From the Pharmacological Laboratory
University of Edinburgh
The Physiological Action of Duboisia

on the Circulation

by

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Preface.

The study of therapeutics has now passed from the domain of empiricism into the clearer light of experimental demonstration and during the last two decades vast strides have been made in the investigation of the actions of remedies. Any addition to our store of knowledge regarding the physiological effects of drugs cannot fail to be of speedy service in clinical application. Notions the actions of single drugs and the antagonisms existing between different substances have been more especially studied, and the
effects of combinations of drugs—a subject promising a rich harvest—have not received the attention they deserve.

Many circumstances have impelled me to give a very considerable amount of attention to the phenomena of the circulation, and it has for some time been my intention to investigate the combined actions of drugs on this system. Very little reflection, however, was sufficient to convince me that before undertaking such an investigation, the conduct of which would be difficult beyond most others, I should of necessity have to undergo a term of training and probation. I resolved therefore to perform a series of experiments with the new substance Duboisia which is of sufficient interest to warrant the expenditure of time.
and labour upon its study. With the sanction of Professor Fraser, whose kindness in granting me the use of his laboratory and apparatus I can never hope in any way to repay, I have been enabled to carry out my intention.

In the following pages I present the results of my observations on the physiological action of Duboisia on the circulation. I have in addition during the past year performed some experiments to test the reciprocal action of Digitalis with Atropa and Duboisia, as well as to observe the antagonism of Duboisia and Muscaria, but all these I have reserved in the meantime both because my thesis might swell beyond due bounds, and because further observations should be carried out before presenting these subjects for
In conclusion I would express the deepest acknowledgement of gratitude to Professors Fraser, Rutherford and Turner for constant assistance and unvarying kindness, and my warmest thanks to Drs. Birch, Cunningham, Noy, and Daycraft for help of the most valuable and instituted kind.

1, Randolph Cliff; 27 January 1881.
Introductory Remarks.

In October, 1877, Dr. Bancroft of Brisbane gave an account of the mydriatic properties of the ritual plant before the Queensland Philosophical Society. Mr. Tredy and Professor Ringer subsequently published a joint paper (1) on the physiological action of this plant, which was followed by a contribution by Professor Tredy (2) and by a further publication by Dr. Ringer (3). From these sources the

Following summary of our knowledge of this substance has been derived.

The Pituri plant yielding the stimulating narcotic used by the Australian tribes has been referred to Baron von Müller's Duboisia Hopwoodii. From Duboisia myoporoides is obtained the alkaloid used by Mr. Sweddy and Dr. Kinger. The genus Duboisia belongs to the family of the Solanaceae, a group standing between the Scrophulariaceae and Solanaceae, but, in spite of its dinamous stamens, it has been relegated to the latter order.

The alkaloid Duboisia dilates the pupil, dries the mouth, quickens the pulse, arrests perspiration, produces headache, causes drowsiness and finally induces tetanus after the lapse of some hours from
the time of administration. As might be expected it acts as an antagonist to Muscarina as well as to Tolosepine. It thus appears that Duboisia bees on the whole a series of actions very similar to those of Atropia, and the physiological effects of the alkaloids therefore lend a powerful support to the botanical reasons for the classification of the plant along with the Solanaceae.
Experimental Details.

It may be well to state that I have taken the elaborate investigation of Atropin by von Bezold and Blochbaum (4) as in some degree a model for my work. For this there are two reasons. In the first place, their method of investigation serves as a valuable guide for any tyro undertaking a study of like nature; secondly, by adopting the same plan the results may be compared step by step with those previously obtained.

4. Untersuchungen aus dem physiologischen Laboratorium in Würzburg, I. Heil, 1867, 26-58 s.
step, a matter of considerable importance in the case of two drugs reported to have such strong affinities.

All my experiments were conducted with the Sulphate of Duboisia. Eighty experiments were performed on thirty-nine rabbits and several more upon frogs. Of these experiments a certain proportion could only be regarded as tentative—of no use save as a discipline. Among those remaining however after the elimination of the earlier work there is a sufficient basis of fact to afford perfectly reliable and important conclusions.

As regards the mode of observation the experiments were in the main conducted by means of the kymograph. The various changes in the blood-pressure and pulse.
rate was recorded upon a roll of paper, carried by the revolving cylinder, upon which time-signals were also registered by a chronograph connected with a Le御rio's timepiece. Each experiment described in the sequel is accompanied by the tracing which belongs to it. The blood-pressure has been expressed in millimetres of mercury and the pulse-rate by the number of beats occurring in fifteen seconds. The rabbit was invariably kept in a state of anaesthesia during the whole experiment, from the observations of the Committee on Anaesthetics of the British Medical Association. (5) The anaesthetic adopted

was either. But I have found that either, contrary to the experience of the Committee, does lower to a certain extent the blood-pressure in rabbits. The fact is not by any means large, it only takes place at the commencement of administration, and it can be taken account of so easily as to cause no trouble in studying the results of the experiments.

After the administration of either the rabbit was tied down upon the rabbit-frame, and the tracheal tube inserted, either for the more convenient prolongation of anaesthesia, or for artificial respiration, with etherized air. The cannula was then inserted in the left carotid artery and connected with the kymograph. The drug was introduced in various ways which will be
noted in the sequel.

Each experiment was performed several times but only one is here described. The details are given graphically on the chart which accompanies the description of each experiment. For convenience it has been assumed, in the construction of the charts, that the number of millimetres of mercury equivalent to the blood-pressure is exactly double the number of beats occurring in fifteen seconds. As a matter of fact this is seldom the case, but some such arbitrary relationship must be assumed in order to draw up a chart at all. The blood-pressure is indicated by the red figures, dots and lines, while the pulse-rate is laid down in blue. When the number of millimetres of blood-pressure is odd, it is marked in the space belong-
ing to ‗the very even number below. The series of experiments falls naturally into the following divisions—

I. The influence of Duboisia upon the circulation as a whole.
II. The influence of Duboisia upon the nervous mechanism controlling the heart and vessels, including—
   1. The intracardiac nervous system.
   2. The cardio-inhibitory system.
   3. The central vasomotor system.
   4. The peripheral vasomotor system.

The accelerator nerves have not been taken up. The whole subject is so complicated that I feared to enter upon it, and as these nervous apparently unaffected by drugs
which exercise a powerful influence over the other cardiac nerve(s), it is in the highest degree improbable that Duboisia could have the least effect upon them.

I. Experiments with Duboisia on the circulation as a whole.

These experiments were conducted without previous interference with the vascular or nervous systems. After placing the Kymograph in connection with the carotid the alkaloid was introduced into the right jugular vein by means of a syringe and cannula.

Experiment I. One milligramme of Duboisia Sulfate in the right

jugular vein. (Tracing I).

Before injecting, rate 63 in 15". Pressure 86 mm.
15" after " " 61 " " " 92 "
30" " " 62 " " " 98 "
45" " " 63 " " " 98 "
1" " " 62 " " " 94 "
2" " " 61 " " " 88 "
3" " " 63 " " " 86 "
4" " " 62 " " " 94 "
5" " " 62 " " " 98 "
6" " " 62 " " " 100 "

At this point the rate and pressure became constant and remained so until, after a little time, another experiment caused a change.

Experiments II. Two milligrams of Duboisia Sulphate in the right jugular vein. (Tracing II).
Before injecting, Rate 60 in 15", Pressure 100 mm.

15" after " " 56 " " " 92 "
30" " " 58 " " " 98 "
45" " " 60 " " " 100 "
1' " " 60 " " " 102 "
2' " " 60 " " " 106 "
3' " " 58 " " " 108 "
4' " " 60 " " " 110 "

From this time on oscillations of the mercury occurred and only slight differences in rate were observed.

Experiment III. Five milligrams of Duboisia Dracophila in the right jugular vein. (Tracing III).

Before injecting, Rate 62 in 15", Pressure 112 mm.

15" after " " 62 " " " 109 "
30" " " 61 " " " 109 "
45" " " 61 " " " 112 "
1' " " 64 " " " 114 "
Between six and seven minutes after the injection of the drug, the animal had a severe tetanic spasm, during the occurrence of which, the blood-pressure fell somewhat. It does not fall within the scope of this paper to take into consideration the action of Durovisia upon the nervous system, but it may be remarked in passing that the drug causes in mammals reflex spasms and convulsions at an early period. It thus approaches
the action of atropin upon spinal nerves, for the latter alkaloid, as has been shown by Professor Fraser (7), induces motor disturbance in mammals before disablement of the peripheral nerves occurs.

Experiment IV. One centigramme of Duboisia Sulfate in the right jugular vein. (Tracing IV).

Before injection, Rate 45 in 15”, Pressure 110 mm.

<table>
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<th>Time (min)</th>
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<th>Pressure (mm)</th>
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<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>110</td>
</tr>
<tr>
<td>15</td>
<td>41</td>
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<td>3</td>
<td>28</td>
<td>76</td>
</tr>
<tr>
<td>3.3</td>
<td></td>
<td>106</td>
</tr>
</tbody>
</table>

3'15" after injecting, Rate 28 in 15", Pressure 60 mm.
4' " " 41 " " 78 "
5' " " 41 " " 92 "
6' " " 41 " " 104 "
7' " " 41 " " 108 "
8' " " 42 " " 108 "

In this as in the preceding experiment the animal had considerable nervous disturbance. A succession of severe spasms began between two and three minutes after the injection of the drug, and were accompanied by marked variations of rate as well as of pressure.

Experiment V. Two centigrammes of Duboisiain Sulphate in the right jugular vein. (Tracing V).

Before injection, Rate 59 in 15", Pressure 100 mm.
15" after " " 48 " " 76 "
50" after injection, Rate 50 in 15", Pressure 74 mm.
45° " " " 52 " " " 76 "
1° " " " 53 " " " 80 "
2° " " " 56 " " " 88 "
3° " " " 54 " " " 96 "
4° " " " 54 " " " 100 "

This experiment was at once succeeded, at too short an interval perhaps, by the next.

Experiment VI. Five centigrammes of Duroxia Sulphate in the right jugular vein. (Tracing VI).

Before injection, Rate 54 in 15", Pressure 100 mm.
15° after " " 41 " " " 28 "
30° " " " 54 " " " 14 "
45° " " " 33 " " " 14 "
1° " " " 36 " " " 10 "
2° " " " 0 " " " 0 "
Experiment VII. One decigramm of Proctodiacic Phosphate in the right jugular vein. (Register VII).

Before injecting, Rate 60 in 15" Pressure 122 mm.
15' after " " 41 " " 34 "
30' " " 18 " " 30 "
45" " " " " 20 "
1' " " " " 10 "
115" " " " " 0 "

Pursing at this point of the inquiry it will be easy to draw definite conclusions from a retrospect of the work done so far. In the first three experiments the drug caused a considerable rise of the blood pressure without appreciable effect upon the pulse-rate. There was no initial sinking of the mercury in the first experiment, but in the second and third it fell slightly.
on injection before rising. The last four experiments show that doses of one centigramme and upwards have a tendency to reduce both the pulse-rate and the blood-pressure. After the injection of one or two centigrammes the pressure falls considerably, but afterwards rises to the normal or nearly so. Five centigrammes is a lethal dose and the pressure rapidly sinks to zero, while the beats of the heart become imperceptible by the stethoscope, and a decigramme causes death still more quickly.

The conclusions are obvious. The drug in small doses increases the blood-pressure without materially affecting the constancy of the pulse-rate. In larger doses it reduces both the rate and the pressure, and finally stops the heart in a state of diastole.
II. Experiments with Deboisiea on the nervous mechanism controlling the heart and vessels.

1. Experiments upon the intracardiac nervous system.

The cardiac musculo-motor apparatus can be satisfactorily investigated after isolation of the heart with its contained ganglia. In the following series of experiments the connections with the central nervous system were severed in the cervical region before administering the Deboisiea. The tracheal tube was placed in connection with the trachea, the cervical spinal cord was then cut between the first and second cervical vertebrae, and artificial respiration commenced. The rabbit was next placed upon the rabbit frame and after section of the pneumogastric
and sympathetic nerve. The cannula was inserted as usual in the left carotid artery. The drug was introduced by the right jugular vein. Each injection was only watched for a limited period of time just enough to permit the alkaloid to pass through the lungs and reach the utmost terminations of the coronary system.

Experiment VIII. One milligramm of Duboisia Hydrate in the right jugular vein. Cor. vagi and sympathetic cut. (Tracing VIII).

Before injection Rate 50 in 15, Pressure 28 mm
15" after " 
45" " 
1' " 
2' "
Experiment XV. Five milligrams of Quinacrin Sulphate in the right jugular vein. Cord, vagi and sympathetics cut. (Tracing VIII).

Before injection, Rate 50 in 15sec, Pressure 26mm.  
15 sec after  46   "   32 "  
30 sec  "  48   "   28 "  
45 sec  "  48   "   28 "  
1 min  "  46   "   28 "  
2 min  "  46   "   28 "

Experiment XV. One centigram of Quinacrin Sulphate in the right jugular vein. Cord, vagi and sympathetics cut. (Tracing VIII).

Before injection, Rate 46 in 15sec, Pressure 28mm.  
15 sec after  46   "   25 "  
30 sec  "  46   "   25 "  
45 sec  "  45   "   26 "  
1 min  "  45   "   27 "

27
2. after injection, Rate 45 in 15, Pressure 23 mm.

Experiment XL. Five centigrammes of Duboisia Sulphate in the right jugular vein. Cord, vagi and sympathetic cut. (Tracing VIII).

Before injection, Rate 45 in 15, Pressure 30 mm.

15" after " 41 " 24 "
30" " 42 " 26 "
45" " 44 " 28 "
1" " 44 " 26 "
1'30" " 46 " 26 "

All these experiments were performed on the same animal. We have already seen that Duboisia has little, if any, influence upon the rate of the heart's action when all the nervous connections are intact. It has, as might well be expected, just as little when injected...
into the heart with its nervous connections severed. The decided action of the drug on the blood-pressure in the unaltered circulation strongly contrasts with its influence on the arterial pressure after isolation of the heart. In this latter series of experiments such doses of the drug as were used appear to be almost destitute of any influence over the blood-pressure. With a dose of one milligramme there is no change in its amount. After the injection of five milligrammes there is a rise of six millimetres followed by a fall nearly to the initial pressure. One centigramme produces a diminution of the pressure and a subsequent rise to the previous level, and finally after five centigrammes there is a fall of six millimetres.
by a rise nearly to the former level of pressure.

From these facts we may conclude that Duboisia diminishes the pulse-rate and in small doses causes a rise, in larger doses a fall of the arterial pressure. The results of former experiments have shown that the largest doses stop the heart in diastole and therefore must destroy the functions of the cardiac ganglia, and muscle.

2. Experiments upon the cardiac inhibitory nervous system.

The influence of Duboisia on the pneumo-gastric nerves has been investigated in three ways. In the first place by injecting the drug towards the brain by means
of the carotid artery its action on the origin of the nerves as well as on the inhibitory centres has been tested. Secondly, the effect of the drug on the cardiac terminations of the vaga has been studied by means of injection toward the heart. Thirdly, the influence of Duboisia on the circulation after section of the pneumogastric nerves has been compared with the results of its administration without removal of the regulator functions. In analysing the results obtained by all these methods of inquiry however it is necessary to bear in mind the well-known fact that the normal restraining influence of the vaga is very slight in the rabbit as compared with many other animals in fact it is very often in complete abeyance.
The experiments upon the origin of the pneumo-gastric nerves only differed from the first series described in this that the cannula, to be afterwards connected with the syringe, was inserted in the peripheral part of the left carotid artery, instead of the central part of the right jugular vein. It only necessary to detail one experiment. The chart which accompanies the description has three seconds as a time-unit instead of fifteen as in the other experiments.

Experiment XII. Five milligrammes of Toluosia Sulphate in the left carotid artery. (Tracing IX).

Before injection, Rate 65 in 15 Pressure 120mm
13 after " 65 " 122 "
6 " 50 " 118 "
9" after injection, rate 45 in 15", pressure 112 mm.
12"       60        110
15"       65        112
18"       65        114
21"       65        116
24"       65        118
36"       65        120
48"       65        120
1"         65        120

In this experiment there is quite a remarkable diminution in the rate of the heart's action immediately succeeding the introduction of the drug. It is attended by a fall of arterial pressure more gradual in character. The former attains its maximum about nine seconds after injection; the latter about twelve after injection. The lowering is only transient being speedily succeeded by a very rapid return to the normal rate of pulse.
and by a much more gradual rise to the normal pressure. The explanation of these facts appears simple. The primary effect following the injection at once is a stimulation of the regulator centres or centres of the origin of the vagus nerve. This shows itself by increased inhibition in consequence of which the slowing as well as the fall is brought about. But at that period of time when the drug has just reached the heart and completed the pulmonary circuit the inhibitory influence is succeeded by something causing a return to former conditions. It has been shown by v. Bezold and Blochbaum that atrophia paralytica of the cardiac terminations of the vagi, and the simplest explanation of this abrupt cessation of inhibition is that Duboisier,
in so many other respects closely resembling Atropia, has the same action and suspends the influence of the cardio-inhibitory apparatus by paralysis of the cardiac ends of the vagi. That this conjecture is correct will be shown immediately, and this part of the investigation may be concluded by the remark that Duboisia stimulates the central inhibitory apparatus but that this is at once rendered nugatory by coincident paralysis of the peripheral inhibitory mechanism.

b. The experiments about to be described form a very definite and exact source of information. After applying the Kymograph, the vagi were cut in the neck. The peripheral portion of the
right veins was then laid upon ordinary metallic electrodes connected with the secondary coil of a DuBois-Raymond's induction apparatus driven by a medium sized dichromate element. An electric stimulus was given in this way to the cardiac end of the divided nerve, which served both to prove that the whole arrangement was in thorough working order, and to show the extent of inhibition which was caused. A dose of Duboisia was then injected into the right jugular vein and the electric stimulus again given for comparison of its effects with the results following stimulation before the administration of the drug. The details of the experiment will not be given.
Experiment XIII. One milligramme of Tobacco Sulphate in the right jugular vein. Stimulation of the right vagus. (Tracing X).

Before section, Rate 64 in 15, Pressure 106mm.

15 after    64     86
30"         65     97
45"         66     102
1'           67     95
1'30"        67     90
1'34"        65     86
1'35"        20     50
1'40"        Current stopped
1'45"        65     76
2"           65     90
2'15"        67     96
2'15"        Drug injected
2'30"        64     96
2'45"        69     100
2'45"        67     102

3"           67     102
The nerve was stimulated after section with the secondary coil separated from the primary by a distance of eighty millimètres. After injecting the Duboisier, the same strength of current was used, but, when no response followed, the secondary was approximated to the primary coil in order to derive the strongest possible stimulus. It was of absolute inutility, as both chart and tracing show. It appeared to be of interest to discover whether a still smaller quantity of the drug than that used above might not have sufficient power to paralyse the cardiac terminations of the vagi and the next experiment was performed to determine this point.

Experiment XIV. One tenth grain of Duboisier Sulfate in...
the right jugular vein. Stimulation of the right vagus. (Tracing XI).

Before section, rate 80 in 15, Kussau 135 mm.  
15 after
15 80 130  
30 80 128  
45 80 127  
1 80 127  
111 Nerve stimulated  
115 33 75  
116 Current stopped  
130 78 124  
145 78 126  
145 Drug injected  
2 77 132  
215 78 135  
215 Nerve again stimulated  
230 78 135  

The same result therefore followed the administration of 0.0001 gm. of Duboisia as that which has been shown above to result from 0.001 gm.
Doubtless thus possesses a specific action on the peripheral inhibitory apparatus which is brought into a state of paralyzing probably more rapidly by this drug than by any other. Only thirty seconds were allowed to elapse between the injection of the Duboisia and the stimulation of the nerve, yet this was quite sufficient for even so minute a dose as the thirtieth of a milligramme.

c. From a knowledge of the facts just detailed it would naturally be expected that after section of the vagi Duboisia would produce less change in the working of the circulation than when administered without previous elimination of the inhibitory influence. It is so sometimes, not always, for the caution previously given must
be borne steadily in view that the normal inhibitory influence in the rabbit is at all times slight and often absent. Even in the few selected tracings which accompany this paper marked contrasts are presented in the results of division of the vagi; in some cases the rate and pressure respectively rise and fall, others show the converse, i.e. the rate diminishes while the pressure is augmented, and yet again in others both rate and pressure appear but little affected. In an animal whose regulatory mechanism is dominant the introduction of a substance which paralyses the cardiac terminations of the pneumogastric will have the same result whether the fibres of inhibitory mandata be intact or severed. If, on the contrary, the
the circulation is more or less under the control of the inhibitory nerves there will be a difference according as the nerves are or are not divided. For these reasons little stress can be laid upon any facts drawn from administration after section of the nerves.

As a matter of experience, however, I have never seen rises of pressure following injection after division of the nerves quite so great as those which are caused by the drug without previous section of the nerves. This of course only tells us that the greatest results follow the administration of Duboisa, when, in addition to its action on other factors shortly to be discussed, the drug paralyses an existing degree of cardiac inhibition.

One experiment of interest as
showing the effects of large doses of Duboisia after division of the vagi will be described here.

Experiment XV. One centigramme and five centigrammes of Duboisia Sulphate in the right jugular vein. Previous division of the vagi. (Tracing XII).

<table>
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<th>Time (sec)</th>
<th>Rate (bpm)</th>
<th>Pressure (mm Hg)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td>15</td>
<td>52</td>
<td>112</td>
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<td>30</td>
<td>51</td>
<td>124</td>
</tr>
<tr>
<td>45</td>
<td>51</td>
<td>138</td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>138</td>
</tr>
<tr>
<td>1'</td>
<td>52</td>
<td>138</td>
</tr>
<tr>
<td>1'15</td>
<td>54</td>
<td>140</td>
</tr>
<tr>
<td>1'30</td>
<td>54</td>
<td>140</td>
</tr>
<tr>
<td>1'30</td>
<td>0.01 gm injected</td>
<td></td>
</tr>
<tr>
<td>1'45</td>
<td>57</td>
<td>116</td>
</tr>
<tr>
<td>2'</td>
<td>57</td>
<td>114</td>
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<td>2'15</td>
<td>59</td>
<td>122</td>
</tr>
<tr>
<td>2'30</td>
<td>58</td>
<td>130</td>
</tr>
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</table>
245" after section, Rate 58 in 15" Pressure 132 mm.
3' " " " 58 " " " 134 "
4' " " " 57 " " " 140 "
5' " " " 57 " " " 142 "
6' " " " 58 " " " 142 "
6' " 0.05 gm. injected
6'15" " " 54 " " " 112 "
6'30" " " 46 " " " 74 "
6'45" " " 46 " " " 60 "
7' " " " 39 " " " 42 "
7'15" " " 33 " " " 28 "
7'30" " " 30 " " " 22 "
7'45" " " 28 " " " 16 "
7'48" " Artificial respiration begun
8' " " " 28 " " " 18 "
8'15" " " 31 " " " 26 "
8'30" " " 37 " " " 42 "
8'45" " " 44 " " " 52 "
9' " " " 47 " " " 58 "
9'3" " Artificial respiration stopped
9'15" " " 51 " " " 74 "
9'20" " Artificial respiration resumed
9'29" " Artificial respiration stopped
44
930° after section. Rate 51 in 15°, Pressure 90 mm.
9'45" " " 52 " " 96 "
9'58" " " Artificial respiration resumed
10' " " 52 " " 94 "
10'15" " " 51 " " 96 "
10'30" " " 51 " " 108 "
10'34" " " Artificial respiration stopped
10'45" " " 52 " " 118 "
11' " " 51 " " 120 "
12' " " 49 " " 98 "
13' " " 50 " " 108 "
14' " " 50 " " 134 "
15' " " 52 " " 138 "
16' " " 53 " " 140 "
17' " " 53 " " 142 "

The comparison of this experiment with those of the first series shows that large doses of Duboisia have very much the same effect whether the capsule be divided or not before administration.

This is not the place for any reference to the action of Duboisia on the respir.
...but the significant fact may be noticed in passing that artificial respiration is able to cause recovery after lethal doses. This would point to the proposition that Duboisia is more fatal to the respiratory than to the circulatory centres.

From the foregoing it may safely be concluded that in small doses Duboisia sometimes has not so much power to raise the arterial pressure after section of the vagi as when they are intact, but that in large doses its effects are the same irrespective of the state of these nerves.

3. Experiments upon the central vasomotor system.

The method adopted to investigate the action of Duboisia on the vasomotor centres was in the first
place to divide the pneumogastric nerves in the neck, so that there could be no inhibitory disturbance, and afterwards to inject the drug into the peripheral part of the carotid artery.

Experiment XVI. Five milligrams of Dihydroxy Sulfate in the left carotid artery. Previous division of the vasi. (Tracing XIII).

Before injection, Rate 46 in 15" Pressure 36 mm.
3" after " 70 "
6" " 74 "
15" " 50 " 68 "
30" " 50 " 78 "
45" " 50 " 80 "
1' " 50 " 82 "
1'30" " 50 " 84 "

An instantaneous and considerable
rise of pressure, accompanied by slight quickening of the rate of pulsation, occurs on injection and before the drug can reach the heart. The increase in pressure is large, the column of mercury ninety seconds after administration being rather more than one and a half times as large as previous to injection.

Experiment XVII. One centigramme of Duboisia Nephrarate in the left carotid artery. Previous division of the vago. (Tracing XIII).

Before injection, Rate 50 in 15, Pressure 84 mm.
5" after " 94 "
6" " 104 "
15" " 48 " 76 "
30" " 48 " 86 "
45" " 48 " 86 "
1" " 48 " 84 "
130 after injection, Rate 50 in 15°, Pressure 78 mm.

During the first six seconds the rise of pressure is exactly equal to that of the same period in the previous experiment, but this is immediately succeeded by a fall. The pulse rate shows a slight diminution.

Experiment XVII. Five centigrammes of Duboisia Sulfate in the left carotid artery. Previous division of the vasi. (Tracing XIII).

Before injection, Rate 50 in 15°, Pressure 80 mm.

3' after " " 86 "
6' " " 86 "
15' " " 49 " 76 "
30' " " 49 " 72 "
45' " " 51 " 72 "
1' " " 52 " 66 "
1'30" " " 52 " 62 "

This experiment shows a still greater tendency downward; the initial rise of pressure even being small.

From these experiments there can be no doubt that Duboisia has a stimulating effect on the vaso-motor centres, by means of which the blood-pressure is increased. This is the primary effect during the few seconds immediately following injection with all doses, but the final result depends upon the amount of the drug administered.

When the quantity is small there is a permanent rise of pressure; when on the contrary it is large a decidedly lowering effect is produced. The quantity required to show this downward tendency is just about the same as that shown to cause a fall in the first series of experiments, i.e. between five milligrammes and one centigramme.
In order to study the manner in which the rise of pressure occurs I have repeatedly examined the web of the frog's hind foot in the greatest care. In doing this, however I approached the investigation with a decided bias. After knowing from the experiments just described that the pressure underwent augmentation on the injection of Duboisia towards the base and far centres it was only natural to expect a diminution in the size of the arterioles. This I confess to let it be distinctly known that it has been difficult for me to be absolutely certain beyond all question that I did not merely see a reflection of my own expectation.

After the injection of a small dose of Duboisia, that is of a quantity not exceeding five milli-
granules, into the cellular tissue of the frog there is a contraction of the arterioles of the web, with doses exceeding a centigramme there is an contrary a dilatation of their calibre.

I cannot allow any weight to these observations. There is to my mind too much scope for the play of the imagination in such investigations, where the alteration in the size of the vessels is so slight. Although I am convinced that such are the appearances following the administration of Duboisia, I should never cite the observations as evidence. The testimony of the experiments lately described is amply sufficient to prove that Duboisia have a clear and definite action on the vasomotor centres. Before leaving this part
of the subject it should be stated that the rise following the injection of Daboisicia toward the brain cannot be attributed to psychical disturbance. In this series of experiments, as in all the others, the animals were in a uniform condition of anaesthesia and gave no indication of nervous irritation. Moreover when the tetanic tendency manifests itself it is only after the expiry of several minutes from the time of administration.

4. Experiments upon the peripheral vaso-motor system.

The rabbit’s ear affords an admirable subject by means of which the influence of Daboisicia on the sympathetic nervous system can
be studied. The effects produced by division of the sympathetic in the neck and by stimulation of the upper end may be turned to advantage for the purpose of seeing whether Duboisia causes any change in the nervous communications between the vasomotor centres and the vessels.

Experiment XIX. Five milligrammes of Duboisia sulphate in the right jugular vein. Stimulation of the sympathetic.

The right sympathetic of a rabbit was divided, the other being left intact for the purpose of comparison. The right ear at once became as usual markedly hyperaemic and formed a decided contrast to the left. The upper end of the
divided nerve was then stimulated by means of the induced current. As in previous experiments, the primary current was from a medium-sized Dicahromate element, and the secondary was separated from the primary coil by a distance of thirty millimetres. The right ear paled immediately, showing that the apparatus was in perfect working order. On the cessation of the current a vivid flush overspread the ear. The drug was injected and in a few minutes the stimulation was repeated. Pallor of the ear resulted first as before, demonstrating beyond question that Duboisie has no tendency in small doses to destroy the function of the sympathetic either in its course or in its vascular terminations. Another rabbit was used to test
the action of larger doses.

Experiment XX. Two centigrammes of Duboisia Sulphate in the right jugular vein. Stimulation of the sympathetic.

The various steps in this experiment were precisely the same as in that just described, and the results differed in no respect. It is therefore quite unnecessary to describe them.

These experiments conclusively prove that Duboisia does not at all paralyse the sympathetic nerve in any part of its course, but they leave it open to question whether the drug may not have a tendency to heighten its action upon the smaller branches of the arterial system.
Conclusion.

Having described the various experimental details of the investigation, it only remains to take a general survey of its results. In this retrospect the effects produced by Deboisine naturally fall into two subdivisions according the quantity of the drug used.

1. Small doses stimulate the inhibitory centres, but at the same time paralyse the intracardiac end of the vagi, so that the central stimulus is either transient or altogether in vain as the drug reaches the brain or the heart first. In the rabbit no
increase of the pulse-rate is caused by the pneumogastric paralysis. The vaso-motor centres are also stimulated and the smaller vessels contract, but there is no influence on the cardiac ganglia or muscle. The summation then of the results following the administration of small doses shows increased arterial pressure caused by the diminished calibre of the arterioles and by the paralysis of inhibition. The increased pressure in the rabbit causes a slowing of the rate, uncompensated by the removal of inhibitory influence, which is merely potential and quite dormant as regards the pulse-rate in that animal.

2. Doses of 0.01 gramme and upwards have a constant tendency to depress the circulation, and to the paralysis of the cardiac ter-
omnations of the vagi is added a diminished influence of the vaso-
motor centres, attended by a consequent dilatation of the arterioles
with lowered arterial pressure. When the quantity administered
reaches five centigrams the cardiac ganglia and muscle suffer
also, and with an extremely rapid fall of blood pressure death
ensues speedily, the heart being afterwards found in a relaxed
condition. Recovery may follow even doses of five centigrams
provided the blood is not permitted to stagnate in the lungs,
and so by engorgement of the right side to prove an obstacle
too powerful for the flagging capabilities of the poisoned heart.
The drug certainly destroys the respiratory functions and by artificially
filling the place of the former until the transitory effects of the drug pass away and the respiratory actions recommence, the circulation may withstand the effect of the drug in doses lethal under ordinary conditions.

It seems unnecessary to enter upon a detailed comparison of the effects of Atropia and Dunbisia. In kind these are identical; in degree they differ but slightly. Atropia would appear to have greater influence over the cardiac ganglia and muscle than Dunbisia, but the latter drug stimulates the vaso-motor centre more powerfully and is the full as energetic as Atropia in paralyzing the intra-cardiac endings of the pneumo-gastric nerves.