcohol ($C_6H_5CH_2OH$), saligenin ($C_6H_4(OH)CH_2OH$) and homosaligenin ($C_6H_3(OH)(CH_3)CH_2OH$), each of which was found to possess local anesthetic properties, we find the $-CH_2OH$ group united to the benzene ring. Since the information regarding this group is so limited it seemed highly advisable to investigate this relation in a scientific manner and to determine the physiological properties of some simple derivatives of the first two of these compounds with the possible hope of throwing more light on the relation between the physiological action and the chemical structure of the substituted phenyl carbinols.

Alterations in the benzene ring were not considered in this article, the work being confined strictly to alterations in the $-CH_2OH$ group of benzyl alcohol and saligenin, and since it was considered highly probable that changes involving the active hydrogen atom (i.e. formation of ethers or esters) would invoke a too radical change in their physiological actions

(Frankel (17) page 64-66) the substitutions were further restricted, with the exception of hydrobenzoin acetate, to the two other hydrogen atoms (which will hereafter be designated as the "inactive hydrogen atoms") of the $-CH_2OH$ group.

Certain of the physiological actions of the compounds so prepared were investigated with the object of determining, if possible, whether or not these two atoms were of vital importance for the special actions of those compounds considered.

Type of Chemical Compounds Synthesized and Investigated.

The following compounds were synthesized and investigated physiologically:- diethyl o-oxyphenyl carbinol; trichlormethyl phenyl carbinol; diethyl phenyl carbinol; diphenyl carbinol; dibenzyl phenyl carbinol; and hydrobenzoin acetate.

The work was carried out with the idea of ascertaining if possible, how the physiological properties of benzyl alcohol would be modified by the following changes:

$C_6H_5CH_2OH$ ----------⟩-- $C_6H_5CH\ (CCl_3)\ OH$

$C_6H_5CH_2OH$ ----------⟩ - $C_6H_5C\ (C_2H_5)_2OH$

$C_6H_5CH_2OH$ ----------⟩ - $C_6H_5CH(C_6H_5)\ OH$

$C_6H_5CH_2OH$ ----------⟩ - $C_6H_5C(CH_2C_6H_5)OH$

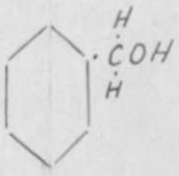
$C_6H_5CH_2OH$ ----------⟩ - $C_6H_5CHOOCCH_3$: $C_6H_5CHOOCCH_3$

In the case of saligenin, the modification investigated was the one represented:-

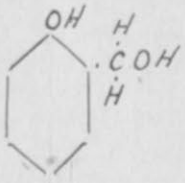
$C_6H_4(OH)CH_2OH$ ----------⟩ - $C_6H_4(OH)C(C_2H_5)_2OH$

STRUCTURAL FORMULAE

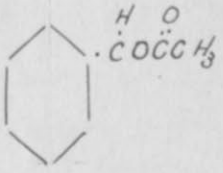
of the Compounds Synthesized and Investigated Physiologically and of Several Compounds with which They are to be Compared.



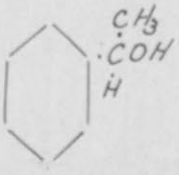
(I) Benzyl Alcohol (Phenyl Carbinol)



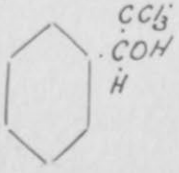
(2) Saligenin (o-Oxyphenyl Carbinol)



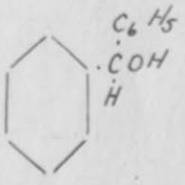
(3) Benzyl Acetate.)



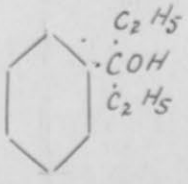
(4) Methyl Phenyl Carbinol)



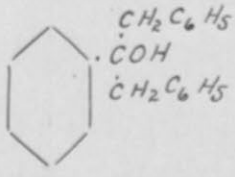
(5) Trichlormethyl Phenyl Carbinol)



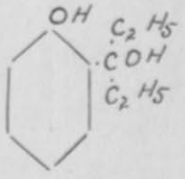
(6) Diphenyl Carbinol)



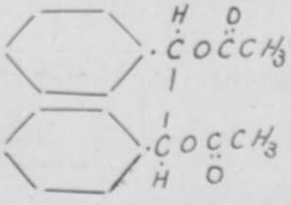
(7) Diethyl Phenyl Carbinol)



(8) Dibenzyl Phenyl Carbinol)



(9) Diethyl o-Oxyphenyl Carbinol.)



(10) Hydrobenzoin Acetate.)

General Theoretical Consideration of the Physiological Properties of the Carbinols.

In a theoretical consideration of these compounds, the fact must be kept in mind that the alterations in structure take place in the side chain and not in the ring. The changes, therefore, should correspond closely with comparible modifications in the structure of aliphatic compounds rather than with those of the aromatic series.

In general it may be assumed, that if the characteristic physiological effects of benzyl alcohol or saligenin are retained, the modifications introduced will result in the production of compounds whose action will be greatly prolonged, both because of the decreased water solubility and their probable increased stability in the organism (they should be less readily oxidized.)

These carbinols are decidedly more soluble in alkalias than in neutral or acid solutions and therefore should be absorbed more readily from those portions of the organism where the alkaline condition prevails. For example if taken internally, absorption (especially of the more insoluble carbinols) should occur chiefly from the intestines.

Just what effect will be obtained through the introduction of an asymmetric carbon atom, as we see in the case of methyl phenyl carbinol, trichlormethyl phenyl carbinol, and hydrobenzoin acetate, is rather problematical. Naturally the compounds as synthesized would be in the racemic modification, or as in the case of hydrobenzoate acetate in the meso form.

Certain substances such as adrenalin depend for their physiological activity to a marked extent on this asymmetric carbon. The racemic form of adrenalin as obtained by a chemical synthesis is only one-half so active as the organic product. When separated into the active forms, however, the l-form is found to be identical in physiological action with the natural adrenalin.

Although one of the optically active (d- or l-) forms of the substances prepared would undoubtedly display greater physiological activity than the racemic (d- l-) form, the compound in question, if at all active would show a part of this activity in an examination of the racemic form. The racemic form of hydrobenzoin acetate would probably display greater physiological activity than the meso form.

Those special results which might be deduced from a theoretical consideration of the modification in structure made in each compound will be considered in a more detailed form in the separate treatment accorded to each compound.

Physiological Properties of Benzyl Alcohol.

In order that the physiological actions of benzyl alcohol may be better compared with those of its derivatives herein considered, an abstract of the findings of Macht (12) is here given.

Benzyl alcohol was found to possess "powerful local anesthetic properties" when applied directly to mucous membrane (tongue, lips, etc.) or when injected subcutaneously as 1-4% solution. Following a primary irritation, a complete anesthesia lasting from 30 minutes to 2 hours was observed.

Benzyl alcohol can also in a measure produce the benzylic action (tonus lowering and inhibitory action on smooth muscle) exhibited by the benzyl esters.

When applied to the sciatic nerve of a single pithed frog, paralysis of the sensory nerve fiber was observed, and with concentrated solutions (4%), motor block was also obtained.

Intravenous injection of a 1% solution produced a fall in blood pressure due to peripheral vaso dilation, but not to any depression of the vaso motor center. Continued injection was without further effect on the heart action or vaso-motor center until toxic doses of the drug were used.

Intravenous injection of 15 mils per Kg. of the 1% solution in dogs produced no appreciable change in the respiration. Injection of small doses produced a primary stimulation of respiration. When pushed to its toxic limit, the respiration began to fail and death occured through paralysis of the respiratory center. The heart continued to beat for five minutes after cessation of respiratory movements.

Intravenous doses of 10 mils per Kg. of the 1% solution in dogs was followed by a sedative action, the animal seeming to be somewhat narcotized. Larger doses showed a deleterious effect on the central nervous system. Convulsions, followed by paralysis of the respiratory center developed from toxic doses.

The subcutaneous injection of 1 mil of the alcohol per Kg. was not always fatal for cats. Rabbits usually recovered from 2 mils per Kg. while the same dose intraperitoneally, intramuscularly or subcutaneously was never fatal for dogs.

Physiological Properties of Saligenin.

According to Hirschfelder (16) saligenin is much less irritating to the tissues than benzyl alcohol, it is less toxic and its anesthetic action from half the concentration lasts longer than that from benzyl alcohol. It is decidedly a practical local anesthetic.

The slow injection of a 4% solution of saligenin into the femoral vein of a dog produced a very gradual fall of blood pressure and a slight slowing of the respiration. After a dose of 0.7 Gm. per Kg. had been reached, a further injection produced a sudden fall of blood pressure ending in the death of the animal. Respiration stopped before cessation of the heart beat.

The rapid injection of saligenin produced a temporary slowing or paralysis of the respiration lasting a few seconds, after which respiration was resumed spontaneously. At each repetition with the same dose, the same phenomenon was observed, and there was a general progressive fall in blood pressure.

Scope of the Investigations on the Physiological Action of the Carbinols.

In studying the carbinols, their effects following subcutaneous injection in mammals on respiration, heart rate, hypnotic action, effect on reflexes, alterations in size of pupils, etc., was observed.

With those compounds which appeared suitable, subcutaneous injection on man was tried in order that more complete information could be ascertained regarding the action of the compound on local

sensation. Small quantities of the carbinols were also applied to the tongue in order that the anesthetic effect on mucous membrane might be investigated.

Since all of the compounds investigated were practically insoluble in water, some difficulty was experienced in obtaining a respiration blood pressure tracing showing the effects of the carbinols.

Several experiments were made to determine the possibility of applying intravenous injections of a concentrated alcohol solution of the compound; to be controlled by injections of a similar quantity of alcohol. It was soon observed that the results were untrustworthy, probably due to the carbinols being precipitated from solution upon coming into contact with the blood stream.

Intramuscular, subcutaneous and intraperitoneal injections of the carbinols also failed to produce reliable results because of the slow rate of absorption of the compounds. Injections into the stomach or the intestines likewise failed for the same reason.

Several of the carbinols investigated form readily soluble salts in 5% sodium hydroxide and it was at first considered possible to use these water soluble sodium salts. However, when the excess alkali is removed, the carbinols readily hydrolize and then precipitate out of solution.

Rapid, dependable results were finally obtained by intravenous injections of a 7% acacia and 0.9% sodium chloride emulsion of the carbinol dissolved in olive oil. Injections of a similarly prepared emulsion of olive oil were used for a control.

Despite the observations of W. T. Porter (18) that the slow intravenous injection of 3 mils of "the official emulsion of olive oil" (no official emulsion is known) in cats produced a rapid fall of blood pressure due to fat embolism; carefully controlled experiments of the manner described, gave results in which the action of the carbinol could be definitely determined.

The animals were prepared for making these tracings as follows:

The animal was anesthetized and the trachea exposed. A cannula was inserted in the trachea and then connected with a tambour and with an ether bottle in such a manner as to permit the preparation of a record of the respiration and to give the animal a sufficient quantity of the anesthetic. A second cannula was placed in one of the carotid arteries and then connected with a manometer for the recording of the blood pressure. Records of the blood pressure and the respiration were made on a roll of smoked paper placed in the proper relation to these recording instruments.

In certain cases, as will be noted later, injections of the materials were made into the femoral vein. In these cases the femoral vein was exposed and a cannula inserted. This canular was connected by means of rubber tubing with a buret containing 0.9% sodium chloride solution. Injections were made by inserting the needle of the hypodermic syringe through the rubber tubing and into the cannula. The saline solution was slowly allowed to flow during the injection as well as for a short time afterwards and in this manner the material was washed into the femoral vein and so into the circulation.

The action of the compounds when applied to the frog's sciatic nerve was investigated for both motor and sensory paralysis. A frog was single pithed and both sciatic nerves carefully exposed. A small pledget of cotton was placed under each nerve. The one on the right leg was then moistened with 0.75% sodium chloride and 7% acacia solution while that on the left leg was treated in a similar manner with an emulsion of the carbinol in 7% acacia and 0.75% sodium chloride. At suitable intervals, both legs were tested for sensory paralysis by dipping the foot into a beaker of 5% sulphuric acid. If this treatment was not followed by flexion of the frog's leg, it was considered that the sensory nerve fibers were paralyzed. Provided the leg behaved in a normal manner, it was assumed that no blocking of sensory impulses had resulted from the applications to the frog's nerve. In either case, the leg was immediately washed by immersion in a beaker of water.

Blocking of motor nerve fibers was recognized by applying electrical stimulus to the nerve at the cerebral side of the cotton pledget. Failure of the stimulus to produce tetanus of the leg was taken to indicate paralysis of the motor nerve fibers.

Both in the experiments on paralysis of motor nerve fibers and of sensory nerve fibers, the nerve moistened only with the sodium chloride and acacia solution (right leg) was used entirely as a control.

In general, it may be stated that substances having a local anesthetic action for man react in this experiment by paralyzing the sensory nerve fibers. Unfortunately, however, the converse,

that substances which paralyze sensory nerve fibers in frogs produce local anesthesia on subcutaneous injection in man and mammals is not necessarily true.

In cases where it appeared advisable, other special experiments, which will be recorded in their proper place, were carried out.

METHYL PHENYL CARBINOL

Secondary Phenyl Ethyl Alcohol.

It was first considered advisable to study the physiological actions of methyl phenyl carbinol ($C_6H_5CHOH\ CH_3$) both because of its relations to its homologue benzyl carbinol ($C_6H_5CH_2\ CH_2OH$), which has been reported by Hirschfelder, et al (16) and by Hjort and Eagan (19) to possess local anesthetic properties, as well as to benzyl alcohol (phenyl carbinol) ($C_6H_5CH_2OH$).

Methyl phenyl carbinol may be prepared according to Klages and Allendorff (20) by the reduction of acetophenone with alcohol and metallic sodium. Hans Stobbe (21) used succinic acid and sodium ethylate to reduce acetophenone, while Emmerling and Engler (22) advised the use of sodium amalgam for this reduction. By each of these synthesis, acetophenone pinacone is formed at the same time and usually in quantities equal to the carbinol.

The admirable work of W. D. Cohen (23) make it appear highly probable that zinc dust and potassium hydroxide would provide a more suitable reducing material than any of the above mentioned reagents, since by this method, the formation of by-products is largely averted. The preparation of methyl phenyl carbinol by this method was not attempted.

As mentioned by Emmerling and Engler in the above recorded reference, it was found that methyl phenyl carbinol readily oxidizes to acetophenone and acetophenone pinacone following short exposure to air. Several attempts were made to prepare the carbinol in a pure condition, but since its boiling point is 203° and that of acetophenone is 202° and no simple method was available for the separation of these two substances, it was felt advisable to forego for the present the study of methyl phenyl carbinol rather than to use a preparation which could not be positively known to be free from acetophenone. Moreover, it was considered probable that methyl phenyl carbinol in the organism would be readily oxidized to acetophenone, so that if its action should be different from that compound, the effect would, at most be only transient.

Since this work was completed Hjort and Kaufman (24) have reported a study of the physiological properties of methyl phenyl carbinol.

According to their conclusions, d l - methyl phenyl carbinol is a more potent local anesthetic on the rabbit's cornea and under the human skin than benzyl alcohol or benzyl carbinol (rose oil), but not in proportion to its greater toxic action. Moreover, the instability of this substance as mentioned before, offered further objection to its practical application.

The preparation used by Hjort and Kaufmann was prepared by the method of Emmerling and Engler (22). This undoubtedly could not have been the pure carbinol for, according to the statement of these latter authors, "despite repeated treatment with sodium amalgam, the alcohol (carbinol) always contained some acetophenone."

Moreover, methyl phenyl carbinol is reported to be a liquid of very disagreeable odor ("von hochst unangenehmen Geruch"). The methyl phenyl carbinol prepared in this laboratory work had an odor to which the above recorded words could very aptly be applied. Hjort and Kaufmann state that the carbinol has an odor "which simulates that of acetophonone." The odor of acetophenone can hardly be characterized as being any more disagreeable than toluene.

The general anesthesia induced by Hjort and Kaufmann by the subcutaneous injection of their product into mice, corresponds very well with the effects from the similar application of acetophenone as reported by Laborde (25), Grasset (26), and Beaumetz (27). Insufficient information regarding the properties of acetophenone pinacone is at hand to draw any conclusions in respect to its presence in the preparation used by Hjort and Kaufmann.

DIETHYL o-OXYPHENYL CARBINOL.

Preparation of Diethyl o-Oxyphenyl Carbinol (isoamylol phenol, ∝-oxy ∝-oxyphenyl pentane, diethyl saligenin.)

According to the method of Hoering and Baum (28) diethyl o-oxyphenyl carbinol (C_6H_4 (OH) C $(C_2H_5)_2$ OH) is obtained by allowing ethyl magnesium iodide to act on the sodium salt of methyl salicylate and then decomposing the resulting products with dilute acetic acid. Although this method probably requires a smaller amount of ethyl magnesium iodide, the method was modified as stated below because of the greater smoothness with which the reaction could be carried out.

A solution of ethyl magnesium iodide in ether was prepared by the slow addition of 234 Gm. ethyl iodide (redistilled) to 36 Gm. magnesium turnings in 200 mils anhydrous ether. The mixture was well cooled during this addition and then refluxed on the water bath for a short time. This solution was placed in the shaker (Figure I) and slowly treated with a solution of 76 Gm. methyl salicylate in 200 mils anhydrous ether. The mixture was shaken for two hours after the addition of the methyl salicylate was completed and then heated on the water bath for 30 minutes.

By this modification of the reaction, the methyl salicylate in small amounts is brought into contact with a large excess of the Grignard's reagent, and the reaction quickly goes to completion. Difficulty was encountered with the Hoering and Baum synthesis because of the insoluble sodium salt of methyl salicylate forming into lumps and by not coming into contact with the ethyl magnesium iodide, remaining unchanged.

The reaction mixture was then treated with ice and dilute acetic acid until solution was complete, the ether layer was drawn off, and the water layer extracted several times with ether. The ether was partly evaporated from the ether solution and then extracted with a 5% sol. of potassium hydroxide. In order to separate the carbinol from any contaminating compounds, the alkali solution was warmed for a time on the water bath, and after cooling, the carbinol was precipitated by the addition of CO_2. The precipitated carbinol was extracted with ether, dried over $CaCl_2$ and crystallized from the ether solution.

Upon recrystallization from ligroin, the diethyl o-oxy phenyl carbinol was obtained as colorless needles. M.P. 55.5 - 56°. It

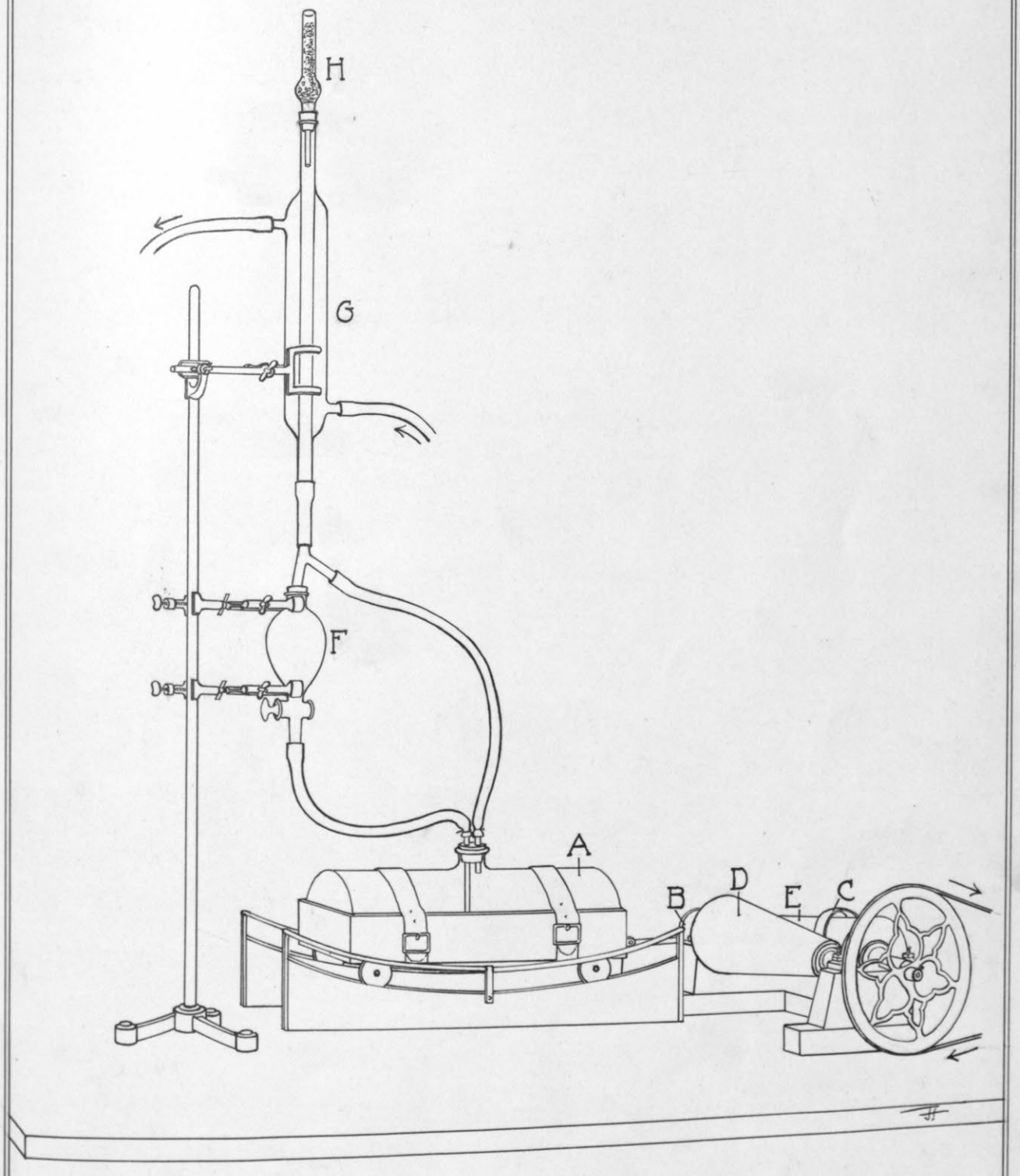


Figure I

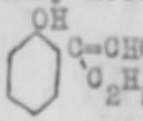
Description of the Shaking Apparatus shown in Figure I.

The side-mouth bottle (A) is placed in a box mounted on wheels and moving in a grooved track. The car is made to shake by means of its connection with the excentric (B). The rate at which the car is shaken can be regulated by moving the leather belt (C) from one side to the other between the inverted cones (D) and (E).

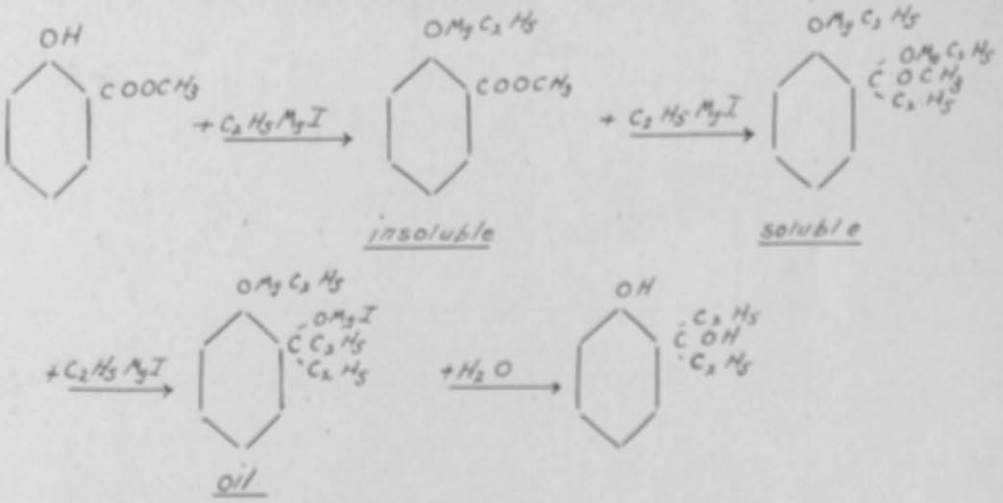
The separatory funnel (F) is connected below with the bottle (A) by means of rubber tubing and thru the T-tube above with the condenser G and again with the bottle (A). The tube (H) containing granular calcium chloride is inserted in the upper end of the condenser.

The apparatus actually used in the preparation of the carbinols in which the Grignard Reaction was employed differed slightly from the one here illustrated in the parts A-E, however, the arrangement as shown in Figure I is considered as being more desirable. The ether solution of the Grignard reagent was placed in the bottle (A) and the material with which this was to react was dissolved in absolute ether and slowly added from the separatory funnel (F). Since these reactions are exothermic some of the ether is volatilized. This is returned by the condenser (G) to the separatory funnel. The tube of calcium chloride serves to prevent the entrance of moisture to the reaction mixture.

is very slightly soluble in water, readily soluble in alkali or in organic solvents.

This compound may easily lose water, thus forming the unsaturated hydrocarbon  . The unsaturated compound polymerizes to form the dimer (Behal (29) which decomposes on heating to again form two molecules of the monomer.

Reaction:-



Theoretical Consideration of Diethyl O-Oxy Phenyl Carbinol.

From an examination of the structural formula of diethyl o-oxyphenyl carbinol ($OHC_6H_4C(C_2H_5)_2OH$) it is seen that this compound differs in its chemical structure from saligenin, only in the substitution of two ethyl groups for the two "inactive hydrogens" of the latter compound. Besides throwing some additional light on the importance of these two hydrogens in determining the physiological action of saligenin, an examination of diethyl o-oxyphenyl carbinol may be expected to assist in a determination

of the effect of an introduction of two ethyl groups in the phenyl carbinols.

Considering the fact that the ethyl groups are substituted in the side chain, the effect obtained, should be simular to the effect obtained by the introduction of ethyl groups in aliphatic compounds and more especially in aliphatic alcohols. This should lead to an increase in the narcotic action of the compound so produced and perhaps a slight increase in toxicity.

Provided the diethyl o-oxyphenyl carbinol retains the local anesthetic effect of saligenin and gains in addition, the narcotic action from the addition of two ethyl groups, its general action should be not unlike that of morphine.

Diethyl o-oxyphenyl carbinol differs in its structural formula from diethyl phenyl carbinol only in the addition of a phenolic (OH) group ortho to the ($-C(C_2H_5)_2OH$) group. From a theoretical point of view at least, a comparison of the physiological properties of this former compound with those of the latter (to be discussed later) should be equal in interest to a simular comparison of saligenin and benzyl alcohol.

Attention is likewise called to the fact that diethyl o-oxyphenyl carbinol differs in its structural formula from phenol thru the introduction of a ($-C(C_2H_5)_2OH$) group ortho to the phenolic (OH) group of phenol, and therefore might be expected to exhibit some more or less modified phenol actions.

Additional interest it lent to the study of diethyl o-oxyphenyl carbinol by the observation that it is one of the tertiary aromatic alcohols.

Investigation of Diethyl o-Oxyphenyl Carbinol.

Diethyl o-oxyphenyl carbinol as prepared was a faintly yellow crystalline substance. After standing for several months it turned a brownish color and partially liquified.

When placed on the tongue, this carbinol has a burning taste. No local anesthesia was encountered during this application.

Due to the insolubility of diethyl o-oxyphenyl carbinol in water it was necessary to find a different solvent for the carbinol. Cottonseed oil appeared to be a suitable solvent and in the majority of administrations the carbinol was given dissolved in this oil, or in olive oil.

Oral administrations of the carbinol were given to rabbits and to a dog. The carbinol was also injected subcutaneously into several rabbits and also applied to the sciatic nerve in a series of frogs.

It was considered inadvisable to investigate the action of this carbinol following subcutaneous injection in man on account of its marked irritant action.

Diethyl o-oxyphenyl carbinol was also injected into a series of animals prepared for the recording of blood pressure and the respiration and a tracing made of the results so obtained.

Effect of Diethyl o-Oxyphenyl Carbinol Following Oral Administration in Rabbits.

Diethyl o-oxyphenyl carbinol dissolved in cottonseed oil was made into an emulsion by shaking with a solution of acacia. This emulsion was administered to several rabbits and to a dog

by means of a stomach tube and the condition noted of the animal under these conditions.

Experiment I.

Rabbit #I. Weight 1300 Gm. 4/28/20

3:20 P.M. Given by stomach tube 0.3 Gm. (0.23 Gm. per Kg.) diethyl o-oxyphenyl carbinol as an emulsion in 7% acacia, 5% cottonseed oil and 0.9% saline.

3:30 P.M. Slight anesthesia to pain from burning or electrical stimulation.

3:40 P.M. Lessened reaction to pain continued. Very quiet.

4:00 P.M. Reaction to pain more normal. Still quiet.

7:00 A.M. 4/29/20 Normal.

Experiment II.

Rabbit #2 Weight 1400 Gm. 4/28/20

3:10 P.M. Given by stomach tube 0.3 Gm. (0.214 Gm. per Kg.) diethyl o-oxyphenyl carbinol as an emulsion in 7% acacia, 5% cottonseed oil and 0.9% saline.

3:15 P.M. Prostrated. Hypersensitive reaction to pain.

3:30 P.M. Condition unchanged.

3:45 P.M. Respiration slower, otherwise condition unchanged.

4:10 P.M. Appears more lively but still unable to stand.

4:50 P.M. Able to stand and move slowly.

7:00 A.M. 4/29/20 Normal.

Experiment III.

Rabbit #3. Weight 1300 Gm. 4/30/20.

11:15 A.M. Given by stomach tube 0.5 Gm. (0.384 Gm. per Kg.) diethyl o-oxyphenyl carbinol as an emulsion in 7% acacia, 5% cottonseed oil and 0.9% saline.

11:20 A.M. No anesthesia to pain observed.

11:25 A.M. No effects observed from the carbinol.

11:30 A.M. No effects observed from carbinol.

12:10 P.M. Appeared to be normal.

Effects Obtained by Oral Administration of Diethyl o-Oxyphenyl Carbinol to a Dog.

Experiment I.

Dog #1 Weight 7.6 Kg. 4/29/20.

11:15 A.M. Given by stomach tube 2 Gm. (0.263 Gm. Per Kg.) diethyl o-oxyphenyl carbinol as an emulsion in 7% acacia, 5% cottonseed oil and 0.9% saline.

11:30 A.M. Animal less active. No anesthesia to pain observed.

11:45 A.M. Animal more quiet. No anesthesia to pain observed.

12:00 M. Condition unchanged.

1:00 P.M. Appeared normal.

Conclusion:

This limited series of experiments would indicate that doses of from 0.21 - 0.38 Gm. per Kg. of diethyl o-oxyphenyl carbinol exert a sedative action on rabbits and dogs. This effect was not constant and was lacking in the rabbit (#3) which obtained the largest dose.

Although a hyposusceptibility to pain was recorded in the case of Rabbit #1 following administration of the carbinol this action was entirely absent in the case of Rabbits #2 and #3 and Dog #1. The apparent anesthesia to pain was probably the result of incorrect observations. It therefore appears likely that this carbinol does not possess an analgesic action simular to that of morphine, but does have some sedative effect.

Effect of Subcutaneous Injection of Diethyl o-Oxyphenyl Carbinol in Rabbits.

Diethyl o-oxyphenyl carbinol dissolved in cottonseed oil was made into an emulsion by shaking with a solution of acacia in physiological salt solution. This emulsion was injected subcutaneously into several rabbits and the action determined of the carbinol under these conditions.

Experiment I.

Rabbit #I Weight 1700 Gm. 4/19/20.

2:05 P.M. Injected subcutaneously an emulsion of 1 Gm. per Kg. in 5% cottonseed oil, 7% acacia and 0.9% saline.

2:30 P.M. Animal appeared normal. Appeared to have slight anesthesia at area of injection.

3:00 P.M. No change noted.

11:00 P.M. Condition unchanged. Slight anesthesia still appeared to be present at point of injection.

7:00 A.M. 4/20/20 Animal appeared normal.
4/26/20 Area of injection blackened and stiffened, otherwise animal appeared to be normal.

5/4/20 Area of injection still has appearance of a severe phenol burn. Animal otherwise normal.

Experiment II.

Rabbit #2 Weight 1300 Gm. 4/19/20.

2:20 P.M. Injected subcutaneously 2.3 Gm. per Kg. of diethyl o-oxyphenyl carbinol in an emulsion of 7% acacia, 5% cottonseed oil and 0.9% saline.

2:45 P.M. Area of injection appeared to be slightly anesthetized. Animal otherwise normal.

3:00 P.M. Animal became more quiet.

11:00 P.M. Animal less active. Area of injection appeared to be slightly anesthetized.

7:00 A.M. 4/20/20 Animal appeared normal.

4/26/20 Area of injection badly burned and blackened. Animal otherwise normal.

5/4/20 Area of injection still has appearance of severe phenol burn. Animal otherwise normal.

Conclusion:

If diethyl o-oxyphenyl carbinol possesses local anesthetic properties following the subcutaneous injection in rabbits, as might appear from these experiments, it is only of a slight degree. Moreover, its corrosive action would mitigate strongly against its further application in this manner, especially to man.

Action of Diethyl o-Oxyphenyl Carbinol Applied to a Frog's Sciatic Nerve.

The sciatic nerve in both legs of a series of frogs was exposed and the action of the carbinol on motor and sensory block was determined in the manner previously described (page 14).

A 2% emulsion of diethyl o-oxyphenyl carbinol in 0.75% saline and 7% acacia was applied to the nerve of the left leg while the right leg, treated with 0.75% saline and 7% acacia, was used as a control.

Results from Diethyl o-Oxyphenyl Carbinol on Sensory Block.

Applied at 2:35 P.M. 5/5/20

+ = No sensory block.
o = Partial sensory block.
- = Complete sensory block.

Time	Left leg. Frog #										Right leg. Frog #									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
2:35	+	o	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
2:40	o	+	o	o	-	+	+	o	o	o	+	+	+	+	o	+	+	+	+	+
2:45	-	o	-	-	o	-	+	-	o	-	+	+	+	+	o	+	+	+	+	+
2:50	-	-	-	-	o	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+
3:50	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+
5:10	-	-	-	o	-	-	-	-	-	-	+	-	-	+	+	+	+	+	o	+

No motor block was encountered throughout the experiment.

Conclusions:

In the manner used, diethyl o-oxyphenyl carbinol is seen to produce sensory block on the sciatic nerve of frogs. This effect came on about ten minutes after application of the carbinol and continued indefinitely. No motor block results from this manner of using the carbinol.

Effect of Diethyl o-Oxyphenyl Carbinol on Blood Pressure and Respiration.

A cat was anesthetized and prepared for the recording of the respiration and blood pressure by the method described (page 13).

Respiration-Blood Pressure Tracing #1.

Male Cat #1 2400 Gm. 4/21/20 Ether anesthesia.

A Injected 0.1 mil 50% solution of diethyl o-oxyphenyl carbinol dissolved in 95% alcohol into the femoral vein. This was followed by 25 mils of 0.9% saline solution. The blood pressure at that time was 60 mm. Following a slight initial rise, the blood pressure fell until one minute after the beginning of injection (A) it was 18 mm. below the normal. The amplitude of the respiration was also decreased.

B Four minutes after (A). The blood pressure had increased until it was 2 mm. below normal. The anesthetic was discontinued.

C Two minutes after (B). The blood pressure had sharply fallen to 50 mm. below normal and the respiration had ceased. Artificial respiration was given for 45 seconds. The blood

pressure rose sharply but fell shortly after the artificial respiration was discontinued. By means of intermittent artificial respiration the animal was kept alive for about two hours. No further injections were made but the blood pressure continued to fall and the respiration ceased in each case shortly after artificial respiration had been stopped.

Conclusions:

It appears probable that the initial fall in blood pressure following the injection at (A) was instituted by the carbinol. The effects following this are thought to have been caused by magnesium sulphate solution which might have flown back from the carotid canulae and thus entered the circulation.

The effect on the respiration seems to be more pronounced than on the blood pressure.

Respiration-Blood Pressure Tracing #2.

Female cat #3 2700 Gm. 4/21/20 Ether anesthesia.

A Injected intravenously 0.1 mil of a solution of diethyl o-oxyphenyl carbinol (0.05 Gm) in 95% alcohol. This resulted in a fall in blood pressure of 27 mm. The pulse rate was not effected. The respiration decreased in amplitude but not in frequency.

B Eighteen minutes after beginning injection (A) the blood pressure spontaneously rose until it was 2 mm. below normal.

C Twenty-four minutes after beginning injection (A) the blood pressure was 4 mm. above normal - injected intravenously 0.1 mil of the same solution as at (A) during a space of 70 seconds. The blood pressure fell 25 mm., rate did not change, respiration stopped but was spontaneously resumed.

D Twenty minutes after (C), blood pressure was 4 mm. below normal - injected intravenously 0.1 mil of the same solution as at (A). Time for injection - 50 seconds. Blood pressure fell to 40 mm. below normal, gradually rose 3 mm., and then fell again. The respiration had stopped and artificial respiration was used to keep the animal alive.

E Forty minutes after (D), injected intravenously 0.2 mils of 1:1000 solution of adrenalin. The blood pressure rose 37 mm. but again quickly fell and artificial respiration was resumed.

F Ten minutes after (E) an intravenous injection of 0.2 mils of 1:1000 adrenalin solution produced a rise in blood pressure of 50 mm. This could not be maintained and the animal soon died.

Conclusions:

As in case #1 the respiration appeared to be effected to a greater extent than the blood pressure. The greater part of the effect may likewise be due here to magnesium sulphate.

The typical effect obtained at (E) and (F) from the injection of adrenalin shows that the mechanism by which this pressor effect is brought about is still functionally active.

It was decided that injections of alcohol solutions would not yield satisfactory results because the carbinol was largely precipitated out of solution upon coming into contact with the blood stream.

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In the experiments where the material was injected into loops of the intestines, an incision was made in the abdomen of the animal, a portion of the intestines exposed, and a hypodermic injection of the warm material made into the intestines.

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Respiration Blood Pressure Tracing #4.

Female rabbit #9 2800 Gm. 4/26/20 Ether Anesthesia

A Injected 0.6 Gm. diethyl o-oxyphenyl carbinol suspended in 3 mils of 7% acacia, 0.9% saline and 10% olive oil into loops of the small intestines.

B Twenty minutes after (A) blood pressure had fallen to 5 mm. below normal. This remained constant for forty minutes, then slowly decreased, ending in the death of the animal. No marked change in the respiration was noted until shortly before death.

Conclusions:

From the results obtained in this experiment it would appear that if diethyl o-oxyphenyl carbinol has any effect when injected into the intestines in the manner here used, it is very slight. This would indicate either that diethyl o-oxyphenyl carbinol when absorbed from the intestines of the rabbit has no

marked effect; or, that it is only slowly absorbed; or, that it is not absorbed at all.

Respiration Blood Pressure Tracing #5.

Male cat #10 3900 Gm. 4/28/20 Ether anesthesia

Effect of the injection of warm diethyl o-oxyphenyl carbinol emulsion into small intestines. Carbinol suspended in 7% acacia, 0.9% saline and 5% cottonseed oil 1 mil = 0.02 Gm. carbinol. Sodium citrate used in the cannula.

A Injected 10 mils of emulsion. No immediate effect.

B Fifteen minutes after (A), blood pressure had risen to 3 mm. above normal.

C Twenty-two minutes after (A) blood pressure was 2 mm. below normal. Injected 10 mils of emulsion. No immediate effect.

D Forty minutes after (C), blood pressure 12 mm. below normal. Injected 10 mils of emulsion. No marked effect.

E Eight minutes after (D) blood pressure 14 mm. below normal. Injected 20 mils of emulsion. No immediate effect.

The condition was but little altered one hour and forty minutes after (E). The blood pressure was 18 mm. below normal. Respiration not effected.

F Injected intravenously 2 mils of 25% magnesium sulphate solution. This was immediately followed by a cessation of the respiration, a fall in blood pressure and death of the animal.

Conclusion:

The results here obtained agree very well with those obtained in case #4 and likewise lead to the inference that diethyl o-oxyphenyl carbinol is not absorbed from the intestines, or very slowly absorbed, or else, that when it is absorbed it is practically without action. The total amount of carbinol injected was 1 Gm.

The results obtained from $MgSO_4$ would tend to confirm the inference that the results obtained in cases #1, and #2 were in a large measure due to this sulphate.

Respiration Blood Pressure Tracing #6.

Female dog #11 15 Kg 4/28/20 Ether anesthesia

Effect of injections into loops of the small intestines of an emulsion of diethyl o-oxyphenyl carbinol (1 mil = 0.02 Gm. carbinol) in 7% acacia, 0.9% saline and 5% cottonseed oil. Animal given 3.5 mils of 4% morphine sulphate. Sodium citrate used in the carotid cannula.

A Injected 14 mils of emulsion. No effect observed.

B Two hours after (A) blood pressure was normal. Injected 10 mils of emulsion.

C Stopped 15 minutes.

D Injected 10 mils of emulsion.

E Stopped 20 minutes.

F Injected 10 mils emulsion.

G Stopped 50 minutes.

H Injected 20 mils emulsion.

All during this time the respiration remained unchanged. The only alteration in the blood pressure was a decrease in the

amplitude.

I Injected 10 mils emulsion 55 minutes after (H)

J Injected 20 mils emulsion 3 minutes after (I)

K Stopped 15 minutes

L Injected 20 mils emulsion 18 minutes after (J)

M One hour after (L) condition practically unchanged. Animal had received a total of 2.3 Gm. of carbinol and had been anesthetized for over eight hours without a fall in blood pressure or important change in respiration.

Conclusion:

It was concluded that diethyl o-oxyphenyl carbinol when injected into the intestines in the manner here described is not absorbed or only slightly absorbed, or, if absorbed is without any marked effect. It was therefore considered advisable to administer the carbinol by another method.

Respiration Blood Pressure Tracing #7.

Male dog #33 9 Kg. 5/17/20 Ether anesthesia.

Effect of intravenous injections of diethyl o-oxyphenyl carbinol made into an emulsion with 7% acacia, 0.9% saline and 10% olive oil (1 mil = 0.1 Gm. carbinol) Animal given 2 mils of 4% morphine sulphate solution subcutaneously. Sodium citrate in cannula. All injections were made intravenously.

A Injected 2 mils carbinol emulsion (anesthetic discontinued). The blood pressure decreased in amplitude and fell to 23 mm below normal. The respiration stopped but restarted spontaneously.

B Five minutes after (A) blood pressure 1 mm. above normal. Injected 2 mils 10% emulsion of olive oil in 7% acacia and 0.9% saline. Gradual fall in blood pressure to 4 mm. below normal.

C Five minutes after (B), blood pressure 4 mm. below normal. Injected 5 mils of carbinol emulsion. Blood pressure quickly fell to 34 mm. below normal. The respiration stopped, but spontaneously restarted.

D Three minutes after (C). Artificial respiration.

E Five minutes after (D). Blood pressure 35 mm. below normal. Injected 0.1 mils 1:1000 adrenalin solution. Blood pressure rose to 11 mm. above normal, and the respiration was resumed.

F Six minutes after (E), blood pressure 10 mm. below normal. Injected 5 mils of a 10% emulsion of olive oil. No effect noted.

G Four minutes after (F), blood pressure 4 mm. below normal. Injected 4 mils carbinol emulsion. Blood pressure fell to 50 mm. below normal and the respiration stopped. Death followed. Considerable fluid was expressed from the lungs after death.

Conclusions:

The intravenous injection of diethyl o-oxyphenyl carbinol dissolved in olive oil and made into an emulsion with acacia and saline appears to give dependable results. A comparison of the effects obtained through the intravenous injection of the carbinol emulsion with those from a simular emulsion

not containing the carbinol permit a definite appreciation of the action of the carbinol alone. The results so obtained show that the administration of diethyl o-oxyphenyl carbinol in the manner here described produces a marked fall in blood pressure with a slight decrease in the frequency of the beats. The respiration is also stopped by this carbinol. The pressor effect obtained by the injection of adrenalin (E) shows that the mechanism by which this is brought about is still functionally active. It is also seen that the injection of the olive oil emulsion exerts only a very slight effect.

The accumulation of fluid noted at the end of the experiment may indicate that the carbinol is carried through the circulation to the lungs and as the result of an irritating action is responsible for the production of this fluid. On the other hand the explanation of Brown (30) for acute edema of the lung may serve to explain this condition. Acute edema of the lung is here considered to be caused by a sudden and temporary dilation of the left ventricle, including the auriculo-ventricular orifice and the consequent acute regurgitation and engorgment of the pulmonary capillaries.

The edema may likewise be caused in a manner analogous to that by which pilocarpine acts, that is by direct stimulation of the secretory glands.

Little may be said regarding the toxicity of the carbinol from this experiment for the manner in which the olive oil would influence the results is not known.

Blood Pressure Respiration Tracing #8

Female Dog #35 5.8 Kg. 5/17/20 Ether anesthesia.

Animal given 1.5 mils 4% morphine sulphate solution subcutaneously.

Effect of intravenous injections of a 10% emulsion of diethyl o-oxyphenyl carbinol in 10% olive oil 7% acacia and 0.9% saline solution. Controlled by injections of 10% olive oil emulsion.

A Injected 1 mil of carbinol emulsion. Blood pressure not recording, respiration decreased in amplitude.

B Stopped to remove blood clot. Anesthetic discontinued.

C Three minutes after (B), blood pressure 8 mm. below normal. Injected 1 mil of carbinol emulsion. Blood pressure fell to 33 mm. below normal. Respiration decreased in amplitude.

D Three minutes after (C), stopped for 5 minutes.

E Four and one half minutes after (D), blood pressure 18 mm. below normal. Injected 2 mils 10% olive oil emulsion. No effect noted.

F Four minutes after (E), blood pressure 11 mm. below normal. Injected 1.5 mils of carbinol emulsion. The blood pressure fell to 37 mm. below normal, and the respiration decreased in amplitude.

G Six minutes after (F), injected 2 mils of 10% olive oil emulsion. No effect noted.

H Three minutes after (G), blood pressure 23 mm. below normal. Injected 2 mils of carbinol emulsion. The blood pressure fell to 44 mm. below normal.

7-20 2M

I Eight minutes after (H), injected 2 mils 10% olive oil emulsion. No effect noted.

J Six minutes after (I), blood pressure 22 mm. below normal Injected 2 mils of carbinol emulsion. The blood pressure fell to 48 mm. below normal and the respiration was greatly decreased in amplitude.

K Seven minutes after (J), blood pressure 41 mm. below normal. Injected 1 mil of carbinol emulsion. The blood pressure fell to 48 mm. below normal and the respiration was slightly decreased in amplitude.

L Four and one half minutes after (K), blood pressure 45 mm. below normal. Injected 1 mil carbinol emulsion. The blood pressure fell to 49 mm. below normal and the respiration was decreased in frequency.

M Five minutes after (L), injected 2 mils of 10% olive oil emulsion. No effect noted.

N Two minutes after (M), injected 2 mils of carbinol emulsion. The blood pressure fell, the respiration ceased and death resulted. Considerable fluid was expressed from the lungs.

Conclusions:

The results obtained here are practically the same as those obtained in Tracing #7 and the same conclusions with the exception of those regarding the use of adrenalin may be drawn in this case.

Summary:-

A final consideration of the experiments on the effects of diethyl o-oxyphenyl carbinol on the respiration and the blood pressure lead to the following conclusions. The intravenous injection of this carbinol dissolved in alcohol does not yield satisfactory results probably due to the carbinol precipitating out of solution when it came into contact with the blood stream.

The injection of an emulsion containing the carbinol into loops of the intestines was without dependable results and lead to the conclusions that the carbinol was not absorbed or only absorbed very slowly, or else, if absorbed, was without any marked effect.

The results obtained thru the intravenous injection of the carbinol emulsion were more dependable and lead to the following conclusions. Smaller doses (0.2 Gm.) of the carbinol produce a marked fall in blood pressure and a cessation of the respiration from which the animal spontaneously recovers. With larger doses a more pronounced action on the blood pressure and respiration is encountered and artificial respiration is necessary to bring about recovery of the animal. The administration of adrenalin at this stage demonstrates that the mechanism through which the pressor effect is obtained is still functionally active. Artificial respiration and adrenalin are ineffective in restoring the animal after the administration of large doses of the carbinol. An explanation of the pulmonary edema observed during these experiments has been attempted in the conclusion of tracing #7 (page 36).

Comparison of the Physiological Actions of Diethyl o-Oxyphenyl Carbinol with Some Chemically Related Compounds.

Diethyl o-oxyphenyl carbinol may be considered as the product obtained by the substitution of two ethyl groups for the two inactive hydrogens of saligenin. From the action of this former compound on the frog's sciatic nerve it appears rather likely that it possesses some local anesthetic action but not to the same degree as saligenin. The irritant action of diethyl o-oxyphenyl carbinol would likewise militate against the application of this carbinol to man.

The sedative action following the oral administration of diethyl o-oxyphenyl carbinol is not unlike that obtained in a simular manner from saligenin, but the presence of the two substituted ethyl groups did not enhance the narcotic action of the compound in the manner which was expected from a theoretical consideration of the compound.

TRICHLORMETHYL PHENYL CARBINOL

Preparation of Trichlormethyl Phenyl Carbinol.

Trichlormethyl phenyl carbinol ($C_6H_5CHOHCCl_3$) was prepared by a modification of the method of Jocitsch (31). Benzaldehyde 50 Gm. (redistilled), chloroform 50 Gm., and anhydrous ether 50 Gm. was slowly treated and shaken with 10 Gm. of finely pulverized dry potassium hydroxide. The mixture was cooled throughout the reaction. The mixture became solid and was allowed to stand for a day or more and shaken occasionally. The flask should not be too tightly stoppered during this time for carbon monoxide and probably hydrogen are set free in small amounts through a side reaction and a violent explosion of the mixture may result.

After having stood for the proper length of time, the mixture became semi-fluid. It was then treated with a sufficient quantity of water to dissolve the solid portion of the mixture. The upper layer was drawn off and the water layer extracted several times with ether. The ether extraction was added to the upper layer previously drawn off and the mixture evaporated under reduced pressure to remove the ether. The remaining liquid was dried over calcium chloride, filtered, and then fractionally distilled under reduced pressure. Yield 30 Gm. carbinol boiling at 154-5° at 25 mm. pressure. Sp.Gr.1.45.

Trichlormethyl phenyl carbinol is a colorless viscous oil with a peculiar sharp irritating odor, very slightly soluble in water, more soluble in alkalies and readily soluble in organic solvents.

Reaction:-

$$C_6H_5CHO + CHCl_3 \text{ -------)- } C_6H_5CHCCl_3(OH)$$

Theoretical Consideration of Trichlormethyl Phenyl Carbinol.

In taking up the study of trichlormethyl phenyl carbinol ($C_6H_5CHOHCCl_3$), it may be advantageous to consider some of the compounds with which it is related in order that the modifications in physiological action induced by the change in chemical structure may be better appreciated.

Trichlormethyl phenyl carbinol may be considered as a substitution product of benzyl alcohol ($C_6H_5CH_2OH$) and an examination of the former compound should show how the substitution of the $-CCl_3$ group for one of the inactive hydrogen atoms alters the local anesthetic action, the toxicity, etc., of benzyl alcohol.

In an inverse manner, trichlormethyl phenyl carbinol may be considered as a substitution product of chloroform, where the hydrogen atom of chloroform has been replaced by the $-CHOH-C_6H_5$ group. It is also the trichlor derivative of methyl phenyl carbinol ($C_6H_5CHOHCH_3$) the physiological action of which has been considered earlier in this article.

According to von Mering (32) chloral hydrate exerts its hypnotic action in the organism after being converted to trichlorethyl alcohol (trichlormethyl carbinol) CCl_3CH_2OH (which, moreover, when administered directly, acts exactly like chloral) Since trichlormethyl phenyl carbinol differs from this compound simply in having one of the hydrogen atoms replaced by a

phenyl (C_6H_5) group, it should possess a more or less modified trichlorethyl alcohol action.

Trichlormethyl dimethyl carbinol (trichlor tertiary butyl alcohol, chloretone) $(CH_3)_2C(OH)CCl_3$), which is a very useful hypnotic, differs from trichlormethyl phenyl carbinol, in that one methyl group has replaced the phenyl group while a second methyl group has been substituted for one of the inactive hydrogen atoms.

The relation of trichlormethyl phenyl carbinol to its parent substance benzene may also be noted, while it is perhaps too distantly related to methyl alcohol (CH_3OH) having the $-CCl_3$ and the C_6H_5 groups substituted for two of the hydrogens) to expect any special simularity to that compound.

Attention is also called to the fact that trichlormethyl phenyl carbinol contains an asymmetric carbon atom. The importance of this fact is too problemetical to formulate any theoretical premises. The preparation used in the following investigations was of course in the racemic (dl-) form.

Investigation of Trichlormethyl Phenyl Carbinol.

Trichlormethyl phenyl carbinol is a heavy liquid possessing a peculiar irritating odor. It vaporizes readily with steam, and when in this condition it has a decided lacrymatory action. On the skin or mucous membrane it exerts a marked burning action, while on the tongue it has a sharp biting taste with no local anesthetic effect.

In an investigation of the physiological action of this compound, subcutaneous injections were made in white rats, frogs,

and rabbits and the effect noted. Trichlormethyl phenyl carbinol was applied to the exposed sciatic nerve of a series of frogs for the purpose of determining its action under these conditions.

A series of animals were prepared for the recording of blood pressure and respiration. The carbinol was injected in these animals and a record made of the results so obtained.

Its action as a general anesthetic was investigated by allowing animals to inhale this substance for various periods of time.

The carbinol appeared to be too irritant in its action to make it advisable that subcutaneous injections in man should be made.

Action of Trichlormethyl Phenyl Carbinol on White Rats

Trichlormethyl phenyl carbinol was injected subcutaneously into a series of white rats and their reaction to this injection was noted. Special regard was placed on those actions which might assist in determining the hypnotic nature of the carbinol.

Experiment I.

Rat #1 Weight 64 Gm. 12-11-19.

4:30 P.M. Injected 0.025 mils trichlormethyl phenyl carbinol subcutaneous (0.39 mils per Kg.)

4:45 P.M. No change noted.

5.00 P.M. Slight difficulty in walking. Partial paralysis of hind legs.

5:05 P.M. No change noted.

5:10 P.M. No change noted.

5:20 P.M. Became more quiet.

6:20 P.M. Quiet, ear veins dilated, respiration rapid.

8:05 P.M. Very quiet, reflexes deadened.

10:00 P.M. Quiet, still able to move, reflexes deadened.

7:00 A.M. 12/12/19 Quiet, appears drowsy.

1:15 P.M. More lively, moves about with but slight difficulty.

4:05 P.M. Normal.

Experiment II.

Rat #2 Weight 63 Gm. 12/11/19

4:30 P.M. Injected 0.05 mils trichlormethyl phenyl carbinol subcutaneously (0.79 mils per Kg.)

4:45 P.M. No change noted.

5:00 P.M. Difficulty in walking.

5:10 P.M. Drowsy.

5:20 P.M. Quiet, respiration more rapid.

6:30 P.M. Very quiet, reflexes deadened, movements uncertain.

8:05 P.M. Deep sleep, reflexes absent, respiration slow and shallow.

10:00 P.M. Deep sleep. Only faintly responds to electrical stimulation.

7:00 A.M. 12/12/19 Dead.

Experiment III.

Rat #3 Weight 70 Gm. 12/11/19.

4:30 P.M. Injected 0.1 mils trichlormethyl phenyl carbinol subcutaneously (1.43 mils per Kg.)

4:45 P.M. No change noted.

5:00 P.M. Difficulty in walking.

5:05 P.M. Drowsy. Sense of direction impaired.

5:10 P.M. Not able to hold head up. Ear veins dilated.

5:20 P.M. Remains in any position except on the back. Breathing slow.

5:25 P.M. Remains on back when so placed.

5:35 P.M. Deep sleep. Reflexes absent. Cries in sleep. Respiration slow and shallow.

8:05 P.M. Deep sleep. Reflexes absent. Cries in sleep. Respiration slow and shallow.

10:00 P.M. Dead. Nothing important noted at necropsy. Heart in diastole.

Conclusions:

These experiments show that trichlormethyl phenyl carbinol when injected in non toxic doses subcutaneously in rats has a decidedly sedative action, but the hypnotic effect is lacking. Toxic doses, first produce a sedative effect, followed, after an interval, partly dependent on the size of the dose, by a complete narcosis.

The toxic dose for white rats is between 0.39 and 0.79 mils per Kg. or, since the specific gravity of the carbinol is 1.45, this would be equivalent to 0.59 - 1.14 Gm. per Kg. If a dose greater than the toxic dose is administered the symptoms

are simular to those obtained from a toxic dose but occur somewhat sooner.

Action of Trichlormethyl Phenyl Carbinol on Frogs.

Varying amounts of trichlormethyl phenyl carbinol were injected into the anterior lymph sac of a series of frogs. These injections were made for the purpose of determining the toxic dose of the carbinol for frogs and also the physiological action under the same conditions.

Experiment I.

Frog #1 Weight 45 Gm. 1/14/20.

3:40 P.M. Injected 0.5 mils trichlormethyl phenyl carbinol in the anterior lymph sac.

3:42 P.M. Very quiet. Able to maintain equilibrium.

3:46 P.M. Not able to turn over.

3:51 P.M. Heart exposed. Reflexes barely present.

4:40 P.M. Reflexes lost.

8:40 P.M. Dead.

Experiment II.

Frog #2 Weight 36 Gm. 1/15/20.

10:00 A.M. Injected 0.1 mil trichlormethyl phenyl carbinol into anterior lymph sac.

11:05 A.M. Prostrated.

6:00 P.M. Dead. Heart in diastole.

Experiment III.

Frog #3 Weight 72 Gm. 1/15/20

10:00 A.M. Injected 0.1 mil trichlormethyl phenyl carbinol into the anterior lymph sac.

10:45 A.M. Partially narcotized.

11:30 A.M. Not able to turn over.

8:30 P.M. Dead. Heart in diastole.

Experiment IV.

Frog #4 Weight 78 Gm. 1/15/20.

10:15 A.M. Injected 0.4 mils trichlormethyl phenyl carbinol into the anterior lymph sac.

11:05 A.M. Partially narcotized.

8:30 P.M. Dead.

Experiment V.

Frog #5 Weight 46 Gm. 1/15/20.

3:10 P.M. Injected 0.5 mils trichlormethyl phenyl carbinol into anterior lymph sac.

3:25 P.M. Partially narcotized.

3:35 P.M. Not able to turn over.

8:00 P.M. Dead.

Experiment VI.

Frog #6 Weight 70 Gm. 1/15/20

3:10 P.M. Injected .025 mils trichlormethyl phenyl into the anterior lymph sac.

3:40 P.M. Not able to turn over.

8:30 P.M. Heart beating strong.

11:25 P.M. Dead.

Experiment VII.

Frog #7 Weight 48 Gm. 1/16/20.

10:00 A.M. Injected 0.1 mil trichlormethyl phenyl carbinol emulsion (1 mil = 0.02 mils) into anterior lymph sac.

12:00 A.M. Appeared normal.

9:00 P.M. Quiet.

8:05 A.M. 1/17/20 Normal.

Experiment VIII.

Frog #8 Weight 32 Gm. 1/16/20.

10:10 A.M. Injected 0.2 mils trichlormethyl phenyl carbinol emulsion (1 mil = 0.02 mils) into the anterior lymph sac.

12:10 P.M. Barely able to turn over.

1:00 P.M. Deep stupor.

9:00 P.M. Still quiet.

8:05 A.M. 1/17/20 Normal

Experiment IX.

Frog #9 Weight 47 Gm. 1/16/20.

2:00 P.M. Injected 0.3 mils trichlormethyl phenyl carbinol emulsion (1 mil = 0.02 mils) into the anterior lymph sac.

4:20 P.M. Quiet.

9:00 P.M. Deeply narcotized.

8:05 A.M. 1/17/20 Normal

Experiment X.

Frog #10 Weight 51 Gm. 1/16/20-

2:00 P.M. Injected 0.2 mils trichlormethyl phenyl carbinol emulsion (1 mil = 0.02 mils) into the anterior lymph sac.

9:00 P.M. Quiet.

8:05 A.M. 1/17/20 Normal

Experiment XI.

Frog #11 Weight 27 Gm. 1/16/20

2:00 P.M. Injected 0.1 mils trichlormethyl phenyl carbinol emulsion (1 mil = 0.02 mils) into the anterior lymph sac.

9:00 P.M. Quiet.

8:05 A.M. 1/17/20 Normal.

Experiment XII - XXI.

Emulsion of trichlormethyl phenyl carbinol (1 mil = 0.01 mil) was injected into the anterior lymph sac of frogs 12 - 21. The result in each case was practically the same:-

Frog	#12	Weight	29 Gm.	3 mils	emulsion	
"	#13	"	37 "	3.5 "	"	
"	#14	"	52 "	4.1 "	"	Injection given 3:20 P.M. 1/23/20.
"	#15	"	30 "	2.1 "	"	
"	#16	"	30 "	1.8 "	"	Complete prostration 7:30 P.M.
"	#17	"	53 "	0.53 "	"	
"	#18	"	29 "	0.87 "	"	Complete prostration 8:30 A.M. 1/24/20.
"	#19	"	30 "	0.6 "	"	Dead 9:00 A.M. 1/25/20.
"	#20	"	20 "	2.6 "	"	
"	#21	"	24 "	1.2 "	"	

Conclusions:-

Toxic or greater than toxic doses of trichlormethyl phenyl carbinol in frogs gives rise to symptoms decidedly simular to those encountered in rats.

In order to administer small doses, it was necessary to give the carbinol in a diluted form. Since this compound is practically insoluble in water it appeared advisable to use an acacia emulsion. This emulsion was far from being hemogenous and therefore it could not be definitely known that equal quantities of the emulsion contained the same amount of carbinol. It may be due to this fact that findings following the administration of the emulsion to frogs were so discordant. The toxicity for frogs appears to be of the same order as for mice.

With toxic or greater than toxic doses, the frog underwent a gradual narcosis. This was superseded by a coma which continued to grow more marked until death took place.

Frogs which received a dose below the toxic dose, simply became more quiet a few hours after the injection, remained in this condition for several hours and then spontaneously recovered.

Action of Trichlormethyl Phenyl Carbinol on Rabbits.

Varying amounts of trichlormethyl phenyl carbinol were injected subcutaneously into a series of rabbits. These injections were made for the purpose of determining the toxic dose of the carbinol for rabbits and also the physiological action of the carbinol under the same conditions.

Experiment I.

Rabbit #1 Weight 1300 Gm. 1/23/20

9:15 A.M. Injected 1.61 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

5:20 P.M. No change noted.

2/11/20 Dead (after 19 days)

Experiment II.

Rabbit #2 Weight 1600 Gm. 1/23/20

9:15 A.M. Injected 0.75 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

5:20 P.M. Sleepy and weakened.

1:30 P.M. Symptoms more marked.

8:30 A.M. 1/24/20 Still weak.

3:00 A.M. Normal.

Experiment III.

Rabbit #3 Weight 1600 Gm. 1/23/20

9:15 A.M. Injected 1.25 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

5:20 P.M. No change noted.

8:30 A.M. 1/24/20 Completely narcotized.

3:00 P.M. 1/24/20 Still sleepy.

8:30 A.M. 1/25/20 Normal.

Experiment IV.

Rabbit #4 Weight 1800 Gm. 1/23/20

1:20 P.M. Injected 1.67 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

4:30 P.M. Partially narcotized.

6:30 P.M. Completely narcotized.

8:45 A.M. 1/24/20 Dead.

Necropsy:- Lungs slightly conjested. Heart in diastole. Liver, stomach and kidneys appeared normal.

Experiment V.

Rabbit #5 Weight 1500 Gm. 1/23/20

1:20 P.M. Injected 2.67 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

5:20 P.M. No change noted.

1/24/20 1/25/20 No change noted.

Experiment VI.

Rabbit #6 Weight 1200 Gm. 1/23/20

1:50 P.M. Injected 3.34 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

4:30 P.M. Ear veins dilated.

5:20 P.M. Partially narcotized. Weakened and sleepy.

6:30 P.M. Completely narcotized.

8:45 A.M. 1/24/20 Dead.

Necropsy:- Lungs conjested, sections blackened. Pleural cavity filled with fluid. (edema)

Experiment VII.

Rabbit #7 Weight 1300 Gm. 2/23/20

10:45 A.M. Injected 2.1 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

9:00 P.M. No change noted.

8:00 A.M. 2/24/20 Normal.

Experiment VIII.

Rabbit #8 Weight 1300 Gm. 2/23/20

10:45 A.M. Injected 1.61 mils trichlormethyl phenyl carbinol subcutaneous.

9:00 P.M. No change noted.

8:00 A.M. 2/24/20 Normal.

Experiment IX.

Rabbit #9 Weight 1300 Gm. 2/27/20

2:15 P.M. Injected 3 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

3:45 P.M. Quiet.

4:40 P.M. Prostrated. Breathing slow and shallow. Pulse rapid. Ear veins dilated. Lid reflexes very weak.

8:30 P.M. No change noted.

10:40 P.M. Complete prostration, coma.

7:00 A.M. 2/28/20 Dead.

Necropsy:- Pupils contracted. Ear veins dilated. Odor of carbinol very noticeable on opening body. Hemorrhagic about point of injection. Lungs slightly hemorrhagic. Heart in mid position. Auricles distended. Liver blanched on under surface.

Experiment X.

Rabbit #10 Weight 2100 Gm. 2/27/20.

2:15 P.M. Injected 2.5 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

6:00 P.M. Slightly weakened. Ear veins dilated.

8:30 P.M. Conditions more marked. Breathing rapid. Not able to walk, but can crawl.

10:40 P.M. Unable to stand.

7:00 A.M. 2/28/20 Completely prostrated. Heart slow. Respiration slow and shallow (26 per minute) Pupils contracted. Odor of carbinol not noticeable in

mouth or in breath. Ear veins not dilated.

8:00 A.M. 2-29-20 Dead.

Experiment IX.

Rabbit #11 Weight 1800 Gm. 2/27/20

2:15 P.M. Injected 2.67 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

10:40 P.M. No change noted.

2:35 P.M. 2/28/20 Normal.

3/1/20 "

3/3/20 "

Experiment XII.

Rabbit #12 Weight 1900 Gm. 2/27/20.

2:15 P.M. Injected 2.48 mils per Kg. trichlormethyl phenyl carbinol subcutaneous.

10:40 P.M. No change noted.

2:35 P.M. 2/28/20 Normal.

3/1/20 "

3/3/20 "

Conclusions:-

Rabbits appear to be relatively more resistant to trichlormethyl phenyl carbinol than frogs or rats, otherwise the effects are very simular.

Non toxic doses administered subcutaneously have a sedative action though it is not of constant appearance. In certain cases it is entirely absent, in other cases, it is barely recognizable, while in other cases it is very noticeable. The appearance of this sedative action does not appear to be directly associated with the size of the dose.

The administration of a toxic dose is uniformly followed by the appearance of the sedative effect. This is followed after several hours by an increasingly pronounced narcotic action. The animal lies in a stupor, reacts slightly or not at all to external stimulation, and the respiration and heart rate are both retarded. This condition merges into coma, during which the animal gradually passes into death.

The exact cause of death was not determined. Following practically all doses of the carbinol given to rabbits, the animals became more quiet. In many cases this was followed by narcosis, but this transition was so gradual and ill-defined that no definite statement can be made regarding the exact quantity of carbinol which comprises the narcotic dose. For this reason, the ratio between the narcotic dose and the toxic dose can not be stated.

The toxic dose following subcutaneous injection in rabbits is about 2.5 mils per Kg. or, since trichlormethyl phenyl carbinol has a specific gravity of 1.45, this would be equivalent to

3.6 Gm. per Kg.

Congestion of the lungs was the most common and important necropsy finding.

The observation in the case of Rabbit #9 that the odor of the carbinol could be distinctly identified on opening the thorax tends to show that this compound is both slowly destroyed and eliminated in the animal organism or else not destroyed at all.

Action of Trichlormethyl Phenyl Carbinol as a General Anesthetic for Frogs.

On account of the relationship in structure which has been pointed out as existing between trichlormethyl phenyl carbinol and chloroform, it was considered as being of at least theoretical importance to administer the carbinol by inhalation and so determine its effectiveness as a general anesthetic.

Experiment I.

9:10 A.M. Frog placed under an inverted funnel with a watch glass containing several drops of trichlormethyl phenyl carbinol.

9:15 A.M. Very restless.

9:35 A.M. More quiet.

10:05 A.M. Not able to turn over when placed on back.

1:00 P.M. Complete anesthesia. Removed from funnel.

3:00 P.M. Dead.

Experiment II.

1:10 P.M. Frog placed under funnel with trichlormethyl phenyl carbinol as in Experiment I.

1:15 P.M. Very restless.

1:20 P.M. Quiet. Partially anesthesia.

1:35 P.M. Not able to turn over.

2:00 P.M. Completely anesthetized.

3:10 P.M. Dead.

Conclusions:-

This limited series of experiments seems to show that although trichlormethyl phenyl carbinol possesses general anesthetic properties, the application of the carbinol for this purpose is precluded by the fact that a considerable interval of time is required for the anesthesia and the frogs used in these experiments did not recover from the sleep so produced.

Trichlormethyl Phenyl Carbinol as a General Anesthetic.
for Guinea Pigs.

Trichlormethyl phenyl carbinol was administered by inhalation to a guinea pig tied to an animal board. An animal ether mask was used for the administration. The gauze was saturated with the carbinol and the animal allowed to inhale the carbinol by breathing through the mask in a manner identical with that by which ether would be administered.

Experiment I.

Guinea Pig #1

10:20 A.M. Administration began.

10:21 A.M. Breathing more rapid and deeper.

10:25 A.M. Animal excited. Respiration rapid and shallow. Pulse rapid.

10:30 A.M. Animal still excited.

10:33 A.M. Dead.

Necropsy:- No findings of importance. No odor of trichlormethyl phenyl carbinol noted on opening the lungs.

Experiment II.

Guinea Pig #2.

8:10 A.M. Administration of trichlormethyl phenyl carbinol begun as in Experiment I.

8:12 A.M. Breathing faster and deeper.

8:14 A.M. No change in sensibility noted. Respiration and pulse rapid.

8:28 A.M. Excited, screams, and kicks about.

8:35 A.M. Respiration irregular.

8:40 A.M. More relaxed. No other signs of anesthesia.

8:50 A.M. Still rather active.

8:55 A.M. Restless, Active, Heart rate increased. Cloudy urine passed.

9:05 A.M. Released, weak; able to stand but cannot walk. Shivers. Pupils not dilated.

10:00 A.M. Normal.

Conclusion:-

The experiments in which trichlormethyl phenyl carbinol was administered to frogs or guinea pigs by inhalation show that this carbinol has general anesthetic properties. Complete anesthesia is only obtained after the administration has been continued for a long period of time and the animals so anesthetized do not recover.

Effect of Trichlormethyl Phenyl Carbinol Applied to a Frog's Sciatic Nerve.

The sciatic nerve in both legs of a series of frogs was exposed and the action of the carbinol on motor and sensory block was determined in the manner described under "Scope of the Physiological Actions of the Carbinols Investigated." (Page 14)

A 2% emulsion of the carbinol in 0.75% sodium chloride and 7% acacia was applied to the sciatic nerve of the left leg, while the nerve of the right leg, treated with 0.75% sodium chloride and 7% acacia solution was used as a control.

Results on Sensory Block.

Applied at 2:45 P.M. 5/4/20

+ = No sensory block.
0 = Partial " "
- = Complete" "

Time	Left Leg Frog #										Right Leg Frog #									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
2:45	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2:53	-	-	0	-	-	-	+	-	-	-	+	+	+	+	-	+	+	+	+	+
3:05	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+
3:05	Cotton pledget removed and nerves thoroly washed.																			
3:15	-	-	-	+	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+
3:30	0	0	-	+	0	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+
3:40	0	+	+	+	+	+	+	+	+	+	+	+	+	0	+	+	+	+	+	+

No motor block was encountered throughout the experiment.

Conclusion:-

Trichlormethyl phenyl carbinol in a 2% emulsion produces complete sensory block without noticeable disturbance to the motor fibres a few minutes after application to a frog's sciatic nerve.

This inhibition of the sensory fibers is not accompanied by motor block and continues for some time but can be made to dissappear by complete removal of the carbinol from the nerve.

Effect of Trichlormethyl Phenyl Carbinol on Blood Pressure and Respiration.

A series of animals were prepared for the recording of the respiration and blood pressure in the manner described (page 13) and trichlormethyl phenyl carbinol then injected with results as follows:

Respiration Blood Pressure Tracing #9.

Female dog #19 7.6 Kg. 5/5/20 Ether anesthesia.

Animal given 1.8 mils of a 4% morphine sulphate solution subcutaneously.

Effect of the intravenous injection of a 10% emulsion of trichlormethyl phenyl carbinol suspended in 7% acacia and 0.9% saline.

A Injected 1 mil of emulsion. Ether discontinued. The blood pressure fell 25 mm. during the injection. Respiration greatly embarrassed.

B Ten minutes after (A), blood pressure 13 mm. below normal. Stopped 15 minutes. The blood pressure rose to normal and the respiration again became normal.

C One and one half minutes after (B), blood pressure 1 mm. above normal. Injected 1 mil of emulsion. The blood pressure fell to 20 mm. below normal during the injection but quickly rose until 1 mm. below normal and remained constant. The respiration was more permanently effected by this injection. The amplitude was increased but the rate was greatly decreased and did not make so rapid a recovery as the blood pressure.

D Five minutes after (C) stopped 5 minutes. Upon restarting, the systolic pressure remained constant but the diastolic pressure had increased so that the amplitude was only one half so great as before.

E Two minutes after (D), injected 1 mil of emulsion. The amplitude of the blood pressure increased and the blood pressure fell, at the lowest point being 20 mm. below normal. It rose quickly to 8 mm. below normal and then remained constant.

F Four and one half minutes after (E), the blood pressure was 6 mm. below normal. Injected 2 mils of the emulsion. The blood pressure quickly fell to 24 mm. below normal. The pulse rate was decreased but soon returned to normal. The respiration rate at first increased, then decreased and finally entirely ceased. An asphyxial rise in the blood pressure occured. Artificial respiration was begun at (G) and continued for 20 minutes to (I).

H One hundred mils of a foamy fluid tinged with blood was expressed from the lungs. Respiration at an increased rate began again at (I). The blood pressure was then 12 mm. below normal.

J Four minutes after (I) stopped 10 minutes. Impossible to express further liquid from the lungs. On restarting, the blood pressure was 23 mm. below normal and the respiration rate was greatly decreased.

K One minute after (J), injected 0.5 mils of emulsion. The blood pressure increased markedly in amplitude but the height gradually fell until 30 mm. below normal. The

respiration rate was greatly decreased.

L Three minutes after (K), expressed 25 mils of fluid from the lungs. The respiration began to improve but the blood pressure continued to fall and death occured despite artificial respiration at (M).

Necropsy disclosed a marked edema of the lungs. The kidney, liver and spleen had a purple tinge.

Conclusions:-

The intravenous injection of trichlormethyl phenyl carbinol in the manner described produces a decided fall in blood pressure and an embarrassment of the respiration. The animal spontaneously recovers from small doses (0.1 mil) of the carbinol. The effects obtained from the first injection of the carbinol are more pronounced than those obtained from subsequent doses of the same magnitude.

The asphyxial rise in blood pressure at (G) as well as the marked embarrassment to the respiration noted after each injection, would indicate that the carbinol produces a more marked effect on the respiration than on the blood pressure. This effect is undoubtedly closely associated with the severe pulmonary edema observed during the latter part of this experiment.

Respiration Blood Pressure Tracing #10-

Male dog #25 5.4 Kg. 5/13/20 Ether anesthesia

Effect of intravenous injections of a 10% emulsion of trichlormethyl phenyl carbinol in 7% acacia and 0.9% saline. Injections of a 10% emulsion of olive oil were given for controls. The animal was given 1.4 mils of a 4% morphine sulphate solu-

tion subcutaneously.

A Injected 1 mil of carbinol emulsion. The blood pressure remained practically constant during the injection but then fell to 20 mm. below normal. The amplitude of the respiration was decreased.

B Six minutes after (A), stopped 5 minutes.

C One half minute after (B) blood pressure 2 mm. below normal. Injected 1 mil of olive oil emulsion. The blood pressure fell to 8 mm. below normal but quickly returned to 2 mm. below normal. The respiration was unaffected.

D Four and a half minutes after (C), blood pressure normal. Injected 1 mil of carbinol emulsion. The blood pressure fell to 22 mm. below normal and became very uneven in character.

E Ten minutes after (D) injected 1 mil of olive oil emulsion. No effect noted.

F Three and a half minutes after (E), blood pressure normal. Injected 1 mil of carbinol emulsion. The blood pressure fell to 30 mm. below normal. The respiration practically stopped but gradually recovered.

G Eleven minutes after (F), blood pressure 4 mm. below normal Injected 1 mil of carbinol emulsion. The blood pressure fell to 30 mm. below normal. The respiration stopped but recovered spotaneously.

H Four minutes after (G), blood pressure 13 mm. below normal. Injected 2 mils of olive oil emulsion. No effect observed.

I Two and a half minutes after (H), blood pressure 13 mm. below normal. Injected 1 mil of carbinol emulsion. The blood pressure fell to 28 mm. below normal, the respiration ceased and death resulted.

Expressed 200 mils of fluid from the lungs.

Conclusions:

The results obtained in this experiment are in close agreement with those obtained in Tracing #9. They show that small doses of the carbinol produce a decided fall in the blood pressure and a slowing in the rate of respiration. The animal shows good recovery from these small doses. The results obtained in this tracing did not seem to indicate that subsequent doses of the carbinol produce a less noticable effect then the initial injection. Considerable pulmonary edema was encountered in this case. The comparison of the effects obtained from the injection of the carbinol with those from a similar dose of olive oil show that the effects ascribed to the carbinol are not the mechanical effects of oil but probably the effects of the trichlormethyl phenyl carbinol following absorption.

Respiration Blood Pressure Tracing #11.

Female Cat #28 2100 Gm. 5/12/20 Ether anesthesis.

Effect of the intravenous injection of a 10% emulsion of trichlormethyl phenyl carbinol suspended in 7% acacia and 0.9% saline solution.

A Injected 1 mil of carbinol emulsion.

The blood pressure fell to 50 mm. below normal, partly recovered and then fell again. The respiration ceased and death took place.

Conclusions:

The results here obtained accord very well with those noted in Tracings #9 and #10, altho the effect following the initial injection is here more marked. A gradual but steady decrease in the amplitude of the respiration is observed following the injection of the carbinol, while the blood pressure fell suddenly, and then partly recovered before the final fall occured. No pulmonary edema was noted in this case.

Summary:

The intravenous injection of trichlormethyl phenyl carbinol in the manner here employed, gives rapid, dependable results. Small doses cause a decided embarrassment of the respiration and a fall in the blood pressure. It could not be definitely stated whether or not the respiration was effected to a greater extent than the blood pressure, altho several observations pointed to such a conclusion.

The observation in Tracing #9/ and #11, that the initial dose produced a greater effect than subsequent injections was not duplicated in the other tracings. The pulmonary edema observed in these experiments would appear to be the direct effect of the carbinol, and since it was absent in Tracing #11 it would appear that an appreciable period of time is required for this edema to become noticable. Since trichlormethyl phenyl carbinol has an irritant action on mucous membrane, the edema may be ascribed to an irritant action of the carbinol in the lungs. Or as in the

case of diethyl o-oxyphenyl carbinol (page 36) it may be the result of an acute dilation of the left ventricle of the heart, or else to a direct stimulation of the secretory glands of the lungs as observed from pilocarpine.

Comparison of the Physiological Actions of Trichlormethyl Phenyl Carbinol with some Chemically Related Compounds.

By the substitution of a $-CCl_3$ group for one of the inactive hydrogen atoms of benzyl alcohol we obtain trichlormethyl phenyl carbinol. From the action of the compound on the frog's sciatic nerve, it appears at least likely that we likewise have here a compound possessing a local anesthetic action. However, its irritant action would preclude the application of trichlormethyl phenyl carbinol as a local anesthetic for man. The toxicity of these two compounds would appear to be of about the same order.

The observation that trichlormethyl phenyl carbinol possesses even a limited action as a general anesthetic throws an interesting light on the results obtained by the substitution of a C_6H_5-CHOH- group for the hydrogen atom of chloroform.

Perhaps the most interesting observation in this regard is that associated with the production of trichlormethyl phenyl carbinol by the substitution of a C_6H_5- group for one of the inactive hydrogens of trichlormethyl-carbinol. Both of these compounds possess hypnotic or narcotic actions. The former, however, from a consideration of the results as recorded, would appear to be too uncertain in its action as well too likely to

produce untoward effects. A similar comparison might be made between chloretone (trichlormethyl dimethyl carbinol) and trichlormethyl phenyl carbinol. These two compounds differ from each other in that the phenyl group of the latter has been replaced by a methyl group, while a second methyl group has taken the place of one of the inactive hydrogens.

In its action on the blood pressure and respiration, trichlormethyl phenyl carbinol bears a decided resemblance to diethyl o-oxyphenyl carbinol. The intravenous injection of either compound produces a fall in blood pressure and an embarrassment of the respiration. The prolonged administration of either substance is followed by a pulmonary edema which may have the same exciting factors.

It is therefore to be noted, that, trichlormethyl phenyl carbinol in its physiological actions, exhibits some striking resemblances to compounds to which it is related in chemical constitution, but on account of other actions previously considered this relationship is of importance for theoretical rather than practical reasons.

DIETHYL PHENYL CARBINOL

Preparation of Diethyl Phenyl Carbinol (γ-oxy γ-phenyl pentane; diethyl benzyl alcohol).

Diethyl phenyl carbinol ($C_6H_5COH(C_2H_5)2$) was prepared by a modification of the method described by Bayer (33). A solution of ethyl magnesium iodide in ether was obtained by the slow addition of 312 Gm. ethyl iodide (redistilled) to a well cooled mixture of 48 Gm. magnesium turnings and 400 Gm. anhydrous

ether. After refluxing on the water bath until solution was complete, the mixture was placed in a shaker (Figure I) and slowly treated with a solution of 136 Gm. methyl benzoate in 300 Gm. anhydrous ether. By this modification of the method of Bayer, the methyl benzoate in small quantities comes into immediate contact with a large excess of the ethyl magnesium iodide thus greatly facilitating the ease with which the reaction goes to completion. The mixture was shaken for several hours after the addition to the Grignard reagent, and after refluxing for half an hour on the water bath it was cooled and treated with ice water and dil. acetic acid until the reaction was acid to litmus. The water layer was drawn off and the ether layer shaken with sodium bicarbonate solution to remove benzoic acid. The ether layer was dried over anhydrous K_2CO_3, the ether evaporated off and the remaining oil distilled under reduced pressure. B. P. at 12 mm. 110°.

Diethyl phenyl carbinol is a colorless oil (becomes yellowish green on standing). It is very slightly soluble in water, more soluble in alkalies and readily soluble in organic solvents.

Reaction:-

$$C_6H_5COOCH_3 + C_2H_5MgI \longrightarrow C_6H_5\overset{OMgI}{\overset{|}{C}}-C_2H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OCH_3$$

$$C_2H_5MgI \longrightarrow C_6H_5\overset{OMgI}{\overset{|}{C}}-C_2H_5 \xrightarrow{H_2O} C_6H_5C(C_2H_5)_2OH$$
$$\qquad\qquad\qquad\qquad\quad C_2H_5$$

Theoretical Consideration of Diethyl Phenyl Carbinol.

Diethyl phenyl carbinol ($C_6H_5C(OH)(C_2H_5)_2$) is to be considered chiefly as the diethyl derivative of benzyl alcohol. This replacement of the two inactive hydrogens by ethyl groups should result in

an increase in the narcotic action of the compound, since the substitution takes place in the side chain and the introduction of ethyl groups in the aliphatic carbinols usually causes an increase in the narcotic effect. The ethyl group seems to possess a special relationship to the nervous system, and compounds containing such a group usually show it by their narcotic action.

Diethyl phenyl carbinol can lose water Behal (29) to form a more toxic unsaturated compound:-

$$C_6H_5C(OH)(C_2H_5)_2 \longrightarrow C_6H_5C{=}CHCH_3(-C_2H_5) + H_2O$$

No direct evidence is now at hand to indicate that this change occurs in the organism, but its possibility must nevertheless be considered.

Diethyl phenyl carbinol is a tertiary alcohol. The tertiary alcohols generally possess greater hypnotic activity than the primary or secondary alcohols. A simular physiological action might be assumed for the carbinol here considered.

A compound of the type described, possessing the local anesthetic action of benzyl alcohol combined with the narcotic action to be expected from a tertiary alcohol containing two ethyl groups, might be simular in its physiological action to morphine.

Investigation of Diethyl Phenyl Carbinol.

Diethyl phenyl carbinol is a colorless liquid possessing a sharp tho not disagreeable odor. Applied to the tongue it has a sharp, burning taste. No local anesthesia was encountered from such an application.

The investigation of the physiological action of the carbind was confined chiefly to its action on the frog's exposed sciatic nerve and to its action following injection in a series of animals prepared for the recording of blood pressure and the respiration.

The actions of the compound so determined did not appear to be of sufficient promise to encourage further work in the determination of toxic dose, etc.. For the same reason and also becuase of its irritant action on the tongue, it was not considered advisable to make subentaneous injections in man.

Action of Diethyl Phenyl Carbinol Applied to the Frogs Sciatic Nerve.

The sciatic nerve in both legs of a series of frogs was exposed and the action of the carbinol on motor and sensory block was determined in the manner previously described. (page 14)

A 2% emulsion of diethyl phenyl carbinol in 0.75% saline and 7% acacia was applied to the nerve of the left leg. The right leg was treated with 0.75% saline and 7% acacia in a simular manner and used as a control thru out the experiment.

Results from Diethyl Phenyl Carbinol on Sensory Block.

Applied at 4:00 P.M. 5/6/20

+ = No sensory block
o = partial sensory block
- = complete " "

Time	Left Leg, Frog # 1	2	3	4	5	6	7	8	9	10	Right Leg, Frog # 1	2	3	4	5	6	7	8	9	10
4:00	+	+	+	o	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4:05	+	+	+	-	+	+	+	+	+	+	+	+	+	o	+	+	+	+	+	+
4:10	+	+	+	-	+	+	+	+	+	+	+	+	+	o	+	+	+	+	+	+
4:15	+	+	+	-	+	+	o	+	+	+	+	+	+	o	+	+	+	+	+	+
4:20	+	+	+	-	+	+	o	+	+	+	+	+	+	-	+	+	+	+	+	+
4:25	+	+	+	-	+	+	o	+	+	+	+	+	+	-	+	+	+	+	+	+
4:30	+	+	+	-	+	+	-	+	+	+	+	+	+	-	+	+	+	-	+	+
4:40	+	+	+	-	+	+	-	+	+	+	+	+	+	-	+	+	o	+	+	+
4:45	+	o	+	-	+	+	-	+	+	+	+	+	+	-	+	+	o	+	+	+
5:00	o	-	+	-	+	+	-	+	+	+	+	+	+	-	+	+	o	+	o	+
5:15	-	-	+	-	+	+	-	+	+	+	+	+	+	-	-	+	-	+	-	-

No motor block was encountered during the experiment.

Conclusions:

From the action of diethyl phenyl carbinol on the frog's sciatic nerve it is seen that the substitution of two ethyl radicles for the two inactive carbon atoms of benzyl alcohol has destroyed the special activity of that compound on the sciatic nerve.

This observation combined with the lack of local anesthetic effect observed following application of the carbinol to the tongue, made it appear very likely that diethyl phenyl carbinol possess no local anesthetic action on man.

Effect of Diethyl Phenyl Carbinol on Blood Pressure and Respiration.

A series of animals were prepared for the recording of the respiration and blood pressure in the manner described (page 13), and diethyl phenyl carbinol then injected as described in the following protocols.

Blood Pressure - Respiration Tracing #12.

Male Dog #22 7.6 Kg. 5/6/20 Ether anesthesia.

Effect of the intravenous injection of a 10% emulsion of diethyl phenyl carbinol suspended in 7% acacia and 0.9% saline solution. The animal was given 2.5 mils of a 4% solution of morphine sulphate subcutaneously.

A Injected 0.5 mils of carbinol emulsion. The blood pressure quickly fell to 27 mm. below normal.

B Three minutes after (A), blood pressure 5 mm. below normal. Injected 0.5 mils of carbinol emulsion. The blood pressure fell to 9 mm. below normal and the respiration rate was slightly increased.

C Three and a half minutes after (B), blood pressure was 4 mm. below normal. Injected 1 mil of carbinol emulsion. The blood pressure fell to 13 mm. below normal but the respiration remained practically unchanged.

D Nineteen minutes after (C), the blood pressure was 1 mm. below normal. Injected 2 mils of the carbinol emulsion. The blood pressure fell to 23 mm. below normal and remained rather constant. The rate of the respiration was increased.

E Twenty nine minutes after (D), the blood pressure was 8 mm. below normal. Injected 2 mils of carbinol emulsion. The blood pressure slowly fell to 20 mm. below normal. The respiration rate was greater than normal.

F. Four and a half minutes after (E) stopped thirty minutes. The death of the animal occured shortly afterwards.

Conclusions:

The intravenous injection of diethyl phenyl carbinol as an emulsion appears to yield satisfactory dependable results. These injections invariably cause a fall in blood pressure which is to some extent directly proportional to the size of the dose administered. However, the first injection appears to exert an effect greater than subsequent injections. With simular injections of benzyl alcohol or saligenin the first injection likewise appears to exert a greater effect than subsequent injections of the same magnitude. It has been suggested by Hirschfelder (34) that this phenomenon may be explained by assuming that the initial injection results in an increased power of oxidation in the organism of the animal for the compound administered. A simular explanation may be used in the case of diethyl phenyl carbinol. The injection does not appear to effect the respiration to so great an extent as it does the blood pressure.

Blood pressure - Respiration Tracing #13.

Female Dog #31. 6.5 Kg. 5/14/20 Ether Anesthesia.

Effect of the intravenous injection of a 10% emulsion of

diethyl phenyl carbinol suspended in 7% acacia and 0.9% saline solution. Results controlled by the injection of a 10% olive oil emulsion simularly prepared. Animal given 1.5 mils of a 4% solution of morphine sulphate subcutaneously.

A Injected 2 mils of carbinol emulsion. The blood pressure fell to 42 mm. below normal, partly recovered, fell again and then slowly recovered. The respiration was decreased in amplitude and rate.

B Stopped five minutes.

C Injected 2 mils of olive oil emulsion. The blood pressure fell slightly but quickly recovered.

D Blood pressure 6 mm. above normal, injected 2 mils of carbinol emulsion. The blood pressure fell to 20 mm. below normal.

E Five minutes after (D) injected 5 mils of olive oil emulsion. No effect of importance was obtained.

F Two and a half minutes after (E), blood pressure 1 mm. below normal. Injected 5 mils of carbinol emulsion. The blood pressure fell to 42 mm. below normal and the respiration was greatly decreased in rate.

G Seventeen minutes after (F), injected 5 mils of olive oil emulsion, without any particular effect.

H Four and a half minutes after (G), blood pressure was 17 mm. below normal. Injected 2 mils of carbinol emulsion. The blood pressure fell to 40 mm. below normal and the respiration was decreased in amplitude.

I Seven minutes after (H), blood pressure 36 mm. below normal. Injected 2 mils of carbinol emulsion. The blood pressure

fell to 50 mm. below normal, and the amplitude of the respiration was further decreased.

J Four minutes after (I), blood pressure 40 mm. below normal. Injected 2 mils of carbinol emulsion. The blood pressure fell to 52 mm. below normal and the respiration was further decreased in amplitude and in rate.

K Fifteen and a half minutes after (J), injected 1 mil of olive oil emulsion without appreciable effect. Expressed 25 mils of fluid from the lungs.

L Four minutes after (K), blood pressure 43 mm. below normal. Injected 1 mil of carbinol emulsion. The blood pressure fell to 50 mm. below normal.

M Stopped five minutes.

N Injected 1 mil of carbinol emulsion. The blood pressure quickly fell, then recovered.

O Injected 1 mil of carbinol emulsion. The blood pressure fell, the respiration ceased, and the death of the animal took place.

A considerable quantity of fluid was expressed from the lungs.

Conclusions:

The effect of injections of diethyl phenyl carbinol as here given agree very well ~~well~~ with those obtained in tracing #12 and lead to the same conclusions.

In addition to this, it is to be noted that the injection of olive oil in the same quantity as the carbinol was practically without effect. This tends to show that the effects on the blood pressure and respiration following the carbinol injections were not the result of the mechanical act-

ion of the carbinol oil but were due to the carbinol following absorption.

The prolonged administration of this carbinol gives rise to a severe pulmonary edema. This may be explained in the same manner as that offered in the case of diethyl o-oxyphenyl carbinol (page 36) excepting that the irritant action of this latter compound is not to be observed in the case of diethyl phenyl carbinol.

Respiration - Blood Pressure Tracing #14.

Male Dog #32 9 Kg 5/14/20 Ether Anesthesia

Effect of the intravenous injections of a 10% emulsion of diethyl phenyl carbinol suspended in 7% acacia and 0.9% saline solution. Results controlled by the injection of a 10% emulsion of olive oil simularly prepared. Animal given 2.2 mils of a 4% solution of morphine sulphate subcutaneously.

A Injected 1 mil of carbinol emulsion. The respiration increased in rate and amplitude and the blood pressure decreased in amplitude and fell to 5 mm. below normal.

B Four minutes after (A), injected 1 mil of olive oil emulsion. The blood pressure remained practically unchanged, but shortly after the injection it increased in amplitude.

C Fourteen minutes after (B), blood pressure 8 mm. below normal. Injected 1 mil of olive oil emulsion, with practically no change in conditions.

D Three minutes after (C), blood pressure 9 mm. above

normal. Injected 1 mil of carbinol emulsion. The blood pressure slowly fell to 4 mm. below normal, and the amplitude was decreased. The respiration showed no change.

E Five minutes after (D), blood pressure 4 mm. above normal. Injected 1 mil of olive oil emulsion. No effect noted.

F Two and a half minutes after (E), blood pressure 3 mm. above normal. Injected 2 mils of carbinol emulsion. The blood pressure slowly fell to 22 mm. below normal and decreased in amplitude.

G Seven minutes after (F), blood pressure 5 mm. below normal. Injected 2 mils carbinol emulsion. The blood pressure fell to 36 mm. below normal and the respiration decreased in amplitude.

H Seven minutes after (G), blood pressure 12 mm. below normal. Injected 2 mils of olive oil emulsion. The blood pressure continued to rise.

I Two and a half minutes after (H), blood pressure 7 mm. below normal. Injected 2.5 mils of carbinol emulsion. The blood pressure fell to 39 mm. below normal and the respiration decreased in amplitude.

J Ten minutes after (I), blood pressure 17 mm. below normal. Injected 5 mils of olive oil emulsion. No effect noted.

K Two minutes after (J), blood pressure 13 mm. below normal. Injected 5 mils of carbinol emulsion. The blood pressure quickly fell to 52 mm. below normal and the respiration was greatly decreased in amplitude.

L Twenty-four minutes after (K), blood pressure 35 mm. below

normal. Injected 10 mils of olive oil emulsion. No effect noted.

M Four minutes after (L), blood pressure 29 mm. below normal. Injected 10 mils of carbinol emulsion. The blood pressure fell to 62 mm. below normal, the respiration ceased, and the death of the animal took place.

Considerable fluid was expressed from the lungs following the death of the animal.

Conculsions:

The results obtained in this case agree very well with those obtained in tracing #13, and lead to the same conclusions.

Summary:

The intravenous injection of diethyl phenyl carbinol in the manner employed in the experiments here described, gives rapid, dependable results. Small doses cause a decided embarrassment of the respiration and a fall in the blood pressure. It could not be definietly stated whether or not the respiration was effected to a greater extent than the blood pressure, altho several observations pointed to such a conclusion.

In the experiments here described with the exception of #14, the initial dose of the carbinol appeared to exert a greater effect than subsequent injections of the carbinol. The assumption of an increased power of oxidation by the animal for the carbinol given in the initial injection might explain this phenomenon.

The explanations for the pulomonary edema offered in the case of diethyl o-oxyphenyl carbinol, may, with the exception of the severe irritating action, be offered in explanation of the

edema observed in tracings #13 and #14.

Comparison of the Physiological Actions of Diethyl Phenyl Carbinol with some Chemically Related Compounds.

The study of this carbinol would at least indicate that the replacement of the two inactive hydrogen atoms of benzyl alcohol by two ethyl groups, gives rise to a compound which no longer possesses a local anesthetic action. The investigation was not carried far enough to permit the formulation of any conclusions regarding the relative narcotic actions or the toxicity of diethyl phenyl carbinol.

It is also to be noted that, whereas the introduction of two ethyl groups for the two inactive hydrogens of benzyl alcohol, produced a compound (diethyl phenyl carbinol) which produced no sensory block when applied to the frog's sciatic nerve, a simular alteration in the structure of saligenin gave the compound (diethyl o-oxyphenyl carbinol) which still retained this sensory anesthesia, but in a lessened degree.

A striking simularity is to be observed in the effects noted of diethyl phenyl carbinol on the blood pressure and the respiration with those obtained under simular conditions from diethyl o-oxyphenyl carbinol and trichlormethyl phenyl carbinol. Each of these compounds produced a fall in blood pressure and a decrease in the rate or amplitude (or both) of the respiration. The pulmonary edema was of fairly constant occurrence with each of these compounds. Altho a definite conclusion could not be

reached, it seemed likely that these compounds with the exception of diethyl phenyl carbinol, had a greater effect on the blood pressure than on the respiration.

DIPHENYL CARBINOL.

Preparation of Diphenyl Carbinol (Benzhydrol; phenyl benzyl alcohol).

Diphenyl carbinol ($(C_6H_5)_2OHOH$) was prepared according to the method of W. D. Cohen (23). A solution of 85 Gm. benzophenone in 90 Gm. KOH and 900 mils 80% alcohol was treated with 150 Gm. zinc dust. The reaction began immediately. The mixture was shaken thoroughly, and after the reaction had moderated, heated on the water bath for two hours. The remaining zinc was filtered off and washed with a small amount of cold 80% alcohol. A large amount of water was added to the alcoholic solution of the carbinol which was at once precipitated. The carbinol was collected on a filter, washed with cold water and dried in a vacuum desiccator. Recrystallized from petroleum ether, it was obtained as colorless needles M.P. 67.5°. Yield almost theoretical.

$$C_6H_5COC_6H_5 \xrightarrow{H_2} C_6H_5CHOHC_6H_5$$

Theoretical Consideration of Diphenyl Carbinol.

A study of the physiological action of diphenyl carbinol $(C_6H_5)_2CH(OH)$ should show the effect obtained by the introduction of a phenyl group into the side chain of benzyl alcohol.

Since the introduction of one phenyl group in methyl alcohol may be considered responsible for the difference in the pharmacodynamical action of that compound and the resultant product, benzyl alcohol, the introduction of a second phenyl group, might be expected to further increase the benzyl group effect.

Attention is also called to the fact that in diphenyl carbinol, a phenyl group has taken the place of one of the "inactive hydrogen atoms" of benzyl alcohol, so that we are now concerned with a substituted benzyl group. The study of diphenyl carbinol should throw more light on the question of whether or not the two hydrogens attached to the carbon of the side chain in benzyl alcohol, can properly be considered "inactive" physiologically.

Diphenyl carbinol is a reduction product of benzophenone ($(C_6H_5)_2CO$) which is stated by Frankel (17) (page 106) to possess a hypnotic action, but is less active in this respect than the aliphatic ketones. Diphenyl carbinol may be expected to exert a hypnotic action, either as itself or following oxidation in the organism to benzophenone.

In diphenyl carbinol we have a secondary alcohol with which to deal. So little is known regarding the physiological action of the aromatic alcohols, that little can be predicted regarding the possible action of a secondary alcohol containing two phenyl groups. Mention might be made, however, of the findings of Macht (34) that the secondary aliphatic alcohols are less toxic than the corresponding primary alcohol. It is not known whether or not a similar relationship exists among the

members of the aromatic series.

Investigation of Diphenyl Carbinol.

Diphenyl carbinol is a white crystaline substance, practically insoluble in water, and apparently entirely stable under ordinary conditions. Placed on mucous surfaces it has a slightly irritant actions, not unlike that of benzyl alcohol or saligenin. Its sharp taste is especially reminiscent of saligenin. It produces no local anesthesia when applied to the tongue in this manner.

Becuase of the insolubility of diphenyl carbinol in water, difficulty was encountered in making injections of this compound. The best results were obtained by dissolving diphenyl carbinol in olive or cottenseed oil, and injecting this as an acacia emulsion.

The investigation of diphenyl carbinol included observation of is action following subcutaneous injection in guinea pigs and rabbits. Its action on the sciatic nerve of a series of frogs and its effect on local sensation following subcutaneous injection in man were also noted. Experiments were likewise carried out with the object of determining the action of this carbinol on the pupil of the cat.

The emulsion obtained by shaking a solution of diphenyl carbinol in olive oil with 7% acacia and 0.9% saline solution could not be used for intravenous injection into animals prepared for the recording of blood pressure and respiration. If a concentrated solution of the carbinol in olive oil were used, the diphenyl carbinol precipitated out on the addition of the emulsifying agents. A dilute solution of the carbinol in olive oil could not

be used, for it would be necessary to inject too large a dose of olive oil into the animal in order to have an appreciable amount of the carbinol carried along. In such a case it might be extremely difficult to differentiate between the effect due to the carbinol and that due to the olive oil.

Action of Diphenyl Carbinol on Guinea Pigs.

Diphenyl carbinol was injected subcutaneously into a series of guinea pigs and the reaction of these animals to the injection was noted. On account of the insolubility of diphenyl carbinol in water, the carbinol was dissolved in olive or cottonseed oil and injected as an acacia emulsion in the manner previously mentioned.

Experiment I.

Guinea Pig #1 Weight 300 Gm. 12-4-19

2:25 P.M. Given subcutaneous injection of 1 gm. (3.3 gm per Kg) diphenyl carbinol in 5 mils cottonseed oil and 10 mils 7% acacia and 0.9% sodium chloride.

2:40 P.M. More quiet.

4:35 P.M. Still quiet.

9:00 P.M. Appeared more lively.

7:00 A.M. 12-5-19 Weakened, experiences difficulty in moving.

9:30 A.M. Weakness increased.

12:30 P.M. Very weak.

4:00 P.M. Dead

Necropsy: Nothing important noted.

Experiment II.

Guinea Pig #2 Weight 303 Gm. 2/9/20

11:25 A. M. Injected 0.47 Gm. per Kg. diphenyl carbinol, in emulsion of acacia and 0.9% sodium chloride subcutaneous.

10:05 P.M. No change noted.

2/12/20 Dead.

Necropsy: No important findings.

Experiment III.

Guinea Pig #3 Weight 283 Gm. 2/9/20-

11:25 A. M. Injected subcutaneously 1.02 Gm. per Kg. diphenyl carbinol in an emulsion of acacia and 0.9% sodium chloride.

10:05 P. M. No change noted.

2/14/20 Dead.

Necropsy: No important findings.

Experiment IV.

Guinea Pig #4 Weight 164 Gm. 2/9/20.

11:25 A. M. Injected subcutaneously 1.96 Gm. per Kg. of diphenyl carbinol in an emulsion of 7% acacia and 0.9% sodium chloride.

10:05 P. M. No change noted.

2/12/20 Dead.

Necropsy: No findings of importance.

Experiment V.

Guinea Pig #5. Weight 155 Gm. 2/9/20.

11:25 A. M. Injected subcutaneously 3 Gm. per Kg. of diethyl carbinol in an emulsion of 7% acacia and 0.9% sodium chloride.

2:55 P. M. Equilibruim partly lost.

3:25 P. M. Marked weakness. Partically narcotized.

4:05 P. M. Completely narcotized.

6:30 P. M. Deep stupor.

11:30 P.M. Stupor continued.

8:00 A. M. 2/10/20 Dead.

Necropsy: No important findings.

Experiment VI.

Guinea Pig #6. Weight 530 Gm. 2/10/20.

3:45 P.M. Injected subcutaneously 2.3 Gm. per Kg. of diphenyl carbinol in an emulsion of cottonseed oil, 7% acacia and 0.9% sodium chloride.

11:00 P. M. No change noted.

11:45 A.M. 2/12/20 Normal.

2/17/20 Normal. (Living)

Experiment VII.

Guinea Pig #7. Weight 448 Gm. 2/10/20

3:45 P. M. Injection subcutaneously 2.7 Gm. per Kg. of diphenyl carbinol in a emulsion of cottonseed

oil, 7% acacia and 0.9% saline.

11:00 P.M. No change noted.

11:45 A.M. 2/12/20 Appeared normal.

2/15/20 Dead.

Necropsy: No important findings.

Experiment VIII.

Guinea Pig #8. Weight 320 Gm. 2/19/20

4:00 P.M. Injected subcutaneously 2.5 Gm. per Kg. diphenyl carbinol in an emulsion of olive oil, 7% acacia and 0.9% saline.

9:00 P.M. No change noted.

8:00 A.M. 2/20/20 Weakened.

2:00 P.M. Completely narcotized, breathing slow and labored.

3:15 P.M. Dead.

Necropsy: No important findings.

Experiment IX.

Guinea Pig #9 Weight 460 Gm. 2/19/20

4:00 P.M. Injected subcutaneously 2.0 Gm. per Kg. diphenyl carbinol in an emulsion of olive oil, 7% acacia and 0.9% saline.

9:00 P.M. No change noted.

2/23/20 Normal - living.

Experiment X.

Guinea Pig #10. Weight 120 Gm. 2/19/20

4:00 P.M. Injected subcutaneously 1.5 Gm. per Kg. of diphenyl

carbinol in an emulsion of cottonseed oil, 7% acacia and 0.9% saline.

11:00 P.M. No change noted.

8:00 A.M. 2/20/20 Prostrated.

9:30 A.M. Dead

Necropsy: No important findings. No signs of congestion at point of injection.

Experiment XI.

Guinea Pig #11. Weight 315 Gm. 2/19/20

4:00 P.M. Injected subcutaneously 3 Gm. per Kg. diphenyl carbinol in an emulsion of cottonseed oil, 7% acacia, and 0.9% saline.

9:00 P.M. Appeared normal.

2/23/20 Dead.

Necropsy: No findings of importance.

Experiment XII.

Guinea Pig #12. Weight 433 Gm. 2/23/20

8:05 A.M. Injected subcutaneously 2.0 Gm. per Kg. of diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/24/20 Appeared normal.

2/26/20 " "

3/1/20 " "

3/2/20 " "

3/3/20 Dead. Weight 310 Gm.

Experiment XIII.

Guinea Pig #13 Weight 423 Gm. 2/23/20.

8:05 A.M. Injected subcutaneously 2.25 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/24/20 Appeared normal.

3/1/20 " "

3/7/20 " " . Living

Experiment XIV.

Guinea Pig #14 Weight 485 Gm. 2/23/20

8:05 A.M. Injected subcutaneously 1.5 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/24/20 Appeared normal.

3/1/20 " "

3/7/20 " " . Living.

Experiment XV.

Guinea Pig #15. Weight 565 Gm. 2/23/20

8:05 A.M. Injected subcutaneously 1.0 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/24/20 Appeared normal.

3/1/20 " "

3/7/20 " " . Living.

Experiment XVI.

Guinea Pig #16. Weight 445 Gm. 2/23/20

8:05 A.M. Injected subcutaneously 2.0 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/24/20 Appeared normal.

3/1/20 " "

3/7/20 " " . Living.

Experiment XVII.

Guinea Pig. #17 Weight 460 Gm. 2/23/20

8:05 A.M. Injected subcutaneously 1.7 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/24/20 Appeared normal.

3/1/20 " "

3/7/20 " " . Living.

Experiment XVIII.

Guinea Pig. #18 Weight 440 Gm. 2/27/20

11:00 A.M. Injected subcutaneously 2.5 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

3/1/20 Appeared normal.

3/7/20 " " Living.

Experiment XIX.

Guinea Pig. #19 Weight 380 Gm. 2/27/20

11:00 A.M. Injected subcutaneously 2.9 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/28/20 Appeared normal.

3/1/20 " "

3/3/20 Dead

Necropsy: No important findings.

Experiment XX.

Guinea Pig #20 Weight 425 Gm. 2/27/20

11:00 A.M. Injected subcutaneously 2.7 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia, and 0.9% saline.

2/28/20 Appeared normal.

2/29/20 Dead

Necropsy: No findings of importance.

Experiment XXI.

Guinea Pig #21 Weight 440 Gm. 2/27/20

11:00 A.M. Injected subcutaneously 2.5 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/28/20 Appeared normal.

3/1/20 " "

3/7/20 " " Living.

Experiment XXII.

Guinea Pig #22 Weight 590 Gm. 2/27/20

11:00 A.M. Injected subcutaneously 2.3 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

2/28/20 Appeared normal.

8:30 A.M. 3/1/20 In deep stupor.

10:30 A.M. Heart beat slow.

12:05 P.M. Dead.

Necropsy: No important findings.

Conclusions:- Non-toxic doses of diphenyl carbinol given by subcutaneous injection to guinea pigs were without noticeable effect. Toxic doses administered in the same manner after a period varying from several hours to as much as a day, usually produced muscular weakness. This was slowly followed by narcosis, coma and finally by death.

Necropsy showed no important alterations in the organs of the body.

The death of animals #2, 3, and 4 is believed to have been caused by improper feeding.

The toxic dose of diphenyl carbinol administered subcutaneously to guinea pigs is about 2.3 Gm. per Kg.

Action of Diphenyl Carbinol on Rabbits.

Diphenyl carbinol was given to a series of rabbits by subcutaneous injections and the reaction of these animals to the injections was noted. The injections were made in a manner analogous to those in which this carbinol was administered to guinea pigs, the cottonseed oil emulsion being used here likewise.

Experiment I.

Rabbit #1. Weight 1800 Gm. 12/3/19.

8:35 A.M. Injected subcutaneously 0.55 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and

0.9% sodium chloride.

12/4/19 Appeared normal.

12/5/19 Dead. Death appeared to have been caused by pneumonia

Experiment II.

Rabbit #2. Weight 1700 Gm. 12/3/19

8:35 A.M. Injected subcutaneously 0.59 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% soldium chloride.

12/4/19 Appeared normal.

12/6/19 " "

12/9/19 " " Living.

Experiment III.

Rabbit #3 Weight 1600 Gm. 12/3/19

8:35 A.M. Injected subcutaneously 0.62 Gm. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% saline.

3:40 P.M. Appeared normal.

7:00 P.M. " "

8:00 A.M. 12/4/19 Dead. Pleurisy thot to have been the cause of death.

Experiment IV.

Rabbit #4. Weight 1460 Gm. 2/7/20

10:25 A.M. Injected subcutaneously 3.4 Gm. per Kg. diphenyl carbinol in emulsion of cottonseed oil, 7% acacia and 0.9% sodium chloride.

11:00 P.M. Appeared normal.

9:00 A.M. 2/8/20 Dead.

Necropsy: Lungs somewhat hemorrhagic. Heart in mid-position. From position of animal it appeared that death came on suddenly.

Conclusions:- Subcutaneous injection of diphenyl carbinol in rabbits gave results very similar to those observed in guinea pigs. Non-toxic doses produced no important effects. Toxic doses likewise gave no observed important effects other than death.

The series of experiments here recorded are too meagre to be used in drawing any important conclusions regarding the physiological action or the toxicity of diphenyl carbinol injected subcutaneously in rabbits. However, it may be noted, that death from diphenyl carbinol even in large doses, does not occur until a comparatively long period has passed after the time of the injection. This may, to a large measure, be due to a relatively slow rate of absorption of the carbinol.

The toxicity of diphenyl carbinol for rabbits is probably of the same order as for guinea pigs.

Importance of Solvent Used in Applying Diphenyl Carbinol to the Frog's Sciatic Nerve.

The sciatic nerve in both legs of each of two single pithed frogs was exposed and a pledget of cotton was placed under each nerve. A few crystals of diphenyl carbinol were placed on the nerve of the left leg of each frog, and then each nerve was treated with solvents as recorded below. The right leg in both cases was

used only as a control.

Sensory block was detected by the method described on page 14.

Experiment I.

Frog #1 5/3/20 4:10 P.M.

Several drops of cottonseed oil was dropped onto the crystals on the left leg and also onto the nerve of the right leg.

Results:

	Left leg	Right leg.
4:10	Reflex normal	Reflex normal
4:20	" "	" "
4:35	" weakened	" "
4:55	" absent	" "
5:30	" "	" "
8:00	" "	" "

Experiment II.

Frog #2 5/3/20 4:10 P.M.

Crystals moistened with solution of 7% acacia and 0.9% saline.

Results:

	Left leg	Right leg.
4:10	Reflex normal	Reflex normal
4:20	" "	" "
4:35	" "	" "
4:55	" weakened	" "
5:30	" absent	" "
8:00	" "	" "

Conclusions:- From these experiments it is seen that a liquid in which the carbinol is readily soluble is of importance in order to obtain the action of the carbinol.

Sensory block was obtained much more readily in the case where cottonseed oil (in which the carbinol is soluble) was applied to the crystals than when acacia and physiological salt (in which the carbinol is but slightly soluble) were used.

Effect of Diphenyl Carbinol Applied to a Frog's Sciatic Nerve.

The sciatic nerve in both legs of a series of frogs was exposed and the action of the carbinol on motor and sensory block determined in the manner described (page 14).

A 2% emulsion of the carbinol in olive oil, 7% acacia and 0.75% sodium chloride was applied to the left leg, while the right leg, treated with 0.75% sodium chloride, 7% acacia and 5% olive oil was used as a control.

Results:

Applied at 6:30 P.M. 5-14-20

+ = No sensory block
o = Partial " "
- = Complete " "

Time.	Left Leg Frog # 1 2 3 4 5 6 7 8 9 10	Right Leg. Frog # 1 2 3 4 5 6 7 8 9 10
6:30	+ + + + + + + o - +	+ + + o + + + + + +
6:35	+ + - + o + o - + +	+ + + + + + + + + +
6:40	o o - - - o - - o +	+ + + + + + + + + +
6;45	- - - - - - - + - o	+ + + + + + + + + +
6:50	- - - - - - - - - -	+ + + + + + + + + +
6:55	- - - - - - - - - -	+ + + + + + + + + +
7:00	- - - - - - - - - -	+ o + + + + + + + +
7:05	- - - - - - - - - -	+ o + + + + + + + +
7:10	- - - - - - - - - -	+ - + + + + + + + +
7:15	- - - - - - - - - -	+ - + + + + + o + +

No motor block was encountered thruout the experiment.

Conclusions: - Diphenyl carbinol applied to the sciatic nerve of a frog in the above described manner, produces sensory block in from 5 - 15 minutes. This action is persistant in character. The carbinol as applied does not produce motor block.

Action of Diphenyl Carbinol as a Local Anesthetic on Man.

Since the other experiments had indicated that diphenyl carbinol was not particularly irritant and also, that it might possess some local anesthetic action, a series of injections of this carbinol were made in man.

Experiment I.

2:35 P.M. Injected subcutaneously 1.5 mils of a 2% emulsion of diphenyl carbinol in emulsion of olive oil, 7% acacia and 0.9% saline.

2:36 P.M. No anesthesia.

2:39 P.M. " "

2:59 P.M. " "

3:45 P.M. " "

Experiment II.

4:20 P.M. Injected subcutaneously 1.5 mils of a 4% emulsion of diphenyl carbinol in emulsion of olive oil, 7% acacia and 0.9% sodium chloride.

4:21 P.M. Irritation, smarting sensation at area of injection.

4:22 P.M. Very slight dullness at area of injection.

4:24 P.M. " " " " " " "

4:30 P.M. Slight dullness at area of injection.

4:40 P.M. " " " " " "

In both Experiment I and II an ulcer was encountered at the point of injection. This ulcer persisted for several weeks.

Conclusion: Diphenyl carbinol in a 2% emulsion has no local anesthetic action for man. In a 4% emulsion its anesthetic action is definite but very slight. Its subcutaneous injection in man is attended with the formation of an ulcer.

Action of Diphenyl Carbinol on the Pupil of the Eye.

A 10% emulsion of diphenyl carbinol in acacia, 0.9% saline and olive oil was dropped into the right conjunctival sac of a cat. The left eye of the animal was used as a control.

Experiment I.

Cat #1 5/27/20.

9:30 A.M. Several drops of emulsion placed in the conjunctival sac. Produced irritation as shown by the excessive ptyalism and excitement of the animal.

9:30 A.M. No dilation of the pupil. Blood vessels conjested.

9:45 A.M. No change noted. Several more drops placed in eye. Same signs of irritation.

9:55 A.M. No change noted.

10:15 A.M. No change noted.

12:30 P.M. Pupil appeared normal. No anesthesia observed.

Experiment II.

Cat #2. 5/27/20

2:20 P.M. Several drops of emulsion placed in eye. Produced irritation as shown by the excessive ptyalism and excitement of the animal.

2:21 P.M. No signs of dilatation. Blood vessels conjested.

2:30 P.M. No change noted.

2:40 P.M. " " " . Several more drops placed in eye. Same signs of irritation.

2:50 P.M. No change noted.

3;15 P.M. " " "

4:30 P.M. Pupil appeared normal.

Conclusion: A 10% emulsion of diphenyl carbinol placed in the eye of a cat produces decided irritation but no alteration in the size of the pupil. Anesthesia of the pupil was not obtained.

Comparison of the Physiological Action of Diphenyl Carbinol With Some Chemically Related Compounds.

Thru the introduction of a phenyl group in the place of one of the inactive hydrogens of benzyl alcohol a compound is obtained which is decidedly less active as a local anesthetic than the primary compound. The toxicity of diphenyl carbinol and benzyl alcohol appear to be of about the same order.

The action of diphenyl carbinol is also seen to be somewhat similar to that of its oxidation product benzophenone in that each exerts a slight narcotic action.

DIBENZYL PHENYL CARBINOL.

Preparation of dibenzyl phenyl carbinol (dibenzyl benzyl alcohol)

The preparation of dibenzyl phenyl carbinol ($C_6H_5C(CH_2C_6H_5)_2OH$) has been described by Klages and Heilmann (36). It was prepared in this laboratory in a manner similar to that used in the preparation of diethyl phenyl carbinol (page 70).

A small amount of dibenzyl phenyl carbinol was prepared by using the reagents in the following proportions: By the slow addition of 171 Gm. benzyl bromide dissolved in 100 Gm. anhydrous ether to 24 Gm. of magnesium turnings and 200 Gm. anhydrous ether in a flask cooled by immersion in ice water, the Grignard reagent, benzyl magnesium bromide was prepared. After refluxing on the water bath for a short time, this solution was slowly treated with a solution 68 Gm. methyl benzoate in 200 mils of anhydrous ether, the shaking apparatus previous described (Figure I) being employed.

The mixture was shaken for several hours after the addition

of the methyl benzoate was completed, refluxed for a short time on the water bath, and then treated with ice water and dilute acetic acid until the solution was slightly acid to litmus. The water layer was drawn off, extracted with ether and this extraction added to the main ether solution. After drying over anhydrous K_2CO_3 and filtering, the carbinol was obtained as beautiful crystals following the spontaneous evaporation of the ether.

Dibenzyl phenyl carbinol was obtained as small colorless needles. M.P.86-87°. It is practically insoluble in water, slightly soluble in alkalies, and readily soluble in organic solutions.

Reaction:-

$$C_6H_5COOCH_3 + C_6H_5CH_2MgI \longrightarrow C_6H_5C(OCH_3)(CH_2C_6H_5)MgI$$

$$C_6H_5CH_2MgI \longrightarrow C_6H_5C(CH_2C_6H_5)_2MgI \xrightarrow{H_2O} C_6H_5C(CH_2C_6H_5)_2OH$$

Theoretical Consideration of Dibenzyl Phenyl Carbinol.

In dibenzyl phenyl carbinol ($C_6H_5C(OH)(CH_2C_6H_5)_2$) we have a very interesting compound. The characteristic actions of benzyl alcohol and benzyl benzoate is generally believed to be primarily dependent on the benzyl($C_6H_5CH_2$) group. In the compound here considered, we find two benzyl groups in direct association with a substituted benzyl group, which still retains the hydroxyl group as in benzyl alcohol. If the accumulation of benzyl radicles about a nucleus can result in the intensification of the benzylic action in the compound so formed, this effect should be very

noticable in dibenzyl phenyl carbinol; for here, two benzyl groups have replaced the inactive hydrogens of a third benzyl radicle. In the case of diethyl phenyl carbinol the replacement has been produced by the introduction of two ethyl groups.

A physiological examination of dibenzyl carbinol should likewise throw some light on the properties of aromatic tertiary alcohols for it is a representative of this class of compounds.

Investigation of Dibenzyl Phenyl Carbinol.

Dibenzyl phenyl carbinol is a crystalline substance, practically odorless at room temperature and apparently quite stable. Applied to the tongue it is tasteless, and under these conditions produces no loss of local sensation.

The quantity of dibenzyl phenyl carbinol at hand was so small as to prevent any extensive investigation of its physiological action. Further work with this carbinol was postponed until a later date. The work at the present time was confined chiefly to an investigation of the possible local anesthetic action of the compound.

Action of Dibenzyl Phenyl Carbinol on Rabbits.

Since nothing was known regarding the physiological action of this compound, it was considered advisable to preform a preliminary experiment with it on an animal before making a subcutaneous injection on man.

Dibenzyl phenyl carbinol is practically insoluble in water but soluble in olive oil. Advantage was taken of this latter fact in preparing the carbinol for injection. The carbinol was dis-

solved in olive oil and this solution used for the injections.

Experiment I.

Rabbit #6. 5/6/20.

8:15 A.M. Injected into the ear of the rabbit 0.2 mils of a 7.5% solution of dibenzyl phenyl carbinol dissolved in olive oil.

8:25 A.M. Area of application appeared to be slightly anesthetized when tested with pin pricks or electrical stimulus.

8:35 A.M. Anesthesia appeared more pronounced.

9:25 A.M. Anesthesia still appeared to be present.

9:35 A.M. Anesthesia disappeared.

5/22/20 No sign of necrosis or abscess formation.

5/28/20 Slight scab formation about point of injection.

Experiment II.

Rabbit #6. 5/6/20.

8:20 A.M. Injected into the ear of the rabbit 0.3 mils of a 7.5% solution of dibenzyl phenyl carbinol in olive oil.

8:35 A.M. No signs of anesthesia.

9:00 A.M. No signs of anesthesia.

10.00 A.M. No signs of anesthesia.

5/22/20 No signs of necrosis or abscess formation.

5/28/20 Slight scab formation about area of injection.

Action of Dibenzyl Phenyl Carbinol as a Local Anesthetic on Man.

Dibenzyl phenyl carbinol dissolved in olive oil was injected subcutaneously in man and the sensibility of the wheal compared with that of the normal skin by observing the effect of pin pricks, electrical stimulation and pressure with a blunt instrument over the

areas.

Experiment I. 6/1/20.

2:20 P.M. Injected subcutaneously 0.3 mils of a 7.5% solution of dibenzyl phenyl carbinol in olive oil.

2:21 P.M. Sensation very slightly dulled at area of injection.

2:25 P.M. Sensation normal.

2:30 P.M. Sensation normal.

2:35 P.M. Slight pain about area of injection. No signs of anesthesia.

2:40 P.M. Slight pain about area of injection. No signs of anesthesia.

3:00 P.M. Slight pain about area of injection. No signs of Anesthesia.

4:00 P.M. Irritation about area of injection continued. No anesthesia.

6:00 P.M. Irritation about area of injection continued. No anesthesia.

9:30 P.M. Irritation about area of injection continued. No anesthesia.

Conclusion:- Dibenzyl phenyl carbinol has no local anesthetic action on the tongue. It likewise had no local anesthetic action for man or rabbits following subcutaneous injection in the manner described. The apparent anesthesia noted in the first experiment with Rabbit #6 probably being an artifact. It, therefore, seems likely that dibenzyl phenyl carbinol possesses no local anesthetic action for man or for animals.

Comparison of the Physiological Action of Dibenzyl Phenyl Carbinol With Some Chemically Related Compounds.

The introduction of two benzyl groups for the two inactive hydrogens of benzyl alcohol give rise to a compound which no longer possesses the local anesthetic action of benzyl alcohol. This result is similar to that obtained when the two inactive hydrogens of benzyl alcohol were replaced by two ethyl groups so as to produce diethyl phenyl carbinol.

The experiments as carried out could not be utilized in forming a conclusion regarding the relative strength of the benzylic action of dibenzyl phenyl carbinol with that of benzyl alcohol.

HYDROBENZOIN ACETATE

Preparation of Hydrobenzoin Acetate.

Hydrobenzoin acetate $C_6H_5CHOOCCH_3$ / $C_6H_5CHOOCCH_3$ was prepared according to the method described by Paal (37). Redistilled benzaldehyde 45 Gm. dissolved in 50 Gm. absolute ether was added to 25 Gm. zinc dust in a flask fitted with a reflux condenser, and the mixture well cooled (ice). A solution of 50 Gm. acetyl chloride in 50 Gm. absolute ether was slowly added, with continual shaking to the cold mixture. After the reaction was complete, the mixture, which had become dark brown in color was shaken with 50 mils of water. The water layer was drawn off and the ether layer shaken out twice with 25 mil portions of water to remove zinc chloride. The ether layer was then shaken out with dilute sodium hydroxide until the reaction was neutral (to remove benzoic acid) and then

washed twice with small portions of water.

Upon evaporation of the ether solution in a vaccum desicator, a sticky, viscous agreeable smelling, dark brown liquid was obtained. This was allowed to stand over a long period of time (about a month) when a small quantity of crystals was obtained. These were filtered off with suction and washed with a small quantity of petroleum ether.

After recrystallizing several times from ether, the compound was obtained pure, as white needles melting at 134-135°. Yield very poor. Hydrobenzoin acetate is insoluble in water but readily soluble in organic solvents.

Theoretical Consideration of the Physiological Properties of Hydrobenzoin Acetate.

Hydrobenzoin acetate is not a carbinol but is the acetate of the carbinol hydrobenzoin $\begin{matrix}(C_6H_5CHOH)\\(C_6H_5CHOH)\end{matrix}$. It is thus seen to correspond in chemical structure with the benzyl esters, benzyl acetate and benzyl benzoate. These latter compounds were found by Macht (10) (15), to produce effects on smooth muscle tissues similar to those of the opium alkaloid papaverin. That is, their action is intended to either inhibit the contractions or to relax the spasm of smooth muscle structures, or both. They also possess the added advantage for therapeutic application of a very low toxicity.

Hydrobenzoin acetate would probably be less readily decomposed in the organism than benzyl acetate and therefore, if it retained any of the antispasmodic action of that compound this effect should be of longer duration.

Benzyl acetate is the acetate of the primary alcohol benzyl alcohol. Hydrobenzoin acetate is the acetate of the secondary alcohol benzoin. Little can be prophesied regarding the modification in physiological action to be expected from such a relation. Mention might be made of the report of Macht (33) that the secondary alcohols of the aliphatic series are less toxic than the corresponding normal alcohols.

Attention is also called to the fact that hydrobenzoin acetate contains two asymmetric carbon atoms. The importance to be attached to this fact is indeed problematical.

The preparation of hydrobenzoin acetate used thruout the work was the meso (internally compensated) modification.

Investigation of Hydrobenzoin Acetate.

Hydrobenzoin acetate as prepared in this laboratory was a white, odorless crystalline compound. Applied to the tongue it was without taste, and under these conditions had no effect on local sensation.

The quantity of this carbinol at hand was very limited and for that reason the investigation of its properties was confined to a series of applications to the sciatic nerve of frogs. On account of its insolubility in water the solution used in these experiments was obtained by dissolving the carbinol in olive oil.

Action of Hydrobenzoin Acetate Applied to the Frog's Sciatic Nerve.

The sciatic nerve in both legs of a series of frogs was exposed and the action of hydrobenzoin acetate on motor and sensory block was determined in the manner previously described (page 14).

A 2% emulsion of hydrobenzoin acetate in 0.75% saline, 7% acacia and 5% olive oil was applied to the nerve of the left leg, while the nerve of the right leg, treated with 0.75% saline, 7% acacia and 5% olive oil, was used as a control.

Results from Hydrobenzoin Acetate on Sensory Block.

Applied at 5:30 P.M. 5/7/20

+ = no sensory block
o = partial " "
- = complete " "

Time	Left Leg Frog # 1 2 3 4 5 6 7 8 9 10	Right Leg Frog # 1 2 3 4 5 6 7 8 9 10
5:30	+ + o + + + + + + +	+ + o + + + + + + +
5:40	+ + + + + + + + + +	+ + + + + + + + + +
5:45	+ + + + o + + + + +	+ + + + + - + + + +
5:50	- + + + + + + + + +	+ + + + + + + + + +
5:55	o + + + + + + + + +	+ + + + + + + + + +
6:30	- + + + + + + + + +	+ + + + + + + + + +

No motor block was encountered during the experiment.

Conclusion: Hydrobenzoin acetate applied to the sciatic nerve of a frog in the manner stated above, produces neither motor or sensory block.

Comparison of the Physiological Actions of Hydrobenzoin Acetate With Some Chemically Related Compounds.

The study of the actions of hydrobenzoin acetate were too limited in scope to draw any comparisons other than to call attention to the fact that this compound like benzyl acetate or benzyl benzoate produces no motor or sensory block when applied to the frog's sciatic nerve, nor local anesthesia when applied to the tongue of man.

GENERAL DISCUSSION.

The investigation here recorded was undertaken primarily for the purpose of investigating the action on local sensation of some substituted phenyl carbinols. The other experiments carried out were more or less incidental to this original idea and were chiefly the results of suggestions as to the possible physiological actions of the particular compound elicited thru a theoretical consideration of the chemical constitution of that compound. This consideration of the chemical constitution of some of the compounds furnished strong indications of possible interesting properties for these substances. Unfortunately, however, time did not permit the working out of a definite answer to all of the questions. It is hoped that further work in the near future will lead to the settlement of the unfinished problems. In many cases where the preliminary experimentation gave promise of nothing of particular interest, further investigation along that line was abandoned.

Of the compounds investigated, diethyl o- oxyphenyl carbinol, trichlormethyl phenyl carbinol and diphenyl carbinol produced a sensory block when applied to the frog's sciatic nerve, but were found to be too irritant for application to man. Diethyl phenyl carbinol and hydrobenzoin acetate did not produce sensory block under these conditions, while no determination was made for dibenzyl phenyl carbinol or methyl phenyl carbinol. The former substance was found to have no local anesthetic action on man, but the latter compound was reported by other investigators to possess a local anesthetic action. None of the compounds which were applied to the frog's sciatic nerve produced a motor block under these conditions, tho Macht (12) found that this effect was obtained with

4% benzyl alcohol. None of the compounds produced a local anesthesia when applied to the tongue.

The results obtained from this investigation may easily be construed as showing that the two inactive hydrogens of the carbinol group are of special importance for the production of the local anesthetic action which this group displays when joined to a phenyl group. When one of the hydrogens is displaced as in the case of trichlormethyl phenyl carbinol, methyl phenyl carbinol and diphenyl carbinol, the local anesthetic effect is apparently retained, tho it is very slight in the case of the latter compound. Substitution of both of the inactive hydrogens, however, would appear to reduce or even destroy the activity of the carbinol group. This is apparent in the case of diethyl phenyl carbinol and dibenzyl phenyl carbinol. Diethyl o- oxyphenyl carbinol still appears to possess some local anesthetic effect, as evidenced by its sensory inhibition action on the frog, but this may be ascribed to the phenolic (OH) group also present in the molecule. When one of the inactive hydrogens and also the active hydrogen were substituted as in hydrobenzoin acetate, as was to have been expected, the compound exhibited no sensory inhibition action.

From this series of observations, the inference might be drawn that the local anesthetic action of the phenyl carbinols requires the presence of one of the inactive hydrogens of the carbinol group and that the best results will probably be obtained when both of these atoms are present. The result to be obtained from replacement of the active hydrogen can not positively be stated, but it would appear at least probable that an increase in the local anesthetic effect of the phenyl carbinols will not be obtained by

making substitutions in the carbinol group itself. A consideration of the actions of other carbinols previously reported appears to agree well with the conclusion that the local anesthetic effect of the phenyl carbinols is more accentuated in the primary alcohols. There would appear to be a slight amount of evidence which indicates that this effect of the carbinols may be associated with their oxidation in the tissues.

The introduction of a 10% emulsion of diphenyl carbinol into the conjunctive sac of the cat produced a decided irritation but no alteration in the size of the pupil. No anesthesia of the pupil was obtained.

Those compounds with which an attempt was made to determine the toxic dose, appear to possess in common with the carbinols previously reported, the valuable property of a comparatively low toxicity. The subcutaneous injection of a dose of 1.77 Gm. per Kg. of diethyl o- oxyphenyl carbinol in a rabbit was without toxic effects. The toxicity of trichlormethyl phenyl carbinol under the same conditions was 3.6 Gm. per Kg., and that of diphenyl carbinol was 2.3 Gm. per Kg. for guinea pigs. The results obtained in preparing the respiration - blood pressure tracings would also tend to show the comparatively low toxicity of diethyl o- oxyphenyl carbinol, trichlormethyl phenyl carbinol, and diethyl phenyl carbinol. This low toxicity, especially following the administration of the compounds by subcutaneous injections, may to some extent be due to the low degree of solubility of these substances in water. Altho it is realized that the acacia and olive or cottonseed oil which was often administered with the carbinol would tend to diminish the activity of that substance, this effect is considered as being

of slight moment. The effect of the morphine which was used in certain cases, and the saline solution which was used to wash the injected material into the femoral vein, were likewise considered as being practically negligable in the final interpretation of the results.

It is also to be noted that the subcutaneous injection of large doses of trichlormethyl phenyl carbinol or of diphenyl carbinol produces a certain degree of narcosis, not unlike that obtained from large doses of benzyl alcohol or saligenin. This action is more marked in the case of the trichlormethyl compound. The oral administration of diethyl o- oxyphenyl carbinol is attended with a slight sedative action, tho this was not noted following the subcutaneous injection of that compound.

These results would tend to show that the effects obtained by the replacement of the active hydrogens of the phenyl carbinols are not in complete agreement with those obtained thru similar changes in the aliphatic carbinols. The introduction of two ethyl groups in a phenyl carbinol did not produce any striking increase in the narcotic action or the toxicity as might have been obtained in the case of aliphatic compounds. No relationship between the primary, secondary, and tertiary alcohols of the aromatic series could be demonstrated which agreed with that of the aliphatic series. Or in other words, altho the substitutions here made were in the side chain, and therefore were expected to produce changes in the physiological action like those of similar changes in aliphatic compounds, this does not seem to have been the case.

As stated earlier in this paper, the carbinols here investigated are practically insoluble in water. Because of this con-

dition, considerable difficulty was encountered in studying the effect of these compounds on the blood pressure and the respiration. The intravenous injection of an alcoholic solution did not yield satisfactory results because the carbinol was precipitated out of solution on coming into contact with the blood stream of the animal. Since no results were obtained following the injection of an emulsion of the carbinols into the intestines of an animal prepared for the recording of the blood pressure and the respiration, it was concluded that the carbinol was not absorbed under these conditions or was only slowly absorbed, or else if absorbed, it was without action. The apparent effects observed in the case of the first few tracings made, are thought to have been the result, at least in part, of magnesium sulphate solution which entered the circulation of the animal thru the carotid cannula. To avoid the possible reoccurrence of such a condition, sodium citrate solution was used in the carotid cannula during the preparation of all tracings after #4.

It is to be noted from certain of the tracings, especially tracings #7, #8, #10, #13, and #14, that the intravenous injection of a 10% emulsion of olive oil in 7% acacia and 0.9% saline solution was practically without effect on the blood pressure and respiration of a dog or cat prepared for the recording of these factors. As previously stated, these findings are entirely opposed to the observations reported by Porter (18). Since these experiments were made, it was found that Miller (38) has stated that the intravenous injection of doses up to 10 mils of olive oil gave no injurious effects with dogs, while rabbits were readily effected with embolization (fatal). These findings are in accord with those

reported by Wiggers (39).

Advantage was taken of this apparent inertness of the olive oil in the intravenous and subcutaneous administration of diethyl o- oxyphenyl carbinol. This carbinol being a solid, insoluble in water, could not well be administered by other methods so satisfactorily as it was when dissolved in olive oil and then emulsified. The injections of emulsions of either of the two liquids trichlormethyl phenyl carbinol and diethyl phenyl carbinol were paralleled by similar injections of the olive oil and the results so obtained were translated as showing that the effects on the blood pressure and the respiration were not the mechanical effects of an oil, but rather, were the direct effects obtained following the absorption of the carbinols. It is, however, a question as to the exact role played by the olive oil in the occurrence of the pulmonary edema which apparently is more noticeable in those cases where the oil was injected than in those cases where it was not used.

The effect on the blood pressure and the respiration observed following the injection of an emulsion of diethyl o-oxyphenyl carbinol, trichlormethyl phenyl carbinol or diethyl phenyl carbinol is practically the same in all cases. The blood pressure fell to a degree and with a sharpness in a measure dependent on the size of the dose administered. The respiration usually decreased in rate and in amplitude. These observations lead to a conclusion that the action following the intravenous injection of either of these carbinols is the same, or else that the action observed is not the result of the carbinol per se but is dependent on some factor associated with the manner in which these carbinols were administered. The former conclusion appears to be the more logical.

In many cases the investigation of a particular carbinol failed to disclose those properties which were to be expected from a theoretical consideration of the chemical constitution of the substance. The introduction of two ethyl groups into the carbinol group of saligenin gave diethyl o- oxyphenyl carbinol (diethyl saligenin) but no evidence was encountered which would show that an increase in the narcotic action over that of the parent substance had taken place following the addition of these two ethyl groups. From its structural relationship to several compounds having a pronounced narcotic action, trichlormethyl phenyl carbinol was expected to possess a similar effect to a much greater extent than that which was disclosed by experimentation.

In other words, a certain grouping does not appear to always exert the same physiological activity regardless of the rest of the molecule with which it is associated, or if it does retain this activity, the ultimate action of the entire molecule will not always be the simple summation of the actions of its component groups. Traube (40) has called attention to the apparent fact that the pharmacological action of a large number of drugs and poisons may be attributed to their physical properties and related properties, but he perhaps becomes too radical when he states, that the chemical constitution and configuration are important only as they determine the above physical properties.

The conclusion reached from the experiments previously detailed would tend to show, that more attention in chemotherapy should be given to the physical properties of the compound, but there can be little doubt but that the chemical constitution of the compound is of importance aside from its influence on the

determination of the physical properties of that substance. It is realized that in the work here recorded insufficient emphasis was placed on the physical properties of the compounds considered.

In conclusion, I wish to express my thanks to Dr. Arthur D. Hirschfelder, at whose suggestion and under whose direction this research was carried out. I also wish to thank Dr. E. D. Brown and Mr. M. C. Hart for helpful suggestions, and Dr. L. McFarlane for assistance in the laboratory preparation of the blood pressure-respiration tracings.

SUMMARY

1. A series of compounds chemically related to benzyl alcohol were synthesized and an investigation made of some of their physiological properties.

2. The compounds so considered were methyl phenyl carbinol, diethyl o- oxyphenyl carbinol, trichlormethyl phenyl carbinol, diphenyl carbinol, dibenzyl phenyl carbinol and hydrobenzoin acetate.

3. With the exception of methyl phenyl carbinol and dibenzyl phenyl carbinol a determination was made of the effect of these substances when applied to the frog's sciatic nerve. Determinations were also made with certain of these compounds as to their effect on local sensation in man, both on mucous membrane and following subcutaneous injection; their action following subcutaneous injection in animals; their toxicity under these conditions and the effect of intravenous injections on the blood pressure and respiration of animals.

4. In several cases the compounds investigated were found to possess some narcotic effect or some local anesthetic action, but

none of these actions are considered to be of practical importance.

5. The presence of the inactive hydrogens of the carbinol group appear to be of importance for the production of the local anesthetic action of the phenyl carbinols.

6. Alterations in the side chain of some of the aromatic carbinols do not appear to agree exactly with similar modifications in the structure of aliphatic carbinols.

7. Incidently it was found that the intravenous injection of moderate doses (up to 10 mils) of a 10% emulsion of olive oil was practically without effect on the blood pressure and respiration of dogs or cats.

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Benzhydrol : 83 & 94
(Cyclohexanol)
Trichlor methyl phenyl carbinol (44)
~~Diethyl~~ Di benzyl phenyl carbinol (104)
Diethyl " " 70
Di Ethyl o-oxyphenyl carbinol (21) for acetophenone
+ acetophenone pinacone is formed
Hydrobenzoin. acetal 109
PS → Methyl phenyl carbinol $C_6H_5CHOHCH_3$ (Hoin + Eagan)
cf (15) β.z. alc — IV mol $^{15}/_{Kg}$ 1% solution no effect.
$^{10}/_{Kg}$ dogs (narcosis)
Toxic doses → convulsions
$^{8}/_{Kg}$ when not always fatal to rabbits

Alcohol pp —
Alk (NaOH) salts hydrolyze in vessels & food

pp
Emulsion of carbinol in 7% acacia + 0.9 NaCl
of carbinol in olive oil
Benzhydrol — fall of BP — depress rate & amplitude resp.
Pulm. oedema. (from oil?)

~~cf. Max~~

Macht #34

Ascending alcohols.

BP - non-lethal doses no variation

lethal mus. contraction ~~to~~ narcosis hr → day.
→ death.

l.d. 2.3 G/kg

Phosphorol crystals on frogs leg - motor block
+ sensory.

Human forearm 1.5% no block until
irritation slight dulling of sensation

Rab. cornea
no anaesthesia pupil normal

R $CHCl_3$
$CHOH$

narcosis → death
in minutes

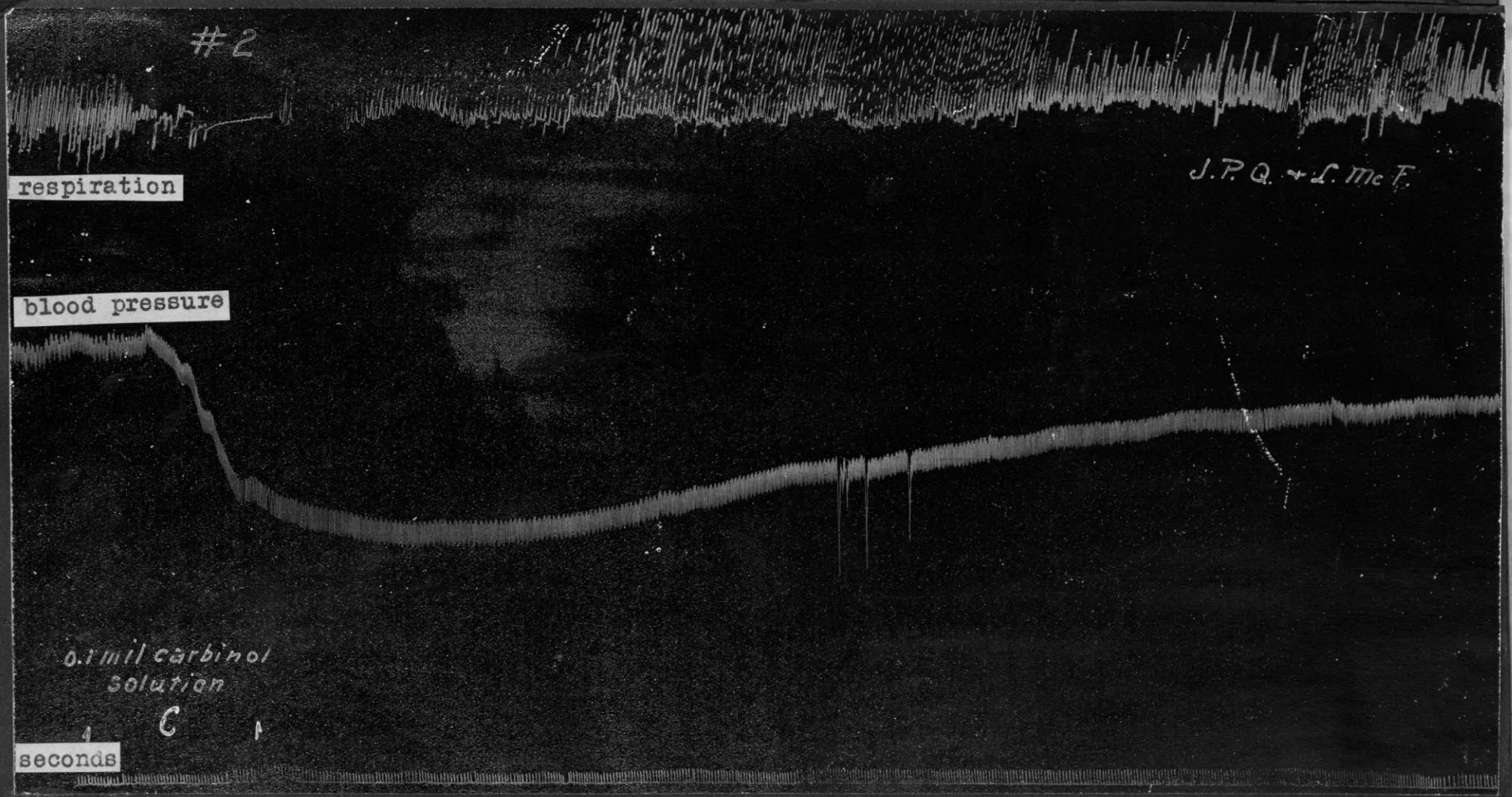
sensory block

resp. ceased.
BP falls - ~~to~~ oedema of lungs.

Contraction
curare - mm

~~Toxicity~~

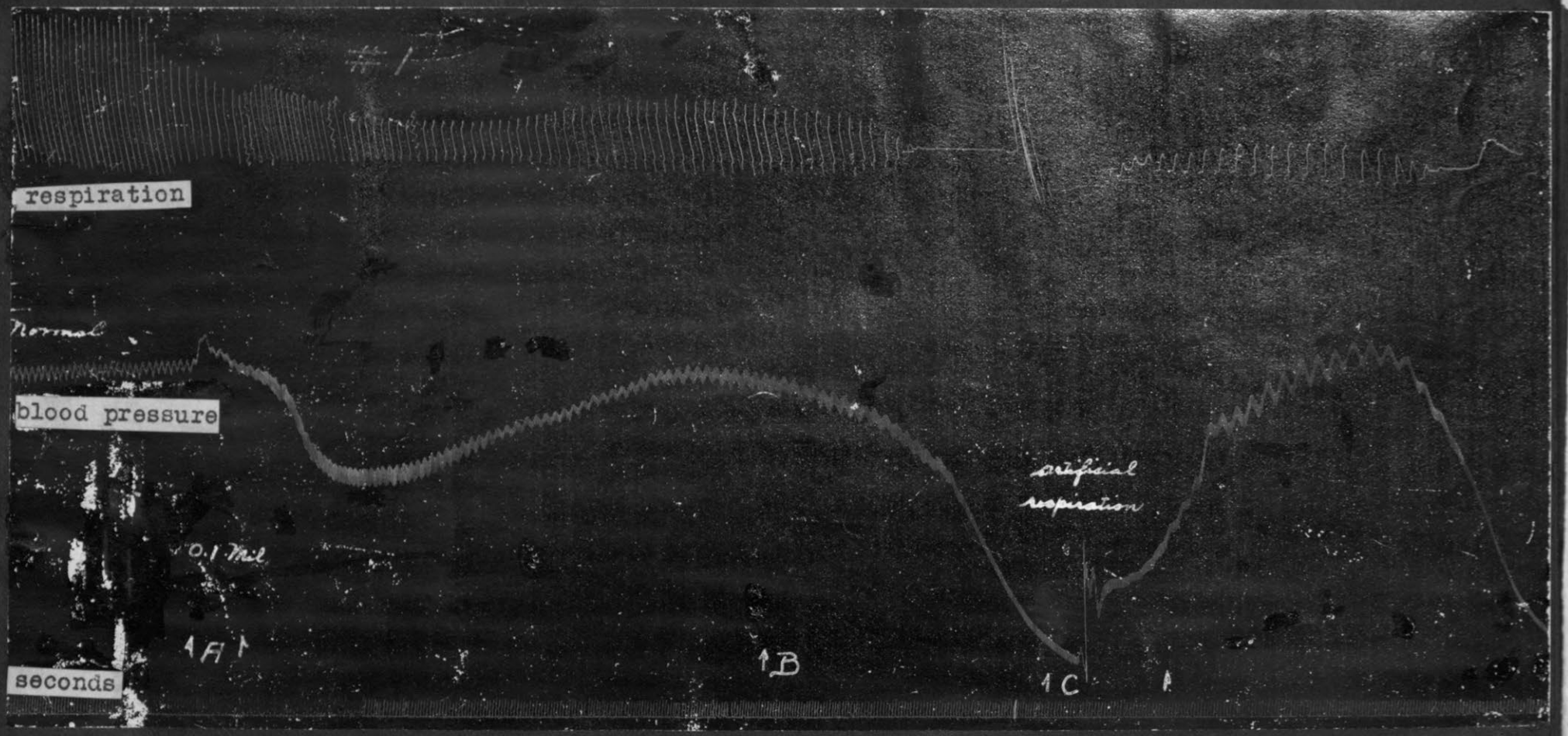
lethal dose for Frogs	lethal dose for ~~mammals~~ mammals Guinea pig 3.3	Effect upon blood pressure


#2
J.P.Q. + L. McF.
respiration
blood pressure
0.1 mil carbinol solution
C
seconds

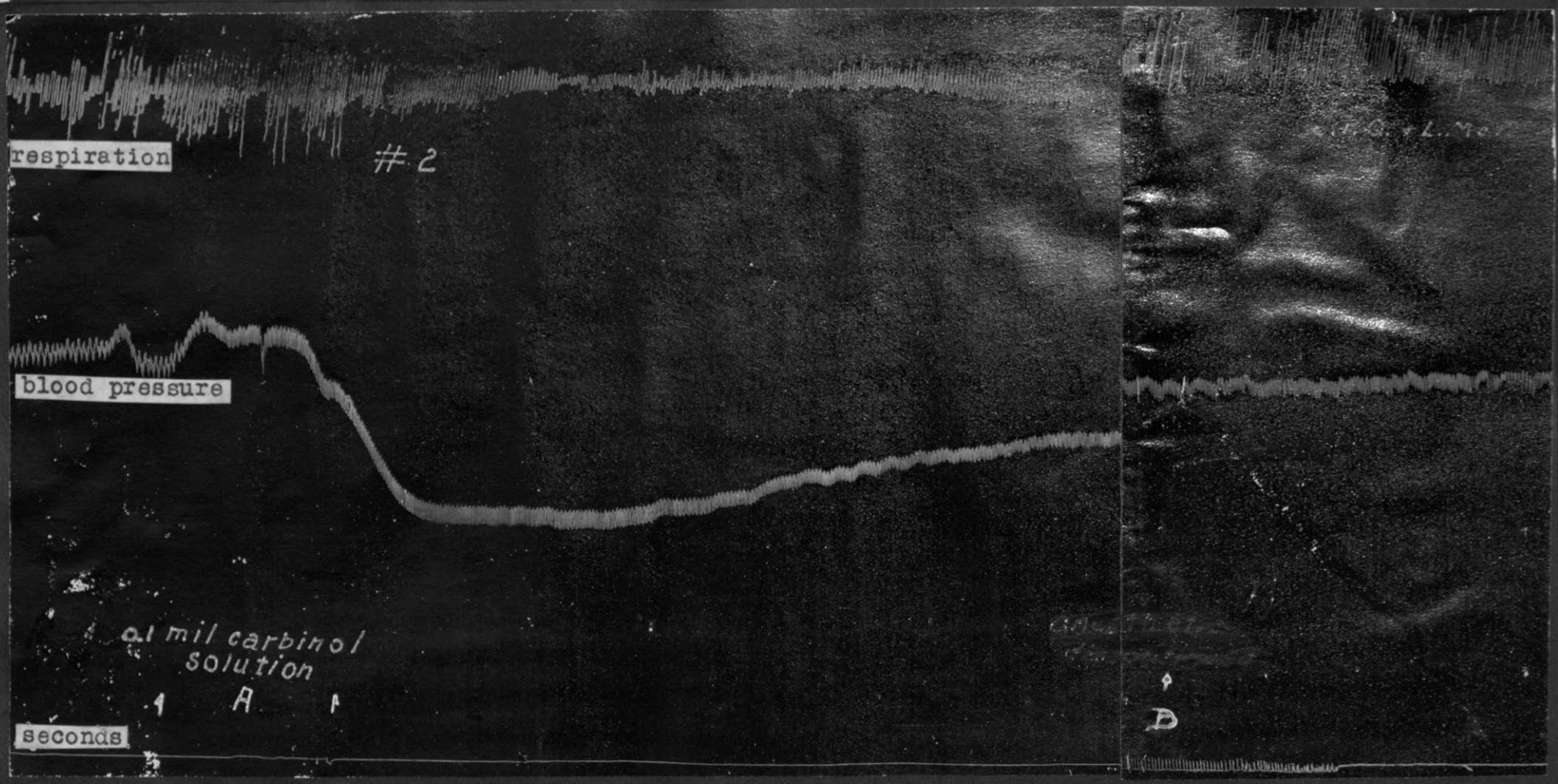
THE RELATION OF CHEMICAL STRUCTURE TO PHYSIOLOGICAL ACTION OF SOME SUBSTITUTED PHENYL CARBINOLS AND RELATED COMPOUNDS

J. Paul Quigley

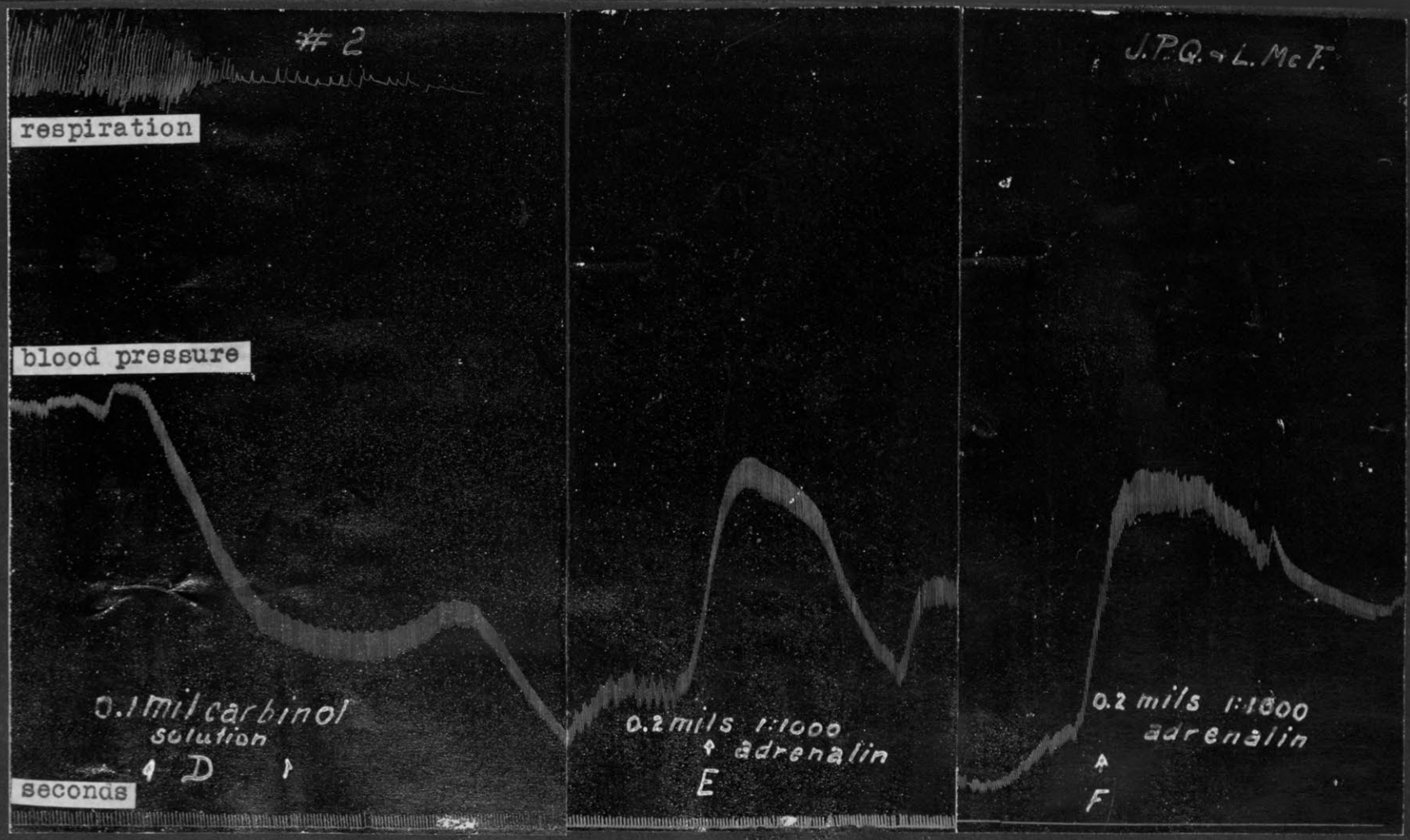
RESPIRATION - BLOOD PRESSURE TRACINGS #I - #I4



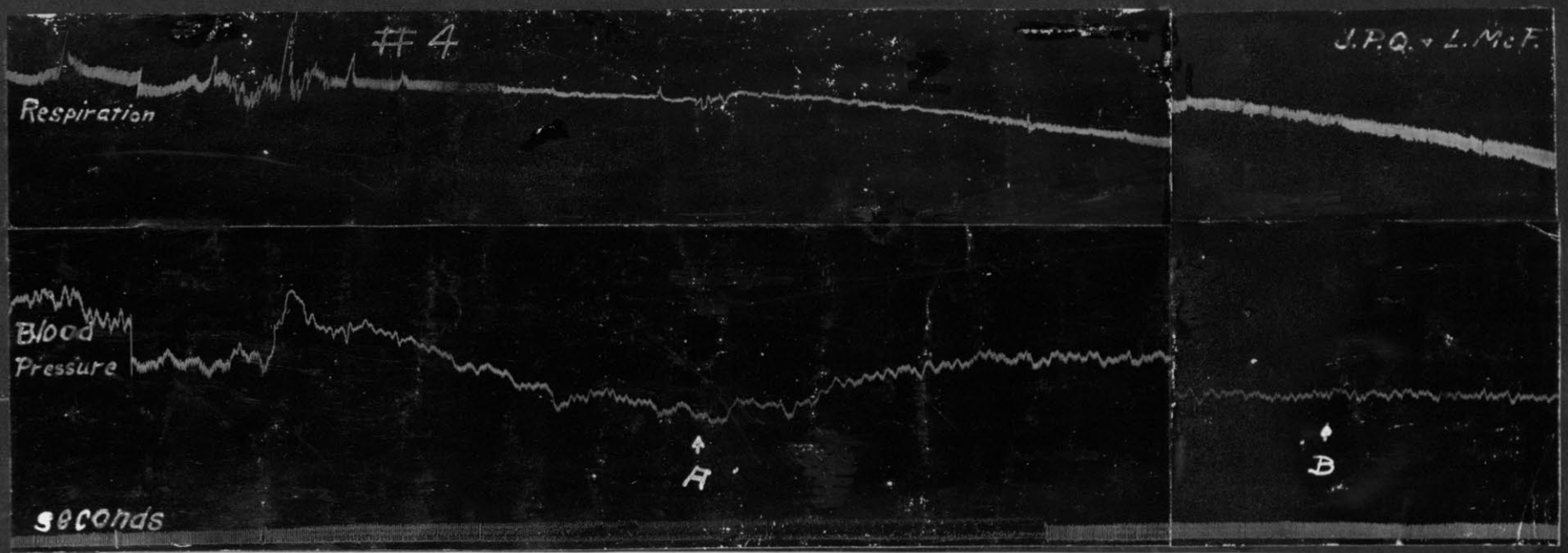
Diethyl o-Oxyphenyl Carbinol as a 50% solution in 95% alcohol injected into the femoral vein of a male cat (2400 Gm.). The initial fall in blood pressure and decrease in the amplitude of respiration is probably due to the carbinol. The effects after (B) are thot to have been caused by magnesium sulphate entering the circulation from the carotid cannula. The respiration appears to have been effected to a greater extent than the blood pressure.



Diethyl o-Oxyphenyl Carbinol (50%) dissolved in 95% alcohol injected into the femoral vein of a 2700 Gm.female cat. The sharp fall in blood pressure and decrease in the amplitude of respiration as shown at (A) is probably due directly to the action of the carbinol. It is to be noted that at (B), I8 minutes after beginning injection (A), the blood pressure had risen until it was 2 mm. below normal. The respiration had also apparently returned to normal.

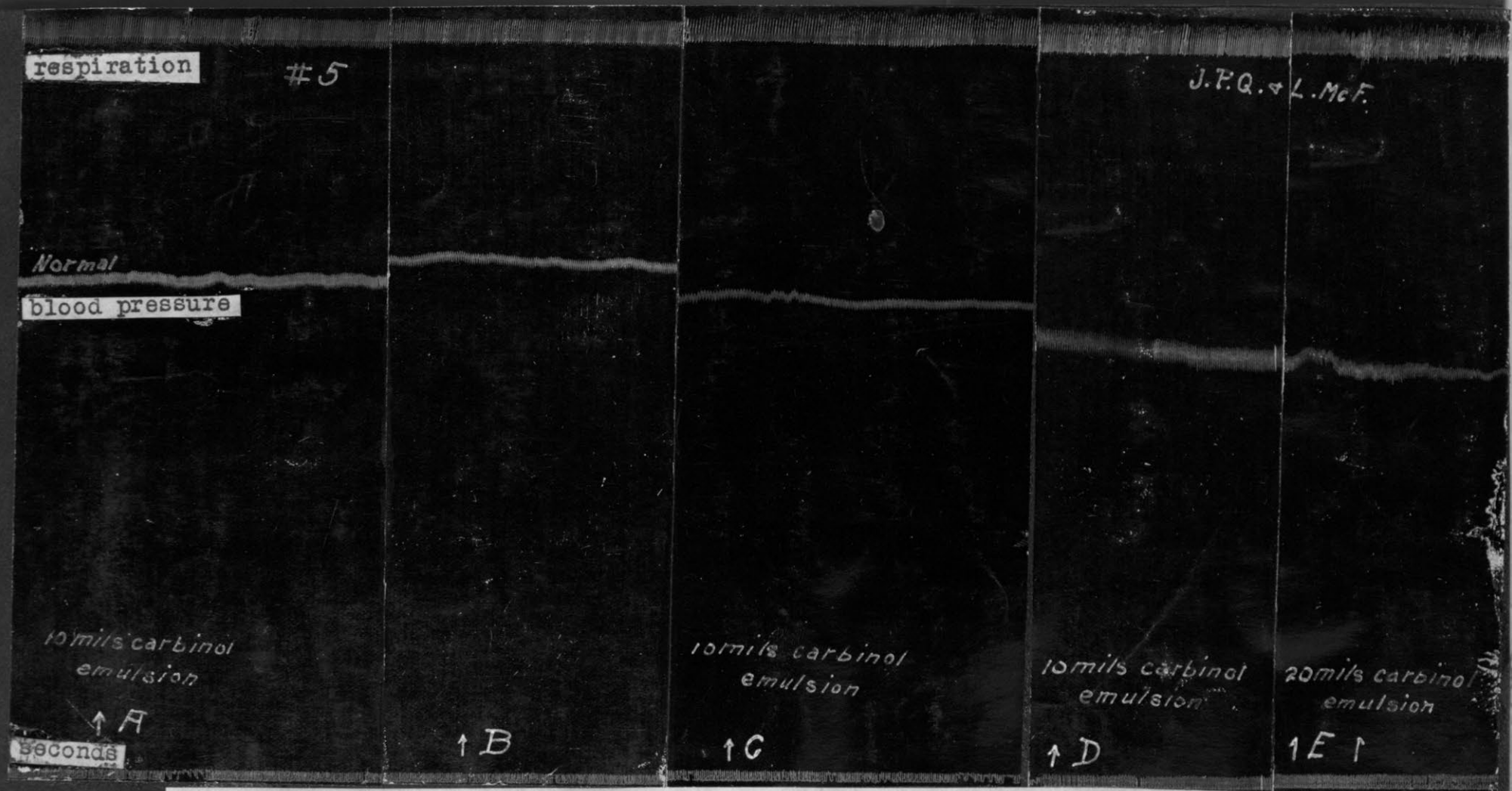


Injection (C) and (D) produced an action on the blood pressure and respiration simular to that obtained at (A), however, the effect at (D) is more marked than either of the other two. The pressor effect following the intravenous injection of adrenalin at (E) and (F) show that the mechanism by which this effect is brought about is still functionally active.



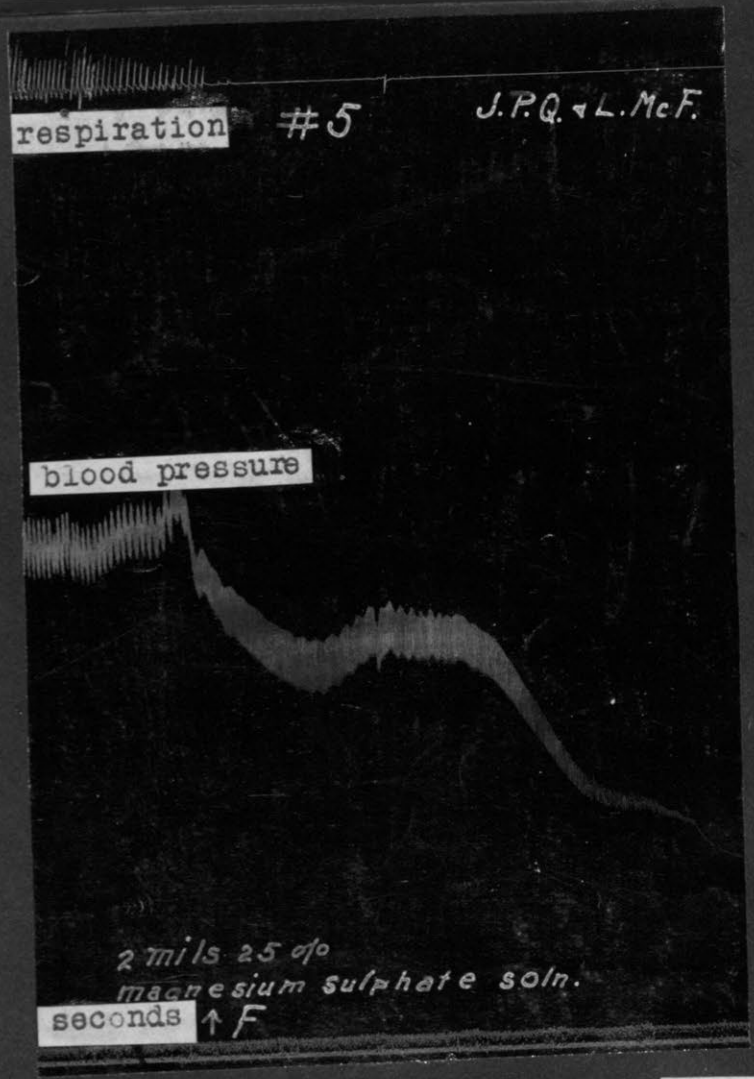
Diethyl o-Oxyphenyl Carbinol (0.06 Gm. in an emulsion of 7% acacia, 0.9% saline and 5% cottonseed oil) injected into a loop of the small intestines at (A). No marked effect observed. The blood pressure remained constant as at (B) for over 40 minutes, then fell gradually, and death resulted. The respiration was practically unaffected until just before death.

Results would indicate that the carbinol is not absorbed at all, or absorbed very slowly from the intestines, or else, if absorbed, it is practically without effect.

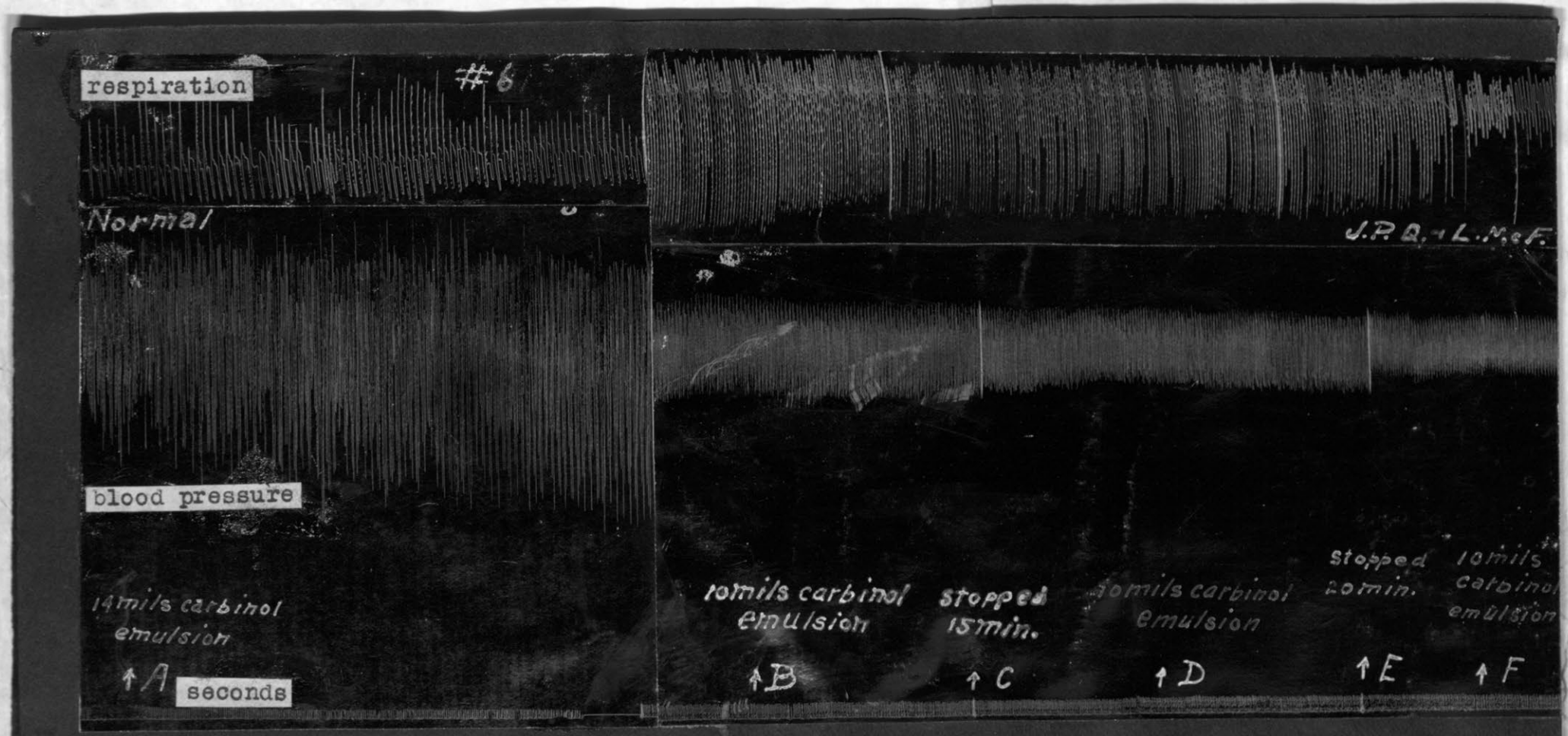


Diethyl o-Oxyphenyl Carbinol as a 2% emulsion in 7% acacia, 09% saline, and 5% cottonseed oil injected into loops of the small intestines of a 3900 Gm.male cat.

The first injection (A) seemed to be without effect,altho at (B), I5 minutes after (A), the blood pressure had risen to 3 mm.above normal. Simular injections at (C), (D), and (E) were apparently without effect. The total amount of carbinol injected was I Gm.. The condition of the animal was practically unaltered at (F), I hour and 40 minutes after (E). this lead to the conclusion that the

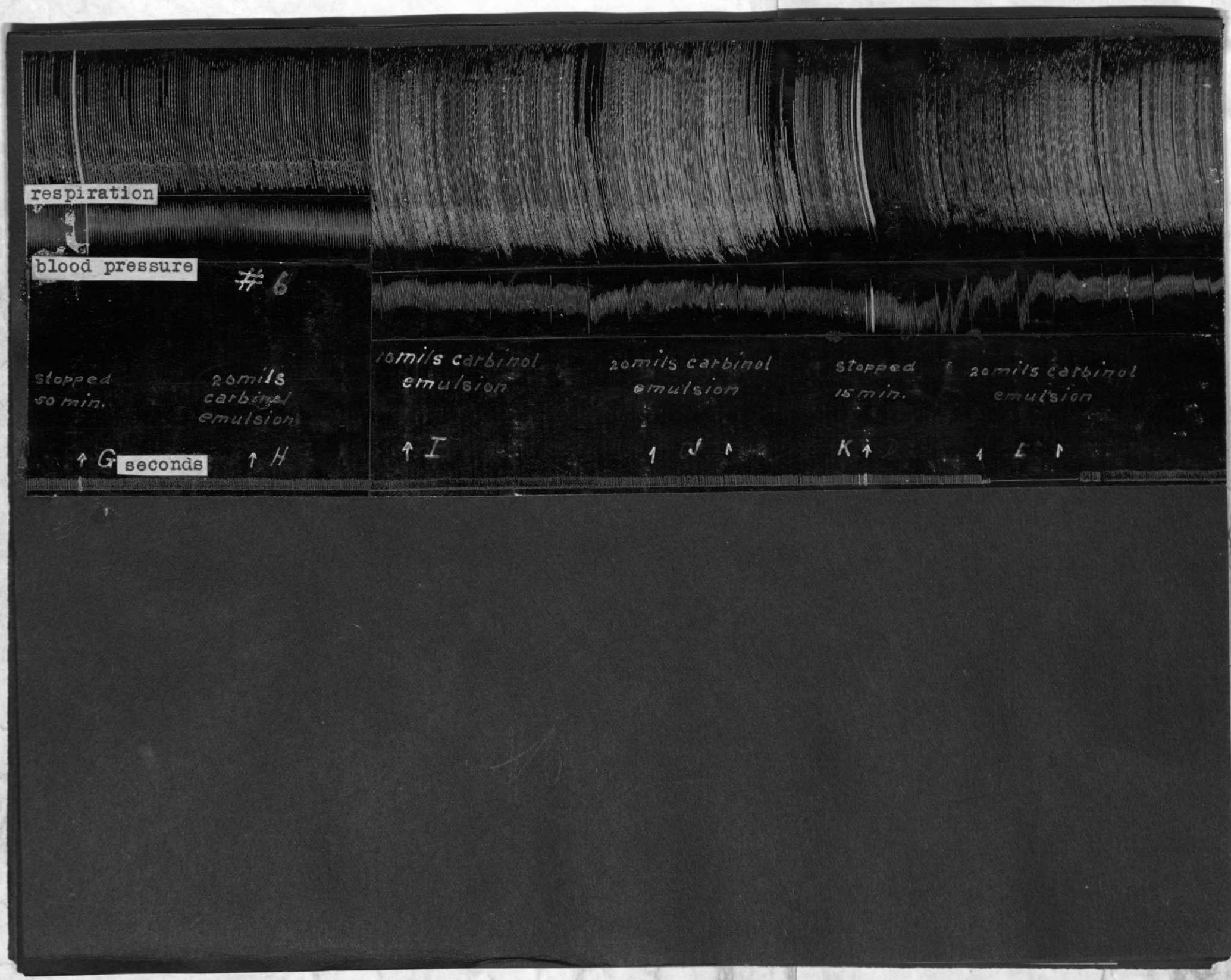


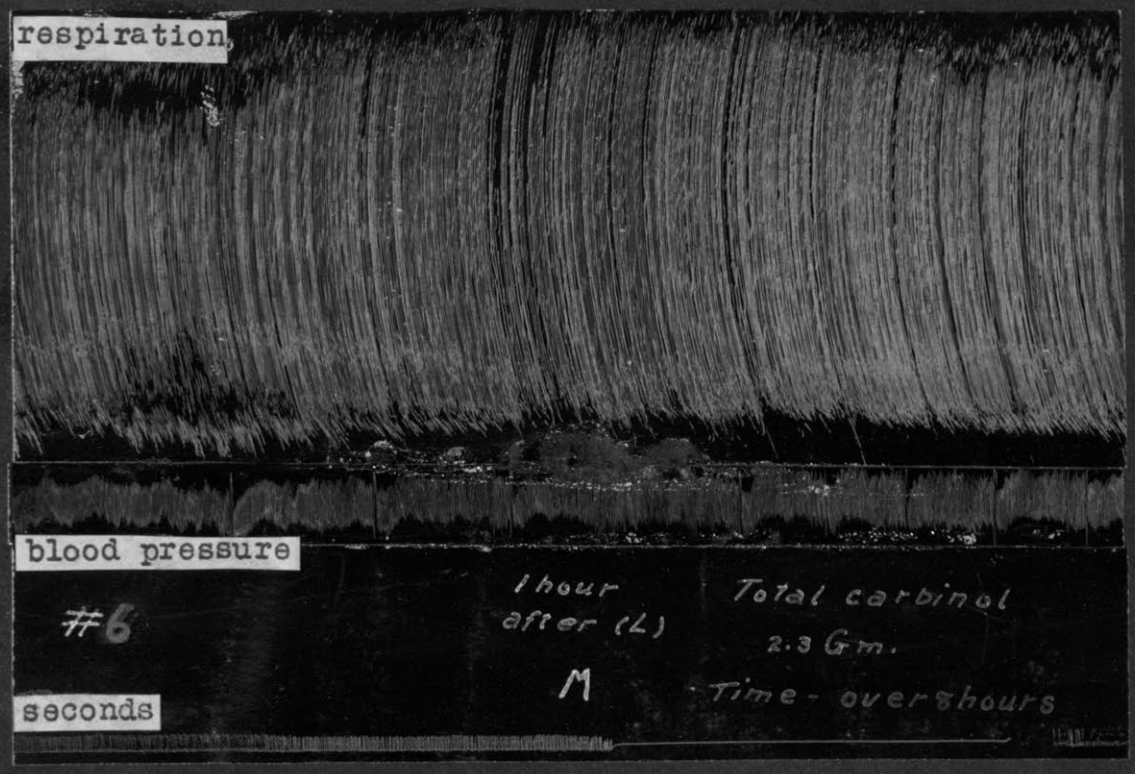
carbinol was slowly absorbed from the intestines or not absorbed at all, or else if absorbed, it was without effect. The injection of magnesium sulphate solution at (F) resulted in a series of effects so simular to those obtained in tracings #1, #2, and #3 as to make it appear very likely that the effects obtained in these cases were due in part at least to magnesium sulphate which entered the circulation from the carotid cannula.



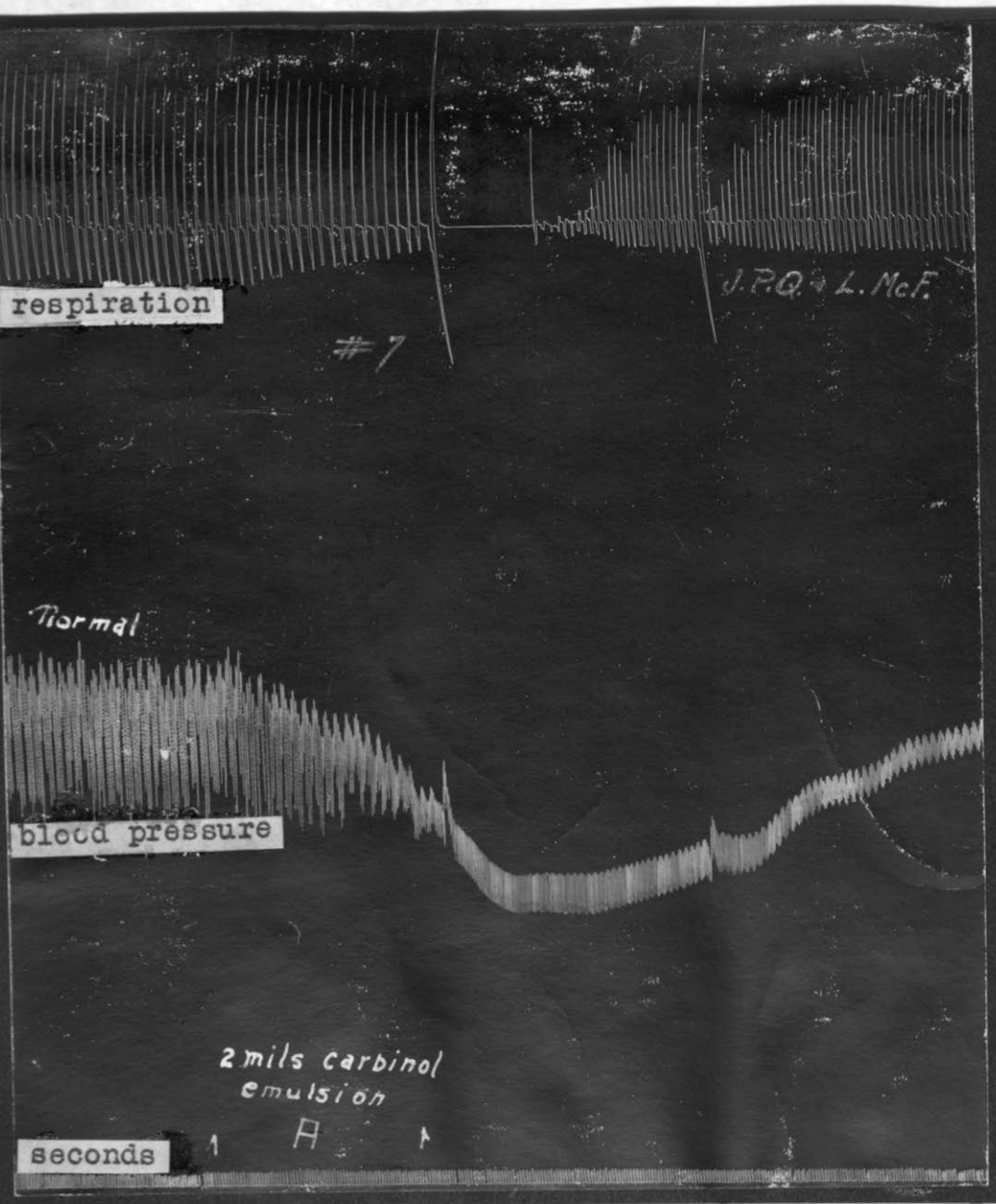
Diethyl o-Oxyphenyl Carbinol as a 2% emulsion injected into loops of the small intestines of a I5 Kg. female dog. Sodium citrate in the carotid cannula.

Between injections (A) and (H) 54 mils of the emulsion had been injected. About three and a half hours had elapsed during that time but, except for a decrease in the amplitude of the blood pressure no change in condition of the animal was noted.


respiration
blood pressure
#6
stopped 50 min.
20 mils carbinol emulsion
10 mils carbinol emulsion
20 mils carbinol emulsion
stopped 15 min.
20 mils carbinol emulsion
G
seconds
H
I
J
K
L



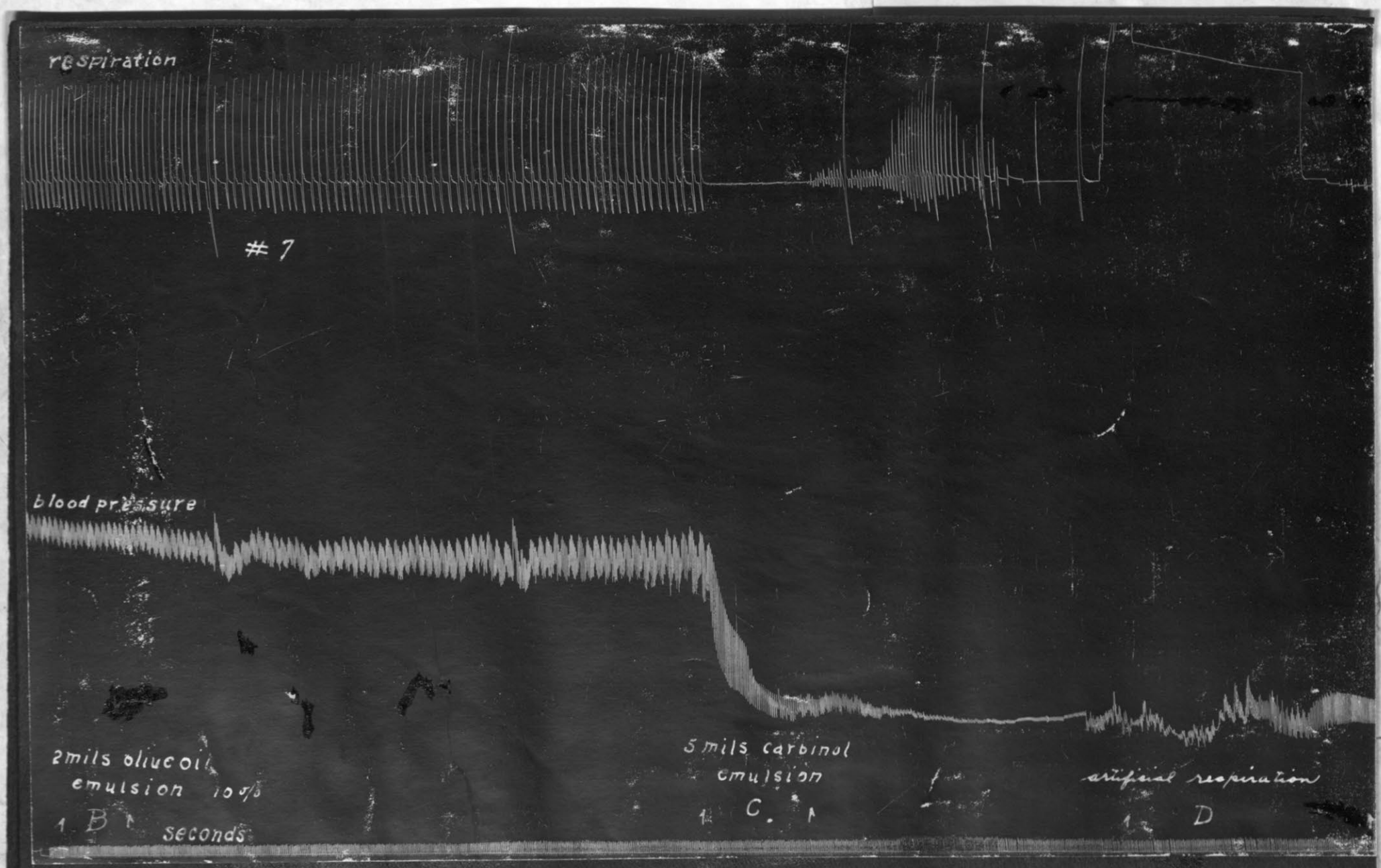
The condition of the animal was practically unchanged at (M) and the conclusion was reached that it would be advisable to administer the carbinol by another method.



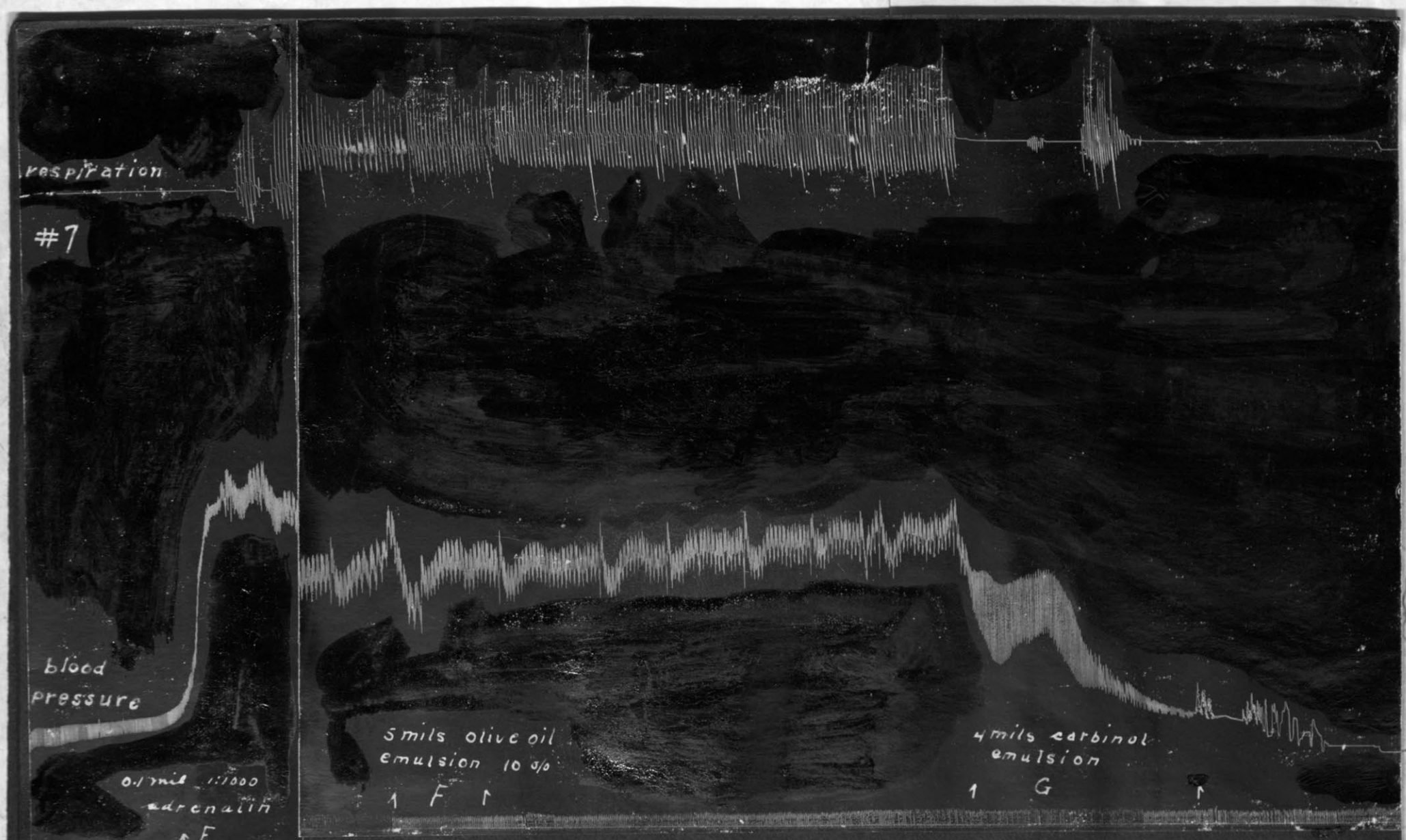
Diethyl o-Oxyphenyl Carbinol as a 10% emulsion injected into the femoral vein of a 9 Kg. dog. Injections controlled by the injection of a simular emulsion without the carbinol.

The injection at (A) produced a fall in blood pressure of 23 mm..

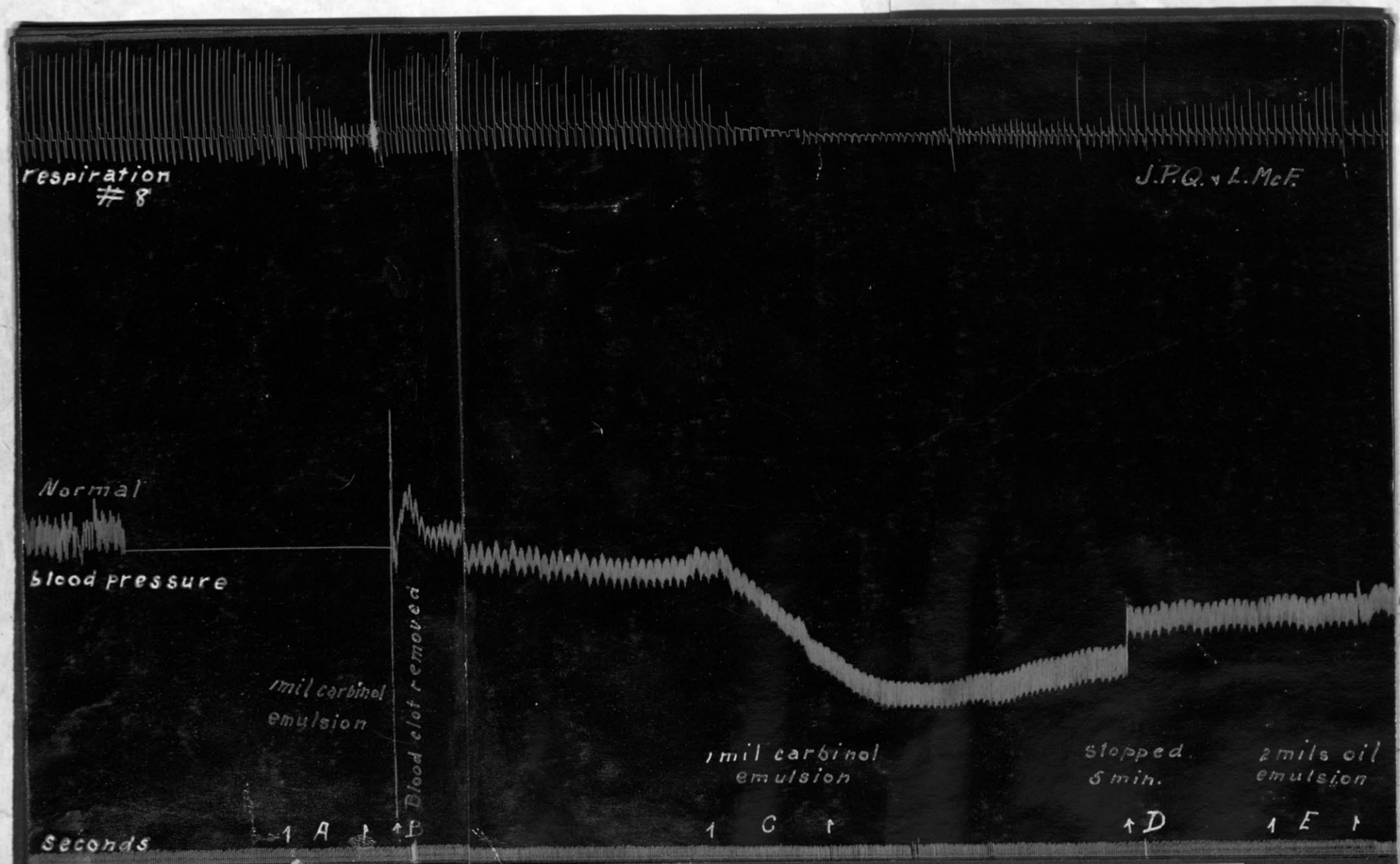
The respiration ceased but restarted spontaneously.



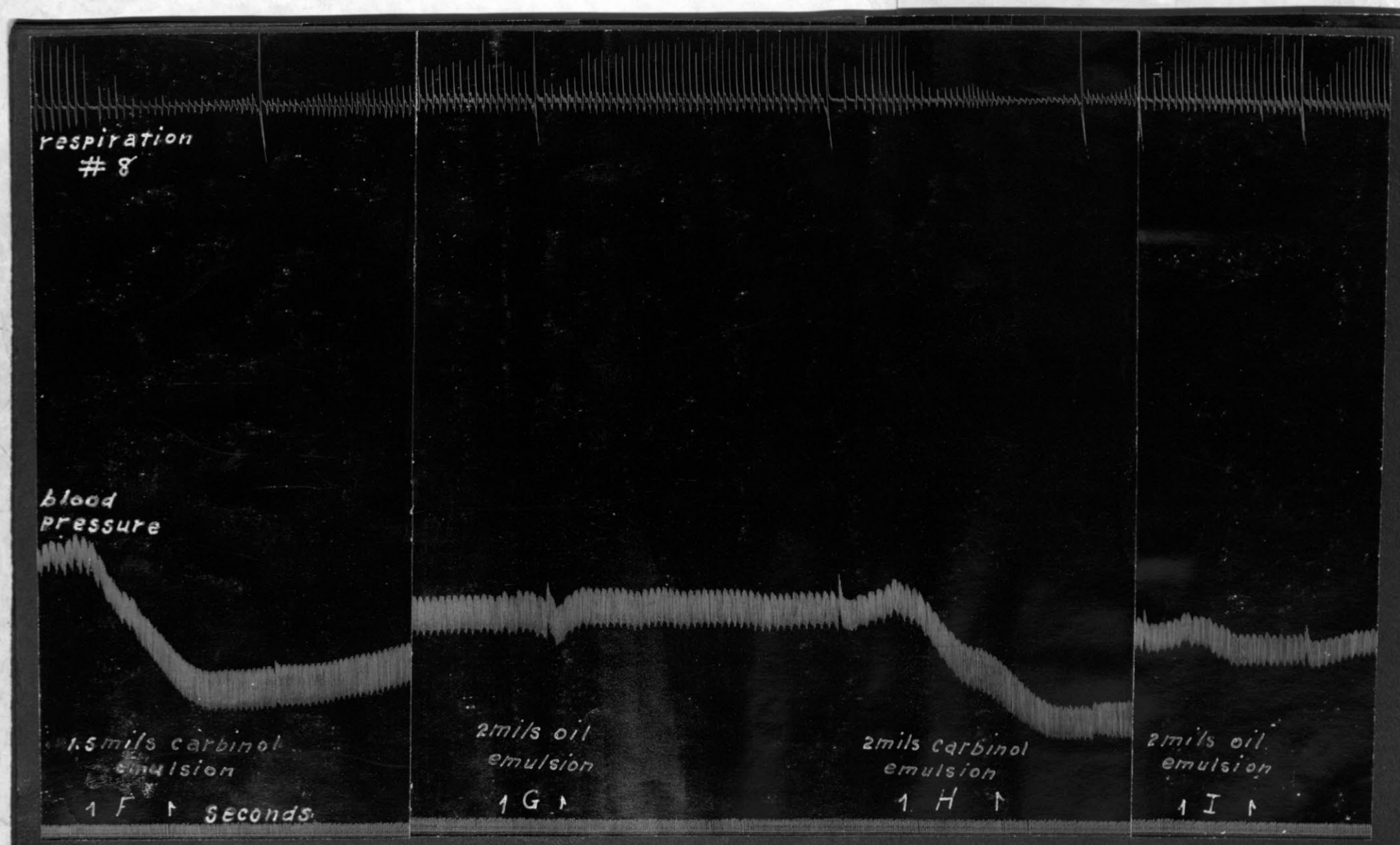
The injection of olive oil emulsion at (B) was practically without effect, while the effect of the carbinol at (C) is very marked. The pressor action following the injection of adrenalin at (E) is typical.



The comparison of effects obtained from the oil emulsion (F) with those from the diethyl-ortho-oxy phenyl-carbinol (G) would tend to show that dependable results may be obtained from this method of administering the carbinol. Following the death of the animal a considerable amount of a frothy blood tinged fluid was expressed from the lungs.

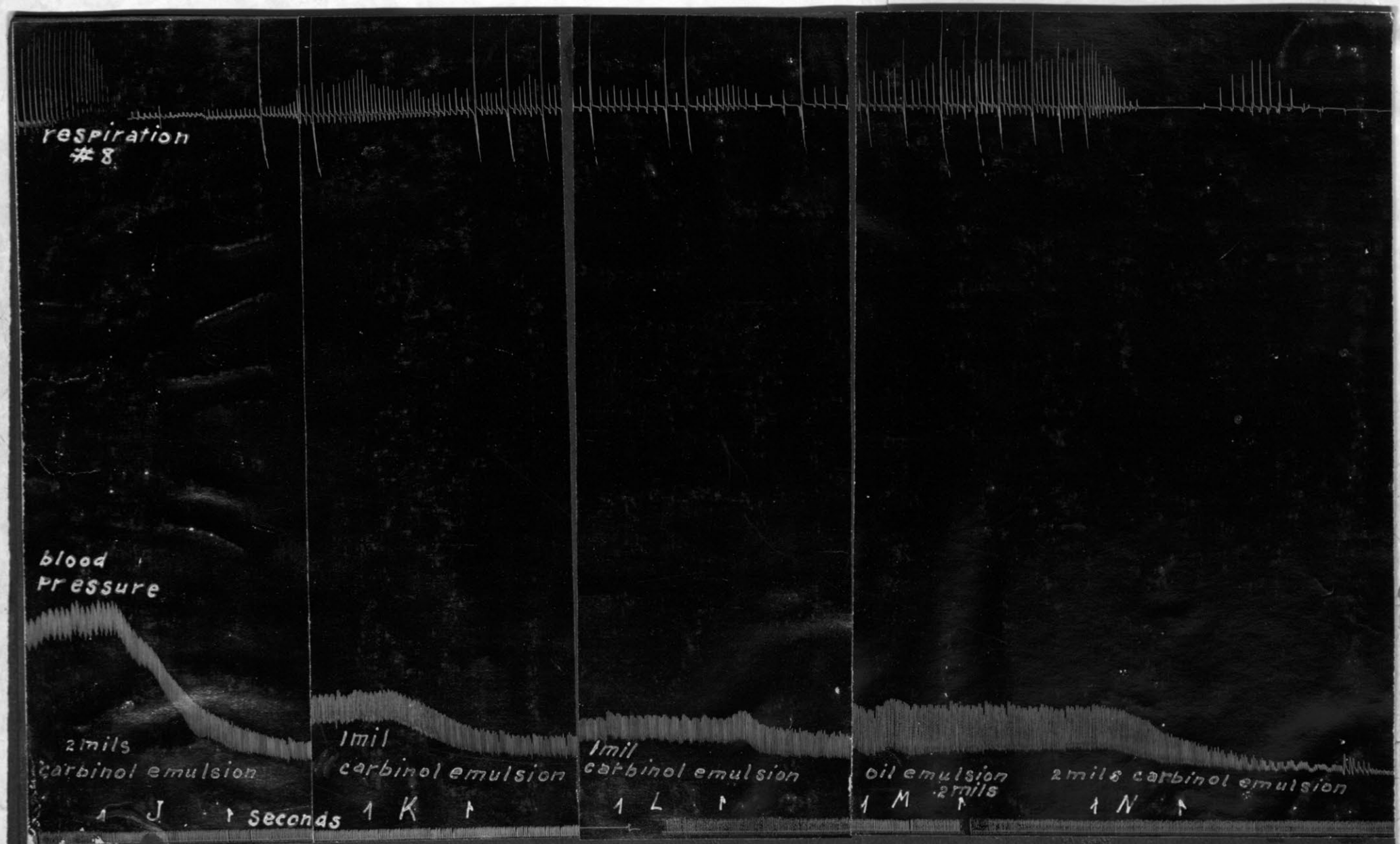


Diethyl o-Oxyphenyl Carbinol as a 10% emulsion injected into the femoral vein of a 5.8 Kg. female dog. Effect of the carbinol controlled by injections of a simular emulsion without the carbinol. Animal given 1.5 mils of 4% morphine sulphate subcutaneously. The effect on the blood pressure of injection (A) was not determined

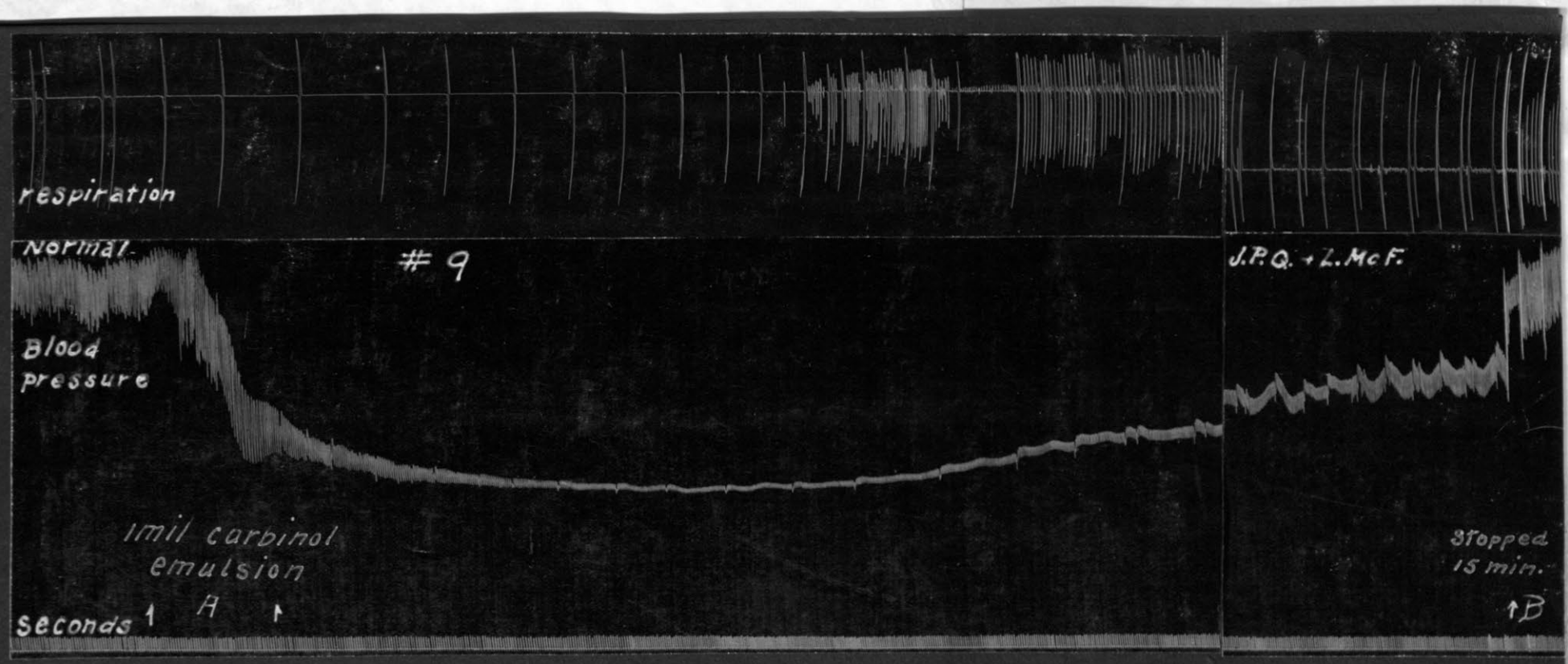


because of a blood clot, however the action on the respiration was very noticable.

A comparison of the effects of injections of the carbinol emulsion with injections of the olive oil emulsion show in a striking manner that the carbinol has a decided action on both the blood pressure and on the respiration. These effects agree well with those obtained

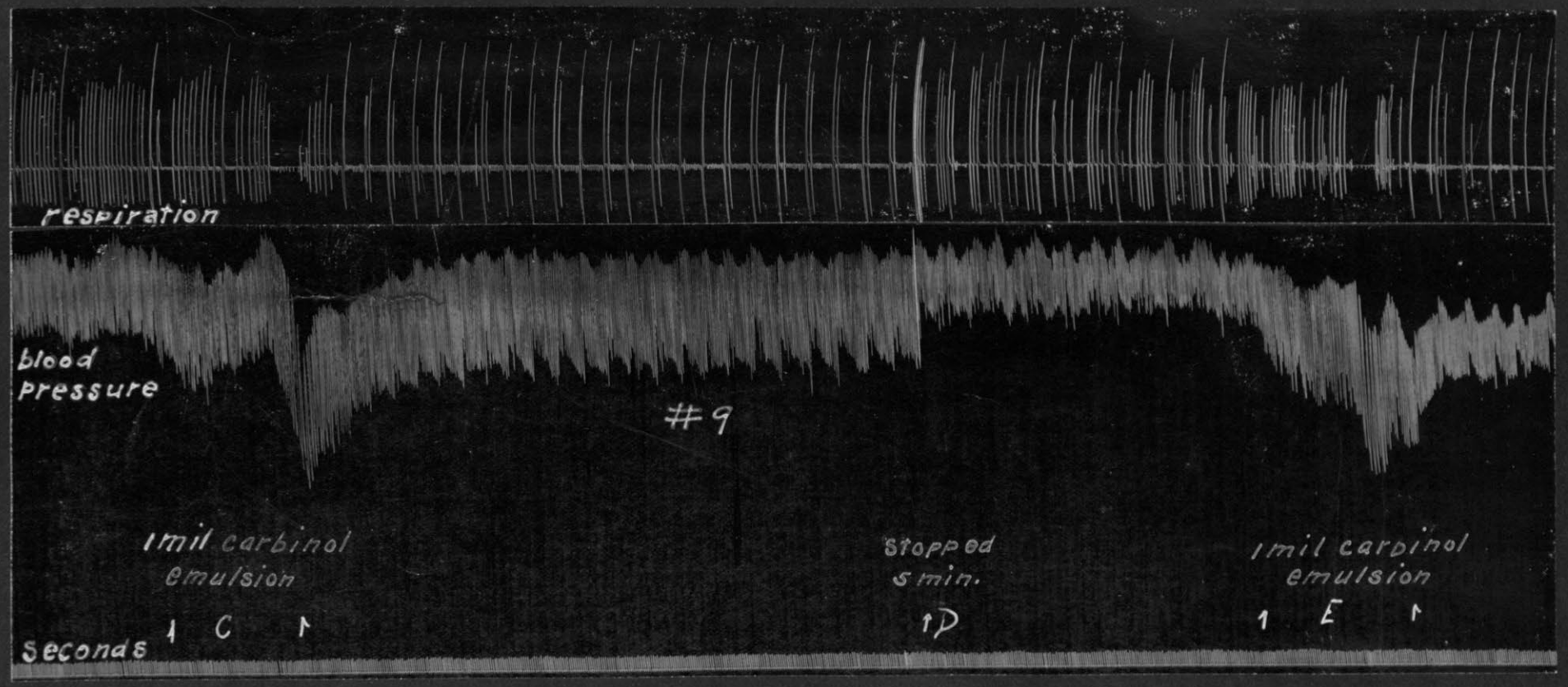


in tracing #7. Considerable fluid was expressed from the lungs following the death of the animal.

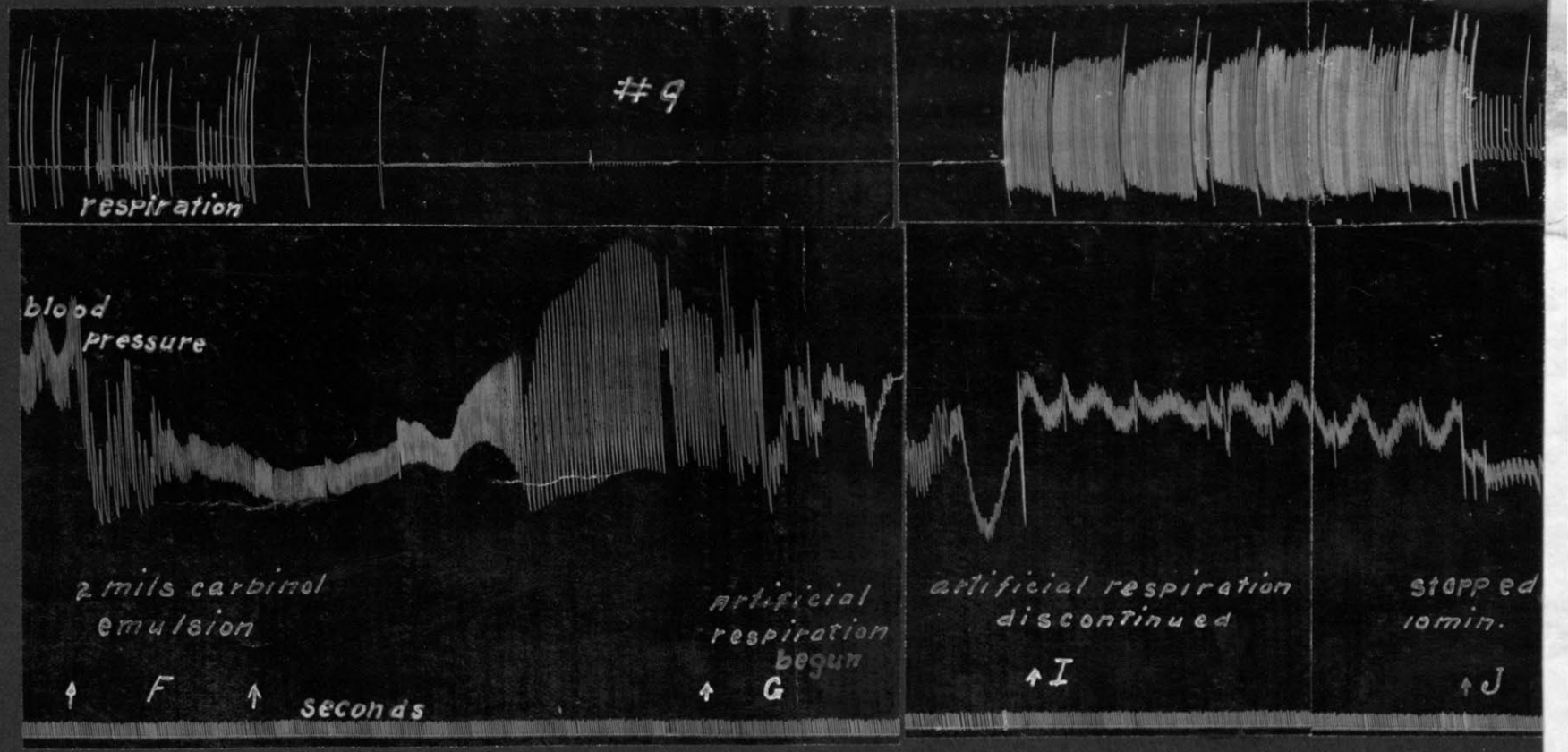


Trichlormethyl Phenyl Carbinol as a 10% emulsion injected into the femoral vein of a 7.6 Kg. female dog. Animal given 1.8 mils of a 4% solution of morphine sulphate.

Injection of the carbinol at (A) produced a fall in blood pressure of 23 mm.

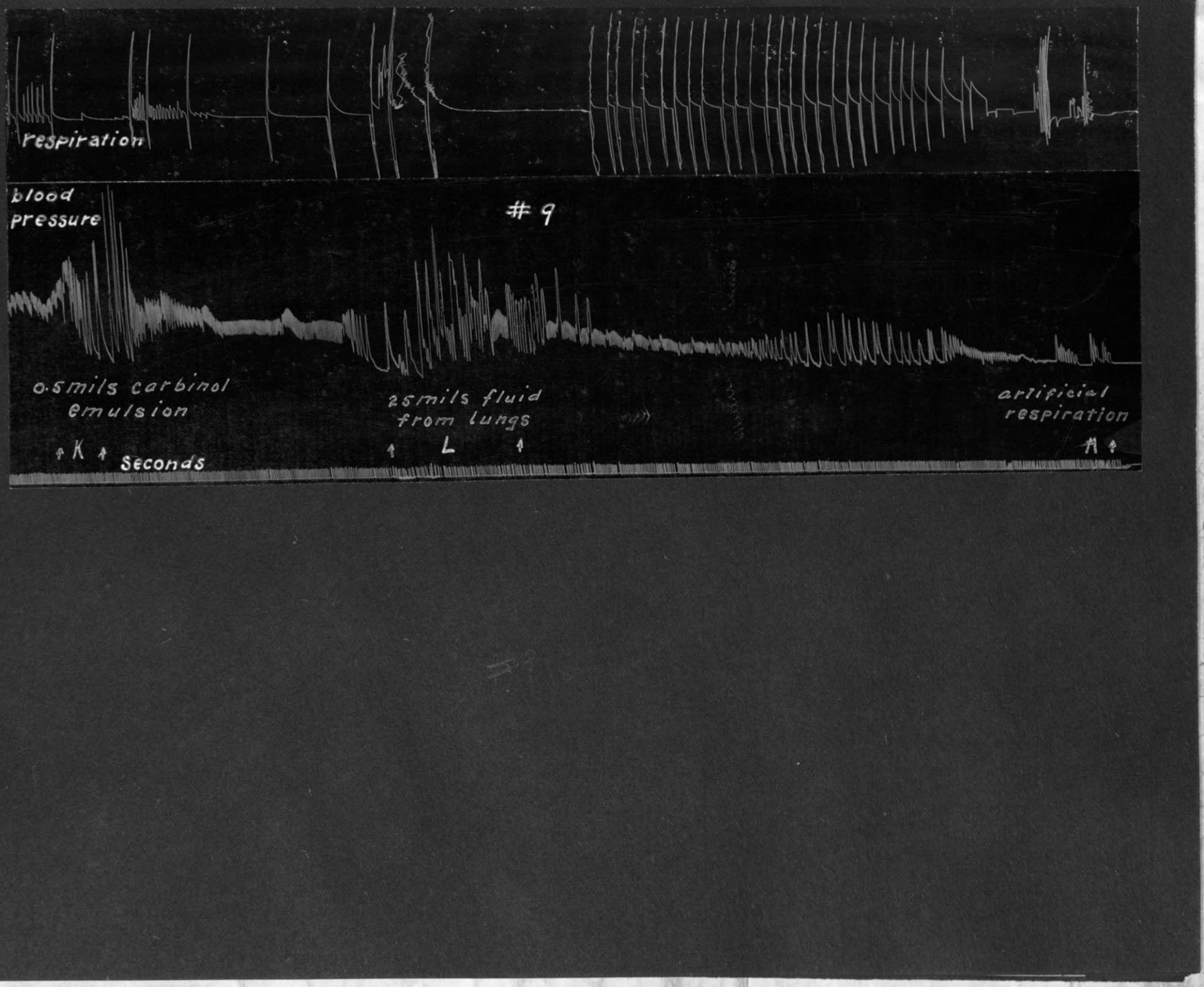


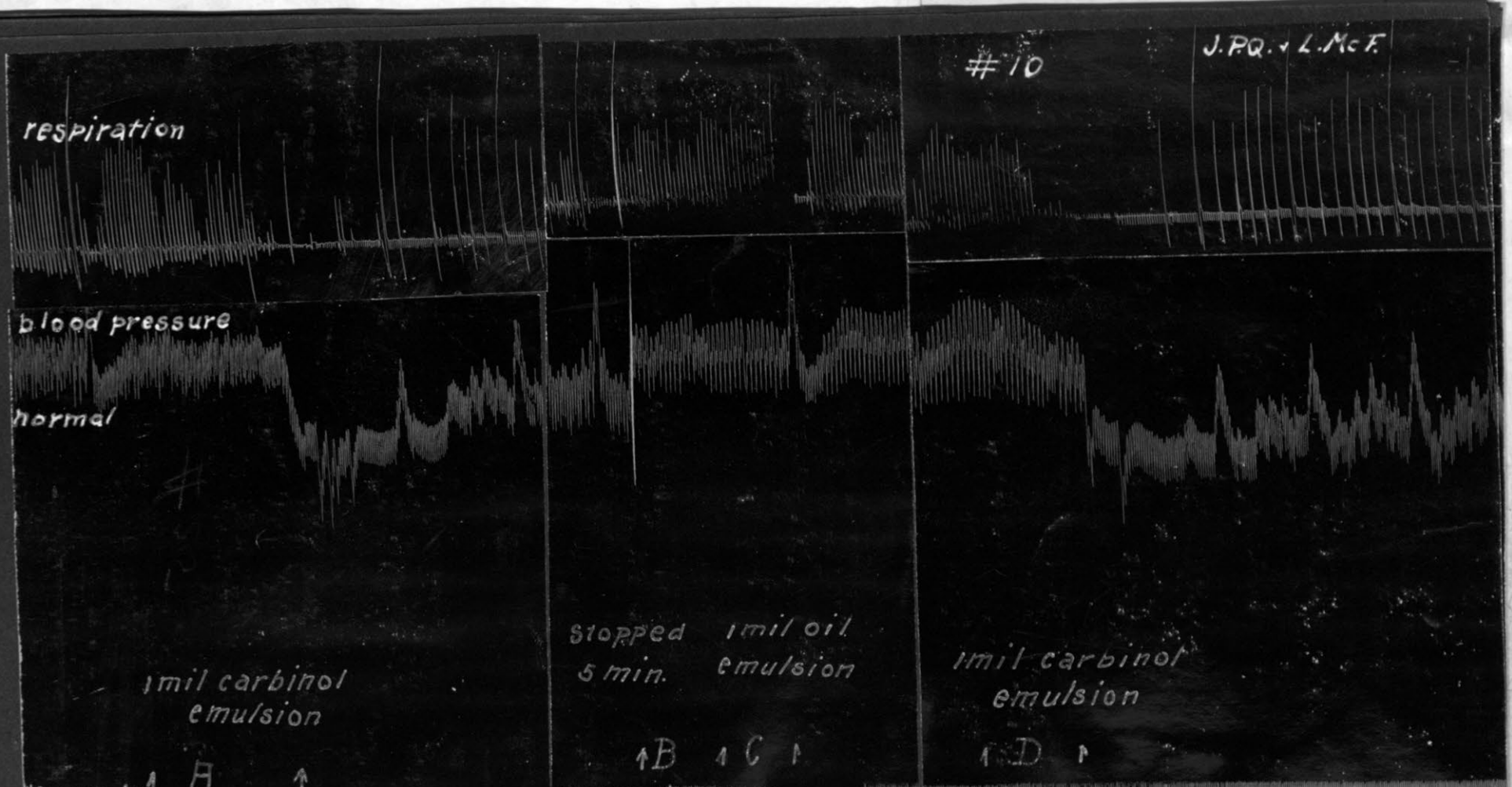
The effect of the carbinol at (C) and (E) was less marked than at (A), but no less certain.



Injection of 0.2 Gm. of carbinol at (F) produced a decided fall in blood pressure and a complete cessation of the respiration. This was followed by an asphyxial rise in blood pressure which was relieved by artificial respiration.

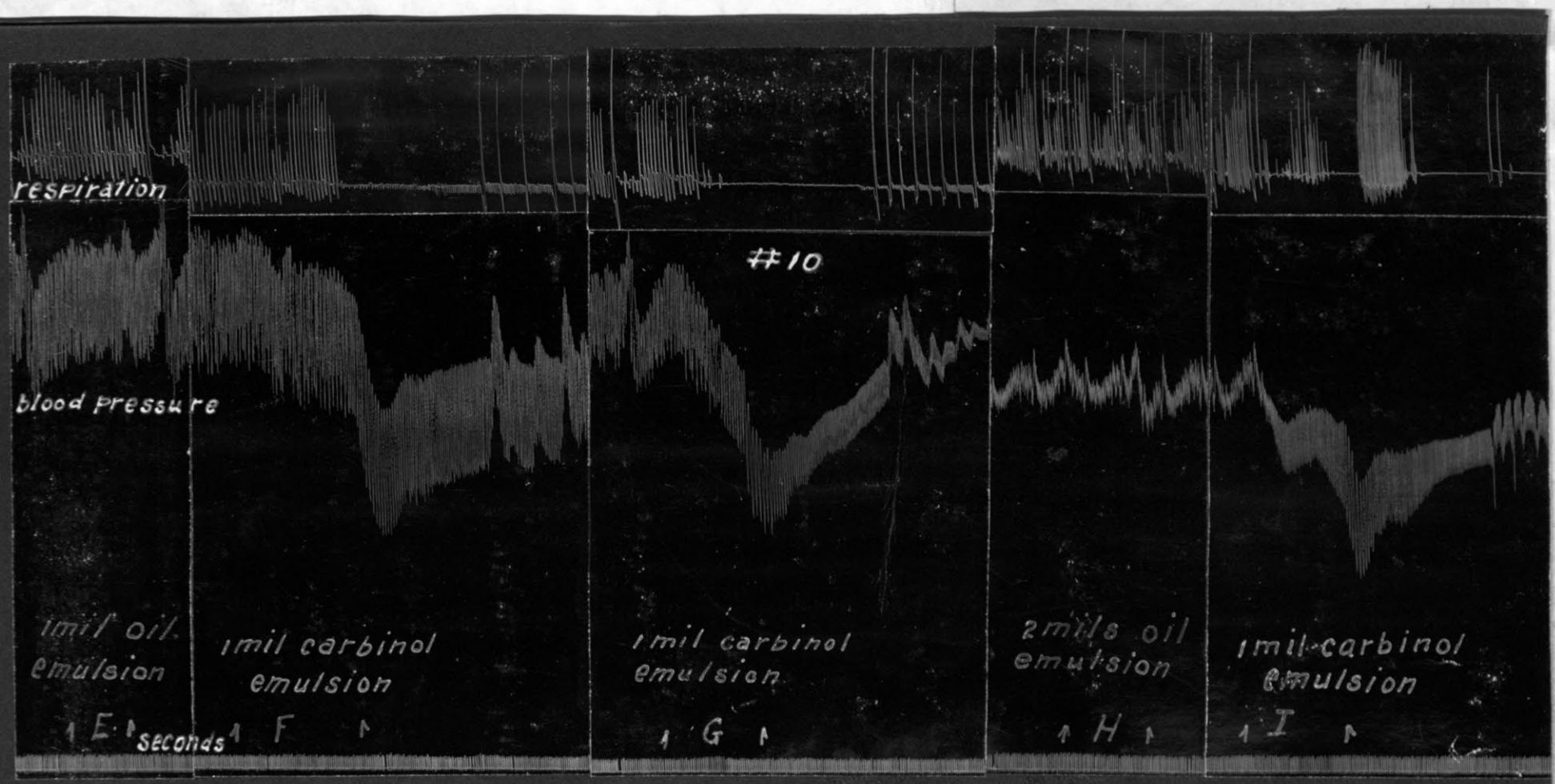
The intravenous injection of trichlormethyl phenyl carbinol emulsion would appear to exert a greater effect on the respiration than on the blood pressure. This is probably closely connected with the marked pulmonary edema noted in the case of this animal.


respiration
blood pressure
#9
0.5mils carbinol emulsion
25mils fluid from lungs
artificial respiration
K
Seconds
L
A

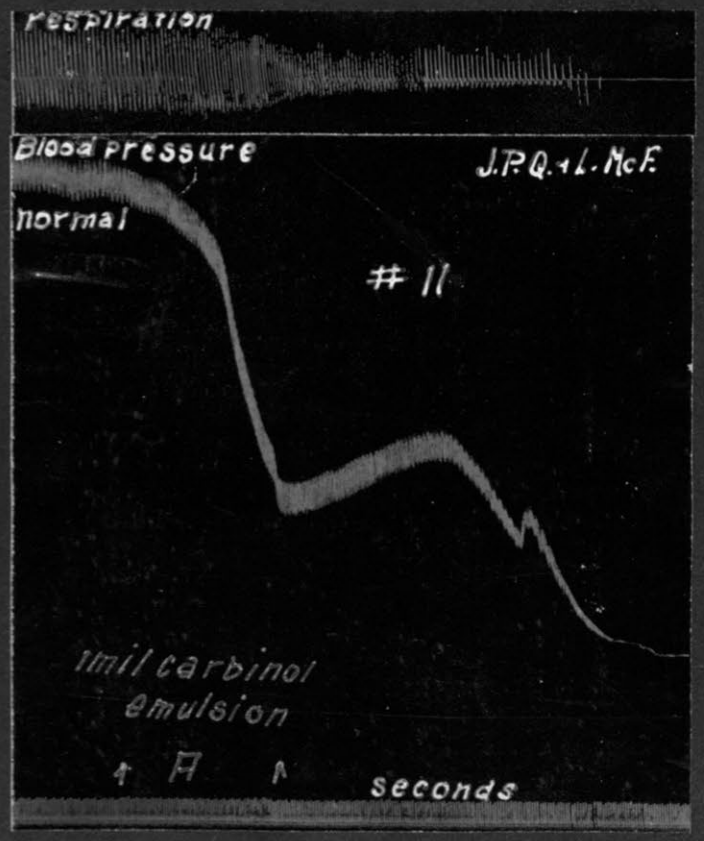


Trichlormethyl Phenyl Carbinol as a 10% emulsion injected into the femoral vein of a 5.4 Kg. male dog. Effects controlled by the injection of a simular 10% olive oil emulsion. Animal given 1.4 mils of a 4% morphine sulphate solution subcutaneously.

Observation of the effects obtained from injections (A), (B), and (C) show that the olive oil emulsion is practically without effect while the carbinol emulsion causes a fall in the blood pressure and an embarrassment of the respiration.



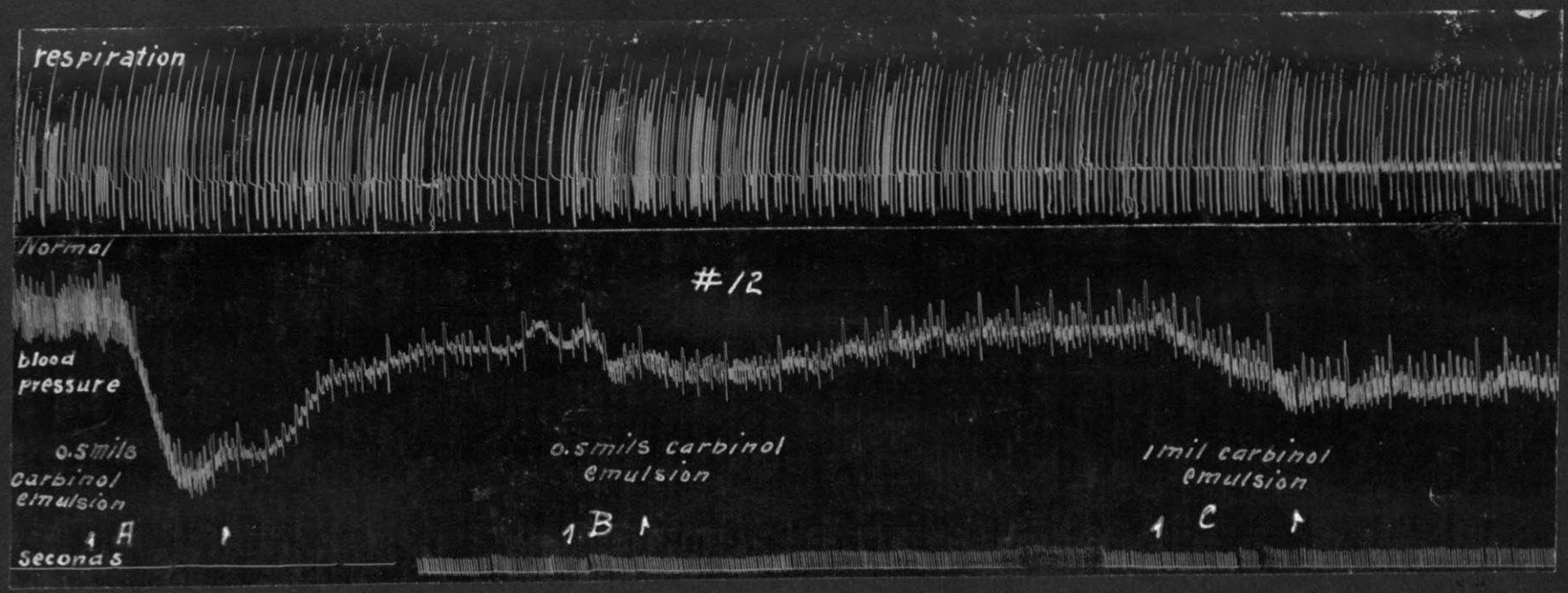
A simular conclusion is to be obtained from an examination of injections (E), (F), (G), (H), and (I). The death of the animal occured shortly after injection (I). About 200 mils of fluid were expressed from the lungs. These results are in close agreement with those noted in tracing # 90.



Trichlormethyl Phenyl Carbinol as a 10% emulsion injected into the femoral vein of a 2100 Gm. female cat.

During the injection of the carbinol at (A) a sharp fall in the blood pressure and a decrease in the amplitude of the respiration was noted. After the injection was completed, the blood pressure began to return to normal but then fell quickly and the death of the animal occured.

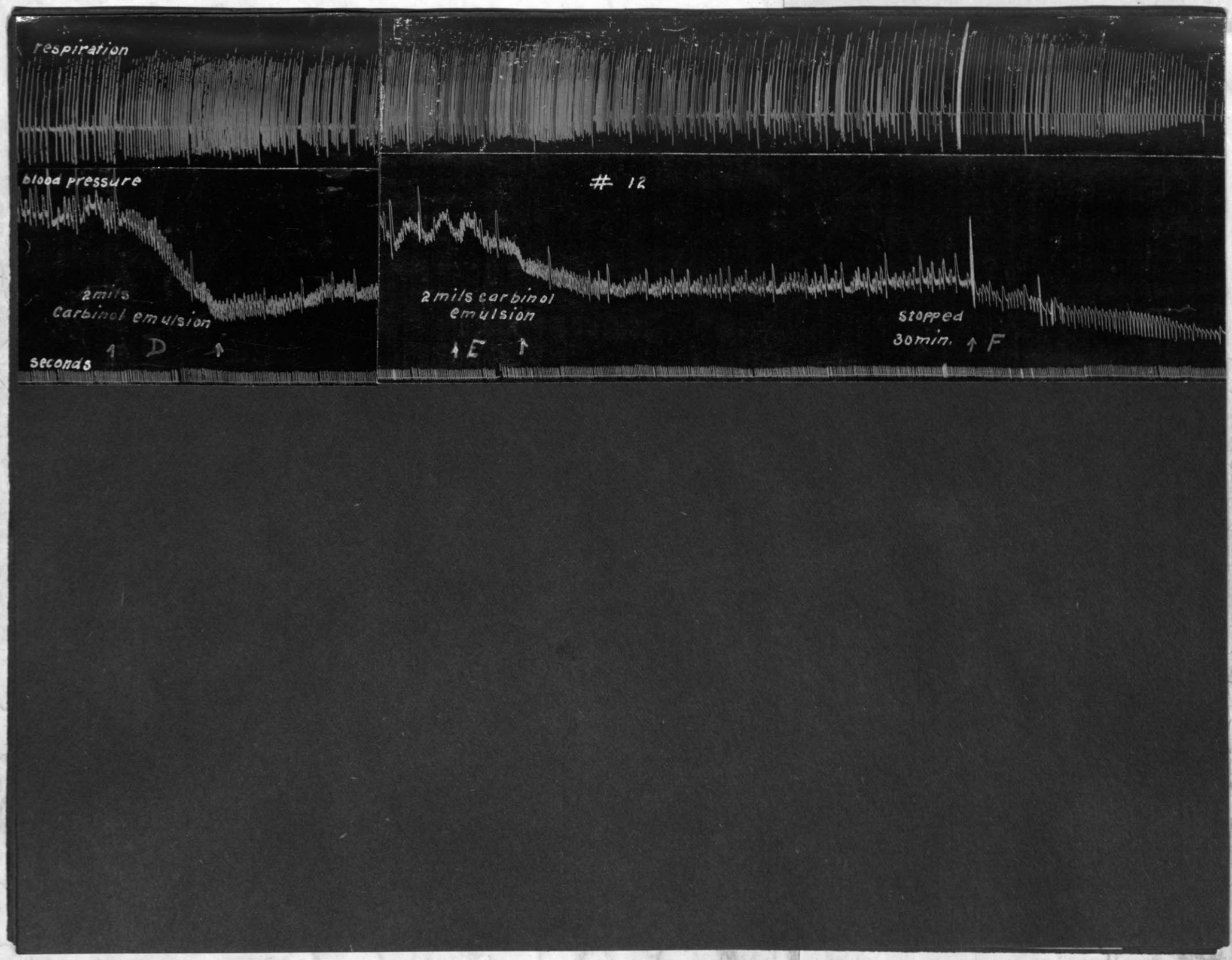
This tracing shows that larger doses in respect to the weight of the animal produce an effect on the blood pressure and respiration simular to those obtained in tracings #9 and #10, but the effect here is more pronounced.

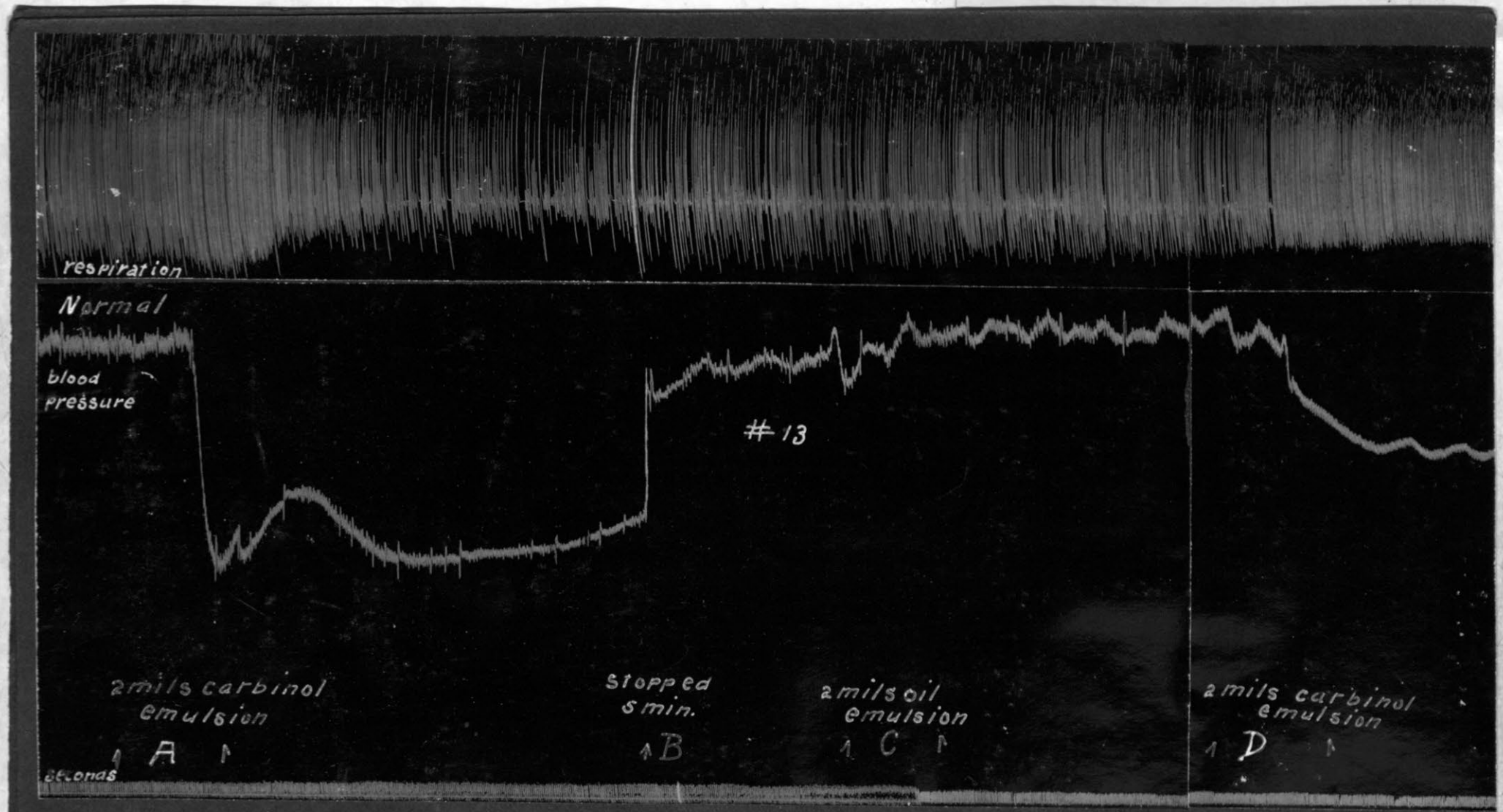


Diethyl Phenyl Carbinol as a 10% emulsion, injected into the femoral vein of a 7.6 Kg.male dog. Animal given 2.5 mils of a 4% solution of morphine sulphate subcutaneously.

The initial injection (A) produced a much more noticable effect on the blood pressure than the injection (B) of the same dose of carbinol.

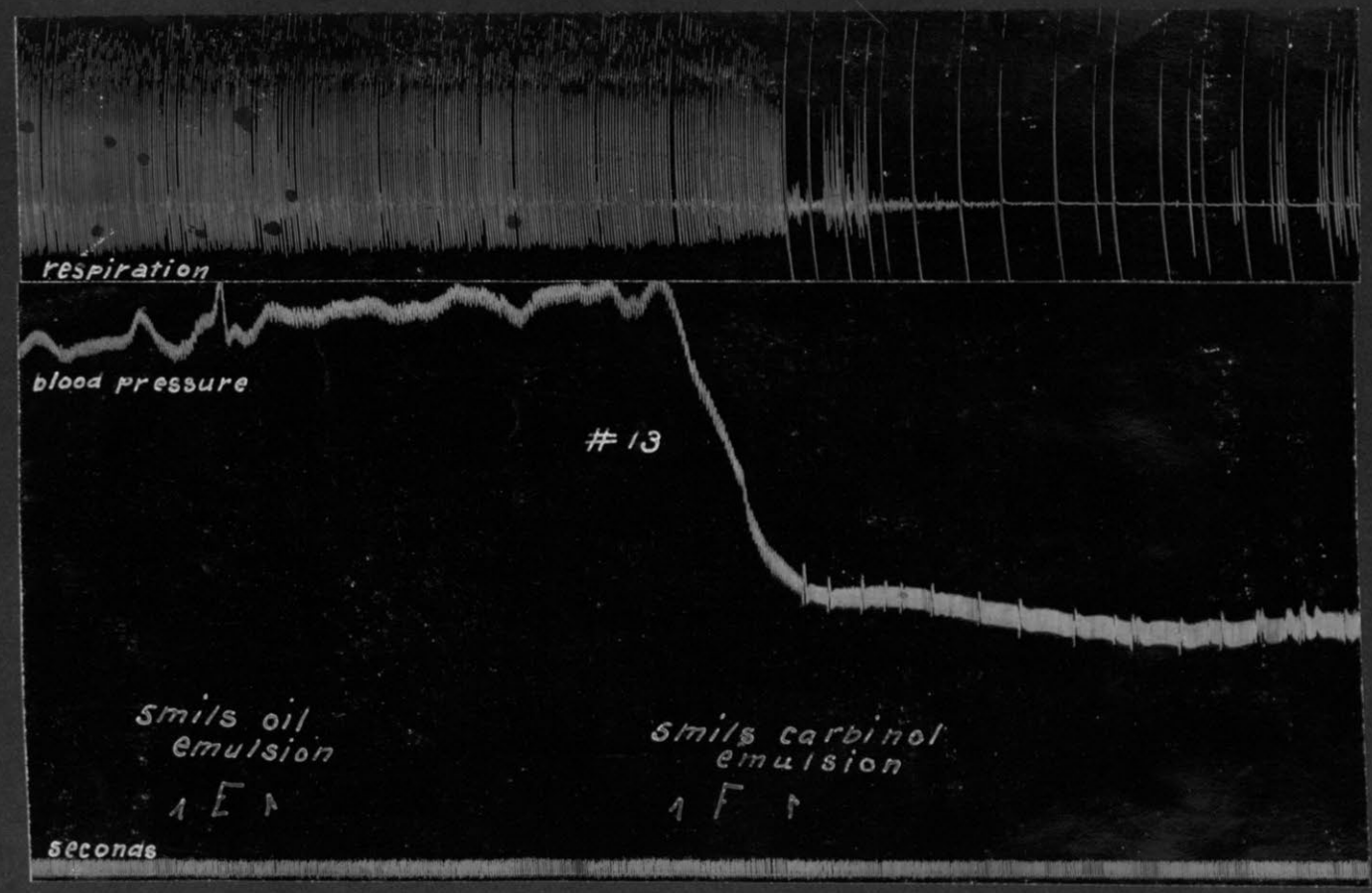
In all cases. the injection of carbinol emulsion produced a fall in blood pressure. The effect on the respiration was less marked.


respiration
blood pressure
2mils
Carbinol emulsion
seconds
D
12
2mils carbinol
emulsion
E
stopped
30min.
F



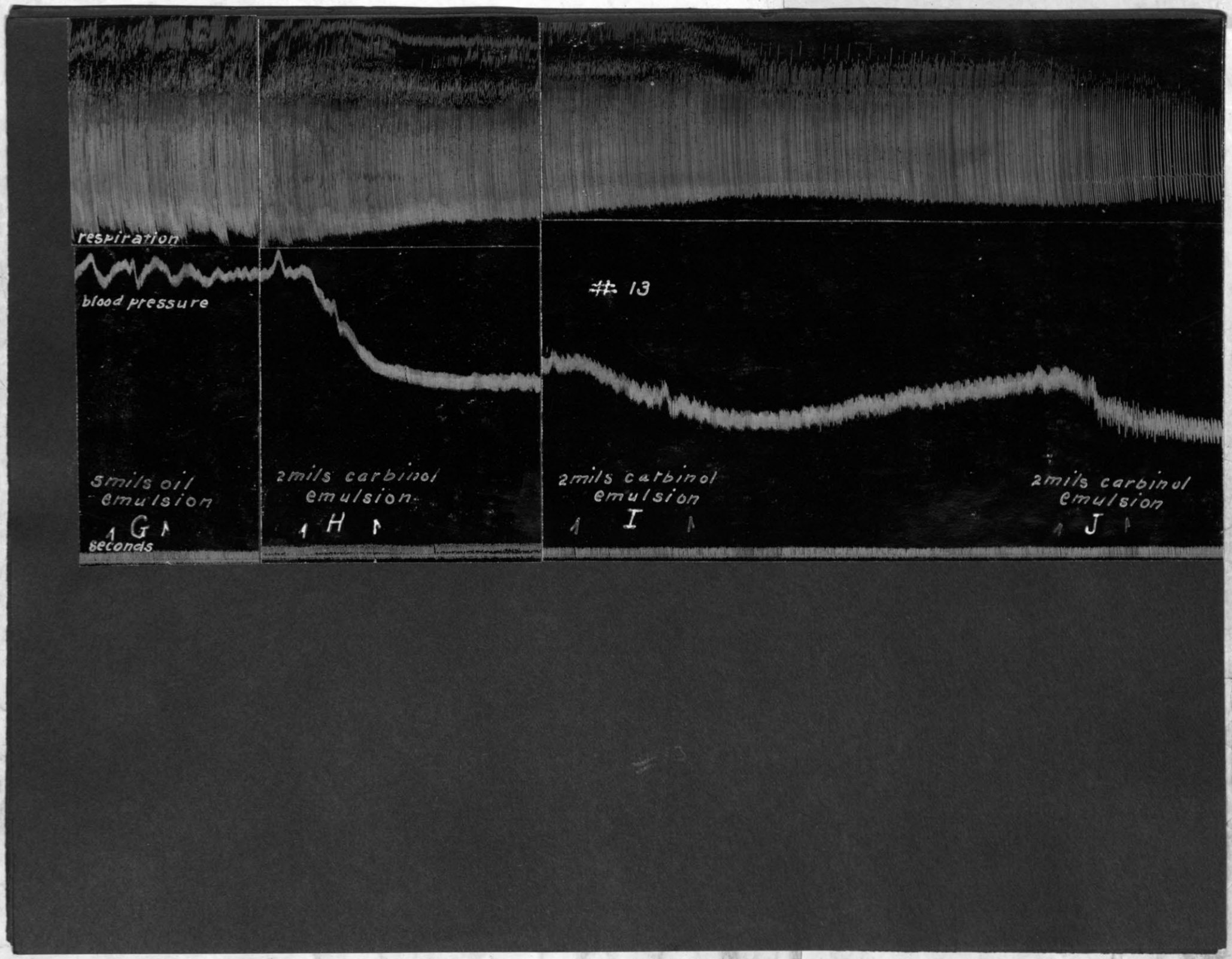
Diethyl Phenyl Carbinol as a 10% emulsion , injected into the femoral vein of a 6.5 Kg. female dog. Results controlled by the injection of a 10% olive oil emulsion simularly prepared. Animal given 1.5 mils of a 4% solution of morphine sulphate subcutaneously.

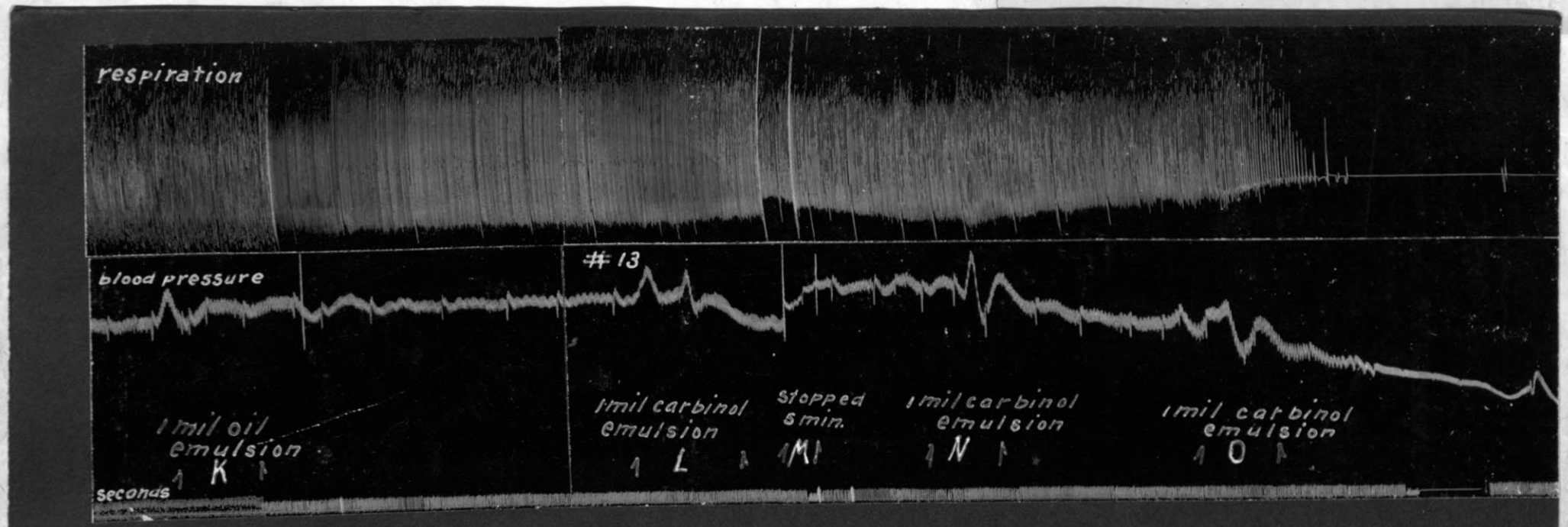
A comparison of injections (A),(C),and (D) show that the olive oil is practically without effect while the carbinol emulsion produces a decided fall in blood

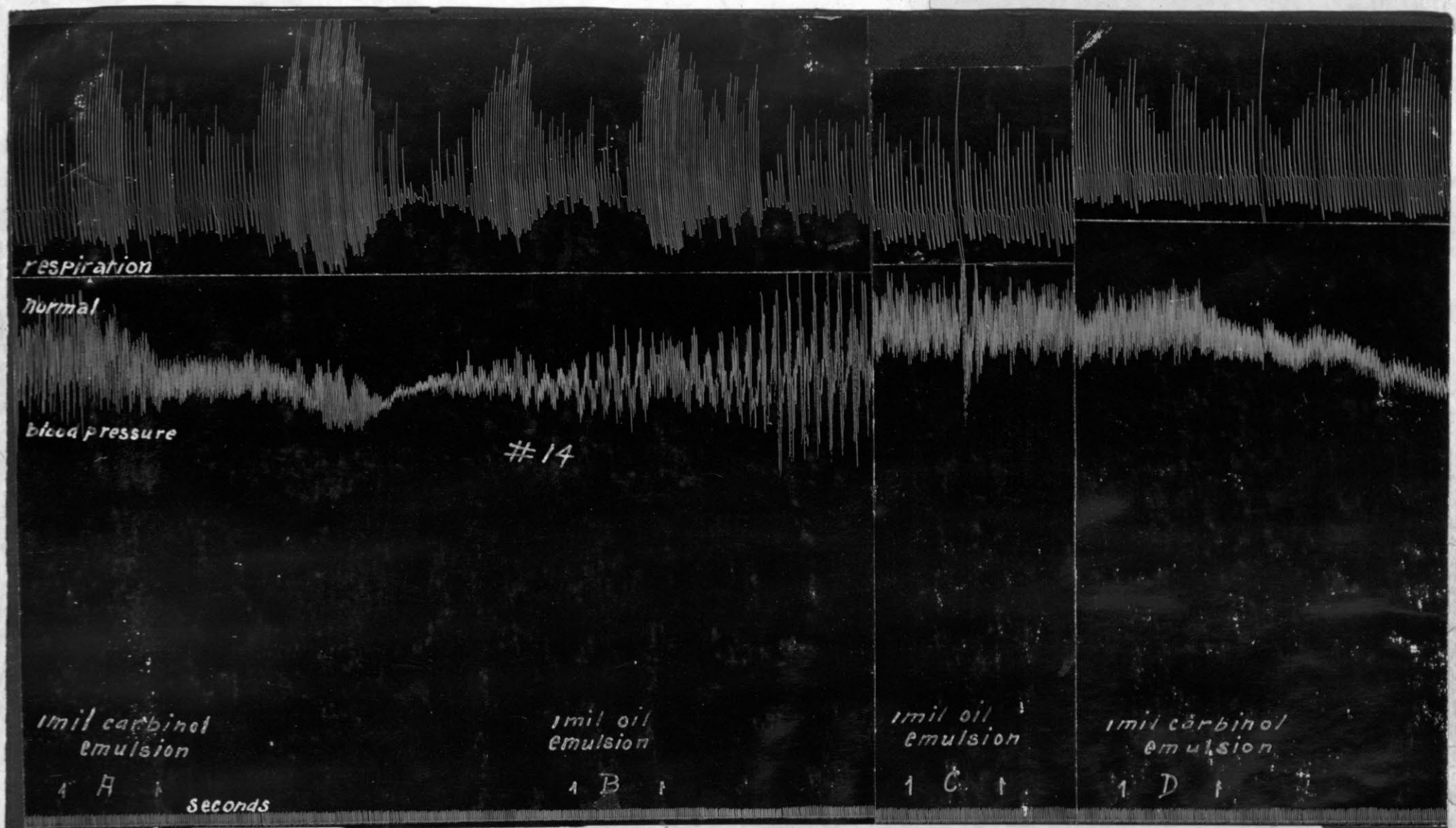


pressure and a decrease in the rate and amplitude of the respiration. The effect obtained from the initial injection is more marked than that from simular doses of the same magnitude.

The results from the injections here agree well with those obtained in tracing #2. Considerable fluid was expressed from the lungs following the death of the animal.

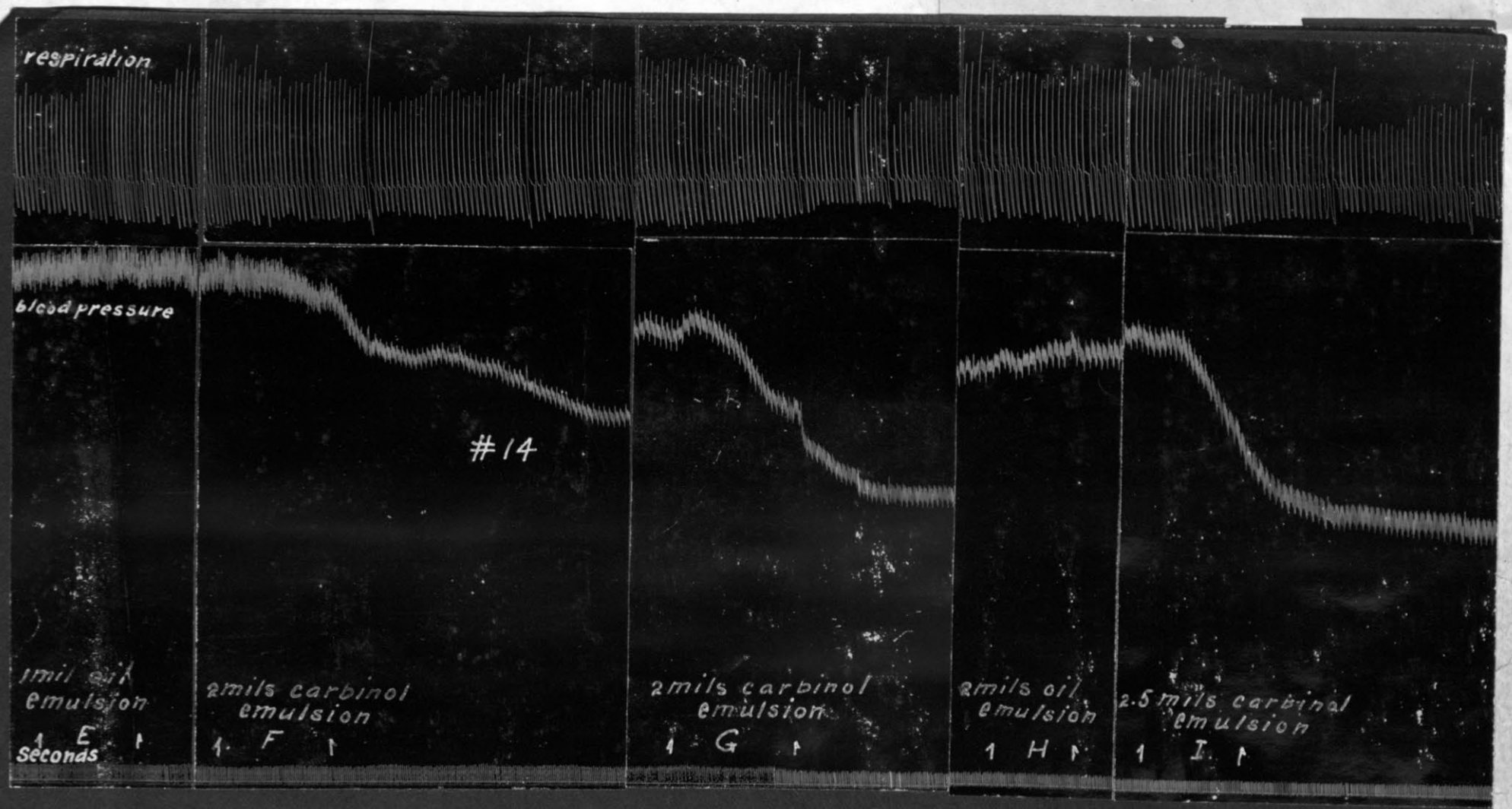

respiration
blood pressure
#. 13
5mils oil emulsion
G
seconds
2mils carbinol emulsion
H
2mils carbinol emulsion
I
2mils carbinol emulsion
J


respiration
blood pressure
#13
1 mil oil emulsion
K
1 mil carbinol emulsion
L
stopped 5 min.
M
1 mil carbinol emulsion
N
1 mil carbinol emulsion
O
seconds

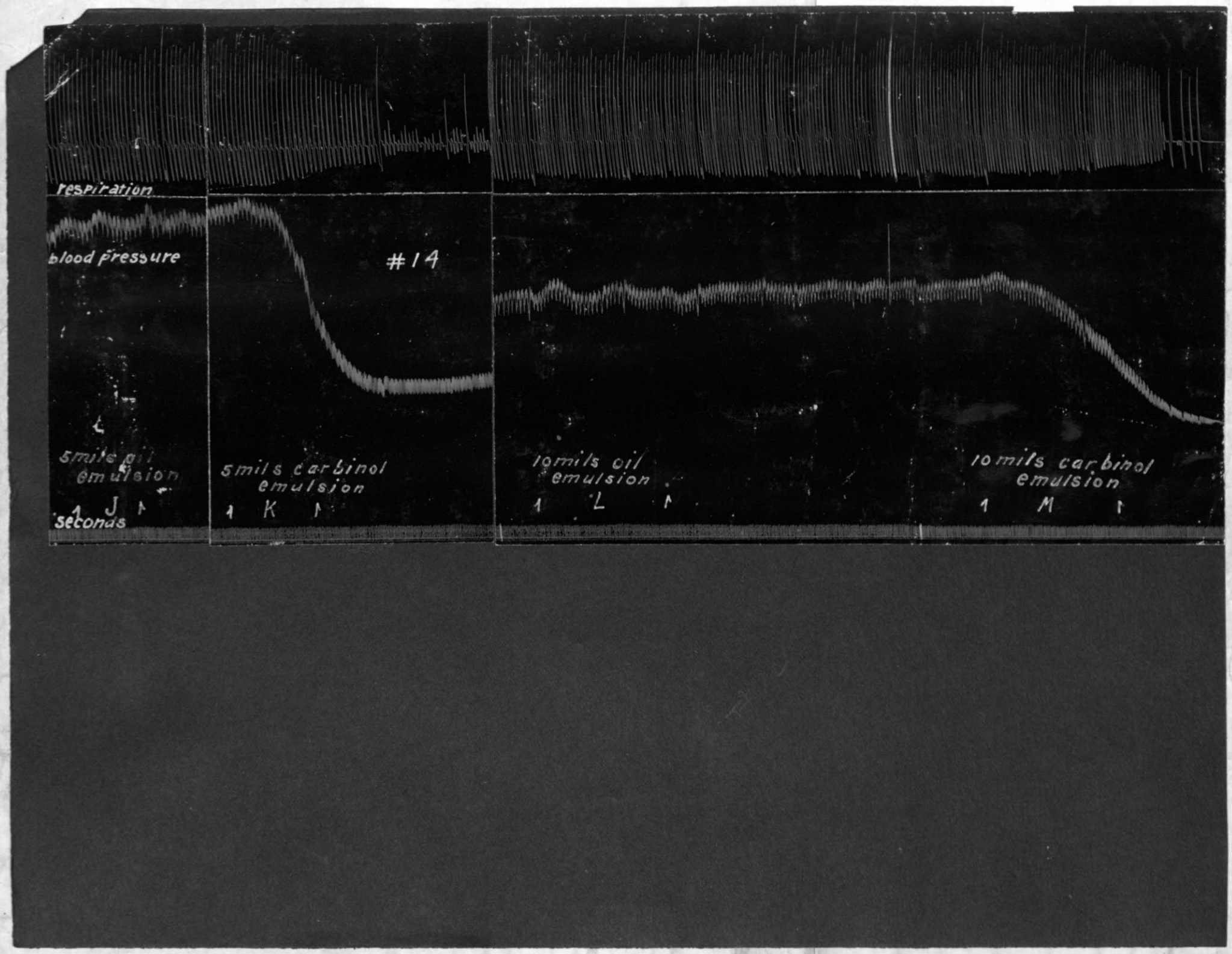


Diethyl Phenyl Carbinol as a 10% emulsion, injected into the femoral vein of a 9 Kg. male dog. Results controlled by the injection of a 10% emulsion of olive oil simularly prepared. Animal given 2.2 mils of a 4% solution of morphine sulphate subcutaneously.

The initial injection of carbinol (A) produced a decrease in the amplitude of the blood pressure but no change in its height. A simular effect is to be noted at (D).



Subsequent injections of larger doses of the carbinol produced a fall in the blood pressure simular to those observed in tracings #I2 and #I3. The injections of the olive oil emulsion were practically without effect. Considerable fluid was expressed from the lungs following the death of the animal.


respiration
blood pressure
#14
5mils oil emulsion
J
seconds
5mils carbinol emulsion
K
10mils oil emulsion
L
10mils carbinol emulsion
M