THE DISCOVERY AND PHARMACOLOGY OF CYCLOPROPANE[1]

G. H. W. LUCAS[2]

IT WAS over thirty years ago, on November 22, 1928, that I prepared, in the laboratory of the Department of Pharmacology of the University of Toronto, the first sample of cyclopropane ever to be used for anaesthetic experiments on laboratory animals. I trust the reader will bear with me, however, if I first go back a few years prior to that date to show how previous research in the Department led to the discovery of cyclopropane. The data I shall present may be gleaned piecemeal from the various departmental publications prior to 1928, but hitherto no one has brought them together in one paper.

I first became acquainted with Professor Velyien E. Henderson, several years before I joined his Department, through my efforts to discover the growth-promoting factor in yeast, under Professor W. Lash Miller of the Department of Chemistry. Certain feeding experiments on animals were carried out in the Department of Pharmacology. Later I served as biochemist for the late Sir Frederick Banting, who had his laboratory in Professor Henderson's Department. Because of this I was aware of some of the research in progress in anaesthesia and when, in 1927, Professor Henderson offered me the opportunity of joining in this research, I accepted without hesitation.

The story from 1927 on involves four persons—the late Professor Velyien E. Henderson, Dr. W. Easson Brown, Mr. Allan Brock, and myself. Mr. Brock, who at the time was laboratory assistant and machinist in the Department, assisted in operations on the animals and in the design and manufacture of any new and essential apparatus.

At least 35 papers dealing with anaesthetics and anaesthesia have been published by members of the Staff in Pharmacology. A worldwide quest for a general anaesthetic more suitable than ether or chloroform or nitrous oxide reached its peak about 1923. The earliest investigations in this field were undertaken by Paul Bert in 1878 on nitrous oxide, but little attention had been paid to his results.

Ethylene was under serious investigation in various laboratories on the North American continent about 1920, and in Toronto, Dr. W. Easson Brown became interested in it. He was aware that in 72 per cent concentration it was not toxic to animals; in August, 1922, he anaesthetized rabbits and mice with 80 per cent ethylene and 20 per cent oxygen. A paper on this subject, which he read before the Toronto Academy of Medicine on February 20, 1923, was published in the March 7 issue of the *Canadian Medical Association Journal* of that year (1). A week later A. B. Luckhardt and J. B. Carter published a report of their work on the same gas in the *Journal of the American Medical Association* (2). In a later

[1]Presented at the Annual Meeting, Canadian Anaesthetists' Society, May 6, 1959.

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publication, on May 19 of the same year, they reported that they had conducted 106 operations in hospitals, using this gas as a general anaesthetic. In the American literature, Brown is not given credit for the earliest publication on the anaesthetic value of ethylene in laboratory animals, possibly because he published his results in a Canadian journal.

Brown meanwhile continued his experimental work on animals in co-operation with Dr. Henderson and extended it to include anaesthetization of some members of the laboratory staff. He used it in several operations on human patients. The fact that ethylene could be used in concentrations of 80 per cent or over for satisfactory anaesthesia, and had been used extensively by Luckhardt, did not satisfy Dr. Brown and Professor Henderson. From the study of the narcotic properties of alcohol, it was postulated that propylene would be a more potent gas than ethylene and its preparation was begun in the laboratory early in 1924. In July of that year Brown reported in the *Journal of Pharmacology and Experimental Therapeutics* (3) that propylene had definite anaesthetic properties and would induce anaesthesia in concentrations as low as 37 per cent in air or oxygen. Anaesthesia, he asserted, could be maintained in concentrations from 20 to 31 per cent in oxygen; in concentrations of 65 per cent or over it was considered toxic.

A chemical engineer, Mr. L. J. Bonham, working on a special grant in the Department of Pharmacology, succeeded in making a very pure sample of propylene and reported his findings in the February, 1925, issue of the *Journal of the American Pharmaceutical Association* (4). Samples of the gas thus made were excellent for anaesthesia on experimental animals. However, when it was tanked in steel alloy tanks, toxic materials developed in it; these were not present in the original gas prepared in the laboratory. As no means were found to account for this unexpected toxic action, or to remove the toxic product, anaesthetic research with this gas came to a standstill.

It was at this juncture that I joined the staff of the Department of Pharmacology. As I reviewed the literature on anaesthesia and became more familiar with the work of Brown and Henderson on propylene, it was apparent that the serious metabolic changes occurring during anaesthesia were in part due anoxaemia. We decided to direct our attention to the work of Paul Bert (5) on nitrous oxide administered with oxygen under pressure. He had maintained that satisfactory anaesthesia could be attained with nitrous oxide–oxygen mixtures under pressure greater than that of the atmosphere. He pointed out that, by increasing the pressure to $1\frac{1}{4}$ atmospheres in a nitrous oxide 80 per cent–oxygen 20 per cent mixture, the partial pressures of the nitrous oxide would be the same as that of pure nitrous oxide. According to Henry's Law of the solution of gases, a patient breathing this mixture under pressure would have in his blood as much nitrous oxide as he would have when he breathed pure nitrous oxide. Bert reported successful surgery with this anaesthetic mixture.

Over a year was spent investigating the anaesthetic value of nitrous oxide–oxygen mixtures under pressure. We experienced much difficulty in designing a suitable tank in which to anaesthetize laboratory animals (rabbits, cats, and rats). After several tanks burst under pressure, a satisfactory one was made from steel tubing heavily reinforced.

Despite the fact that pressures up to 2 atmospheres were employed and partial pressures of nitrous oxide were 1½ times that of pure nitrous oxide when inhaled, a satisfactory state of deep surgical anaesthesia was not reached. Animals when stimulated could move about in the cage. Anaesthesia could be secured at these high partial pressures of nitrous oxide only when the partial pressure of oxygen was so low that anoxaemia was present.[3] Thus ended another anaesthetic venture. We seemed to have come to a dead end.

During the researches on nitrous oxide and oxygen under pressure, little attention had been paid to the tank of propylene, prepared by E. R. Squibb and Sons several years previously, which had developed peculiar toxic products. Professor Henderson now drew my attention to this unsuccessful experiment and suggested that I give the matter some attention to learn, if possible, what substance could have formed in the tanked gas. While searching the literature, I found that cyclopropane, which is an isomer of propylene, might be formed during any chemical reaction in which propylene was prepared. I performed some qualitative analyses on the sample of toxic gas and came to the conclusion that some cyclopropane was present. I suggested that this gas might be the toxic material; I could not find any data in the literature regarding its toxic effects when inhaled. Professor Henderson therefore decided that I should prepare cyclopropane, employing the method published by Wilstätter in which trimethylenebromide was reduced by zinc to cyclopropane in the presence of alcohol and traces of water. Since we suspected the gas was poisonous, it was approached with a great deal of care.

According to my notebook, the first sample of cyclopropane was prepared for anaesthesia on November 22, 1928 (Fig. 1). It was employed to anaesthetize cats in a manner similar to that used for propylene. Needless to say, the stage was set for anaesthetic experiments on this gas because much apparatus had been designed for research on ethylene and propylene. To our amazement, the cyclopropane was not toxic but anaesthetized animals in concentrations lower than those observed for any other anaesthetic gas. The animals recovered rapidly. It was evident that cyclopropane was a gas which invited further investigation.

I shall not burden you with minor details of the ensuing experiments. However, it is interesting to note that, as cyclopropane was soluble in sulphuric acid, it was relatively easy to measure concentrations in any mixture employed for anaesthesia. An impurity in the gas, probably saturated hydrocarbons, was obtained in quantity by dissolving out the cyclopropane in sulphuric acid and leaving this gas as a residue. When this residue was tested, it had no anaesthetic value. Experiments with cyclopropane showed that it was anaesthetic in a concentration of approximately 12 per cent in oxygen and that the concentration could be increased up to 30 per cent or so without causing serious toxic effects on the heart, but respiration at higher concentrations was somewhat shallow. Repeated administration of the gas to animals did not cause toxic effects (7, 8). The changes in metabolism were measured; these were practically nil. The gas was

[3]Although these results were published in the *Journal of Pharmacology and Experimental Therapeutics* in August, 1927 (6), some textbooks still state that nitrous oxide–oxygen mixtures under pressure give satisfactory anaesthesia.

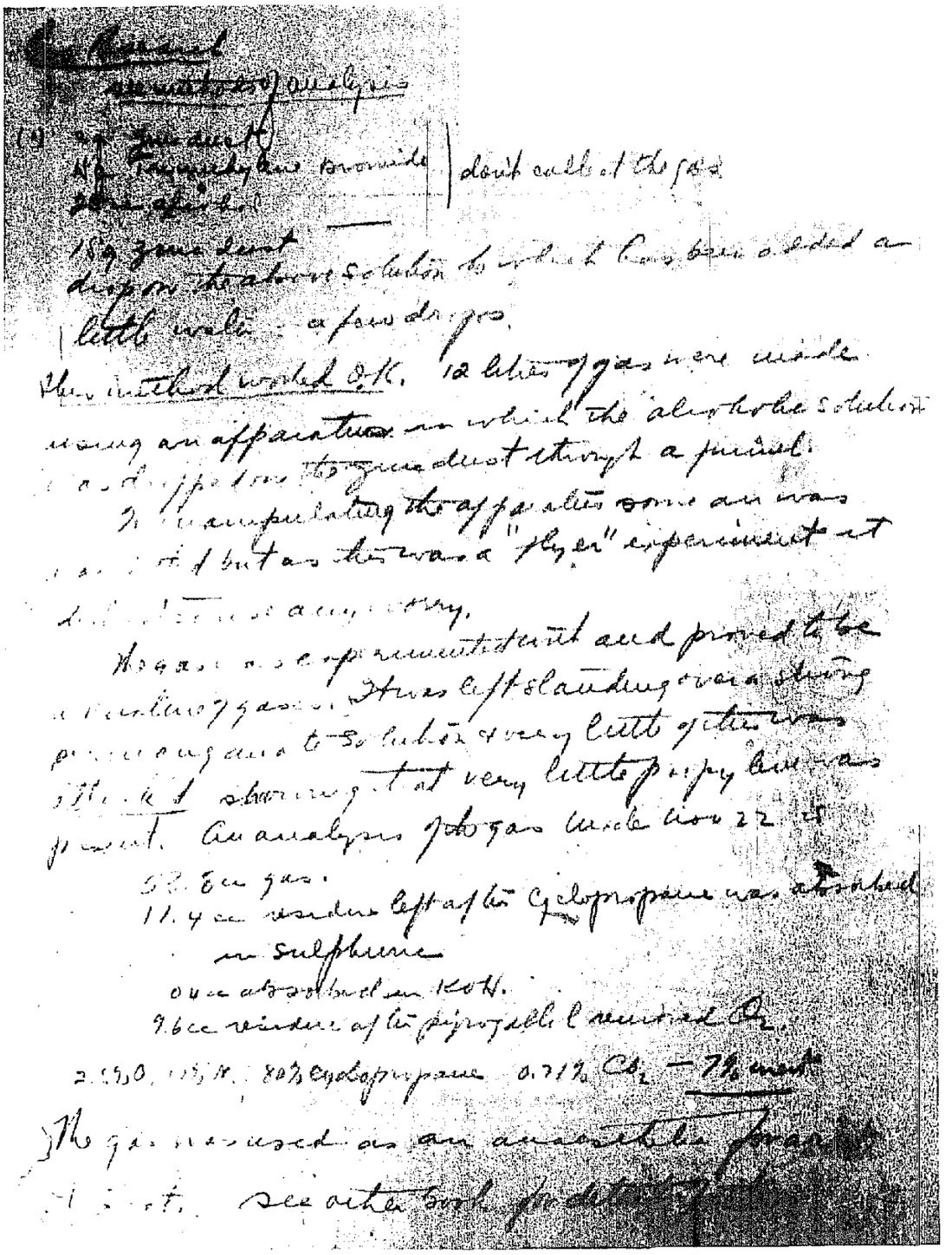

FIGURE 1. Facsimile of a page from the author's notebook describing the first preparation of cyclopropane for anaesthetic purposes on November 22, 1928.

found to be explosive in air or in oxygen in anaesthetic concentrations the oil water partition coefficient was determined for it

Professor Henderson reported briefly the results of our discovery at the Annual Meeting of the Canadian Medical Association June 21 1929 (9) and in October of the same year I presented a longer paper at the Annual Congress of Anaesthetists in Chicago (10) At that time we had not experimented on humans because we felt the gas was too impure

The gas was subsequently prepared in pure state and the crucial test was performed namely tanking it under pressure in steel alloy tanks to ascertain whether or not impurities formed in the gas as they did with propylene About 120 L of gas were manufactured purified and then liquefied by being passed through a glass cooling coil immersed in liquid air A small steel tank fitted with a connection for an anaesthetic machine and with a small removable plug was also cooled in liquid air (Fig 2) The liquid cyclopropane was poured into the steel tank and the plug was inserted and secured The tank was then permitted to remain in the laboratory at room temperature for about one month As experiments on animals showed that the gas had not become toxic on standing we proceeded to the experiments on humans

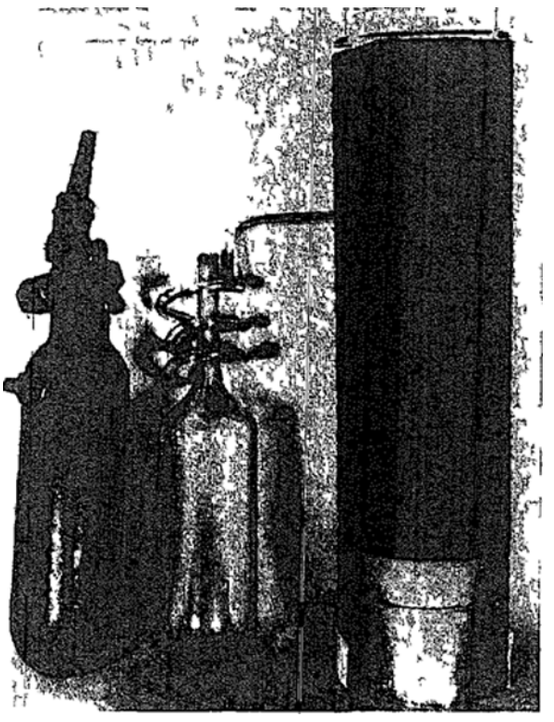

FIGURE 2 The equipment first used to liquify and the first tank used to contain cyclopropane for anaesthetic purposes

Dr. W. Easson Brown had not been actively engaged in research on cyclopropane up to this date; he had discussed the experiments with Professor Henderson and me and we had agreed that his contribution would be mainly in the human experimentation. He was the first doctor in the world to administer cyclopropane in anaesthetic concentrations to humans, the first patient being Professor Velyien E. Henderson. At this first sitting, my task, as the analyst, was to check concentrations of the administered cyclopropane rapidly. Mr. Brock regulated the flow of gas and Dr. Brown looked after his patient. Both induction and recovery were rapid following a short anaesthetic. No ill effects followed. Dr. Brown then anaesthetized several members of the staff, myself included. We knew then that the gas was ready for experimental use in the hospital; we had at hand all the necessary equipment for measuring and controlling the anaesthetic concentrations.

At this particular time our luck changed. Three deaths which had occurred in Toronto in a relatively short period from the administration of ethyl chloride to patients gave rise to considerable newspaper publicity. Dr. Brown, who was on the anaesthetic staff of the Toronto General Hospital, begged the privilege of administering some of our sample of non-toxic cyclopropane to a patient, even for a short surgical procedure. A demonstration was put on one evening in our laboratory when Dr. Brown anaesthetized Dr. Frederick Banting before a number of physicians, but this was of no avail. Dr. Samuel Johnston, Head of the Department of Anaesthesia, who was present, observed the effects of cyclopropane, but in view of the unfortunate ethyl chloride deaths he forbade the use of cyclopropane in the hospital. It remained for others at a later date to investigate the anaesthetic value of this gas in surgery.

In Toronto we experimented with laboratory animals using commercial cyclopropane supplied by E. R. Squibb and Sons (Fig. 3) and then turned our attention to cyclopropane derivatives, hoping to discover one which would be an ideal liquid anaesthetic at room temperature, would have a boiling point about that of chloroform and could be administered by means of a mask. I prepared several chlor-derivatives of cyclopropane and also ethyl- and methyl-derivatives. None of these, however, to my mind was of value. Either they were too toxic or the boiling point was too high. I decided to abandon research in anaesthesia.

Professor Henderson continued a more extensive study of cyclopropane derivatives but found nothing of anaesthetic value. A chemist, Mr. A. H. R. Smith (11), was engaged to investigate the old tanked propylene and discovered hexenes in it; these were extremely toxic to laboratory animals. It would appear that Professor Henderson persevered until he had established the toxic component of the tanked propylene. It was fortunate for both of us that, when we began our experiments in 1928, I had come to the conclusion that cyclopropane was a constituent of the tanked propylene.

The stage for further cyclopropane experimentation was now moved to Wisconsin. Dr. Ralph M. Waters, in the Wisconsin General Hospital at Madison, had heard my paper on cyclopropane in Chicago and was very interested in the new anaesthetic. He and Professor Henderson were close friends and judging by a letter written to Professor Henderson in August, 1930, Professor Henderson

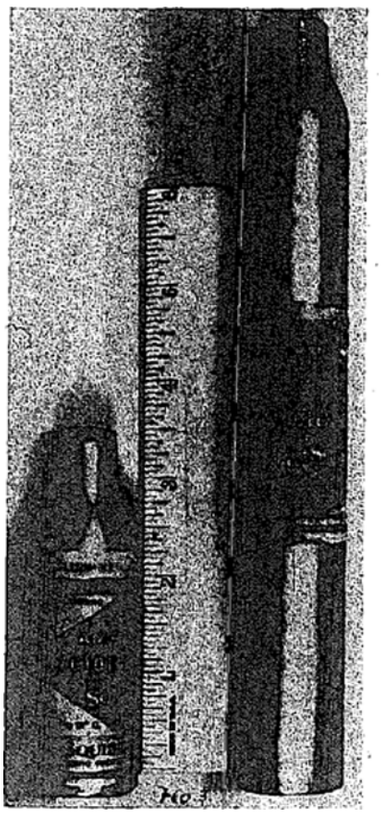

FIGURE 3. The first commercial "tanks" of cyclopropane supplied by E. R. Squibb & Sons.

must have encouraged Dr. Waters to use cyclopropane as an anaesthetic on patients, following our failure to try it in the Toronto General Hospital. After Professor Henderson's death I was asked to examine departmental files and records and discovered Dr. Waters' letter to Professor Henderson dated August 20, 1930 (Fig. 4). In this letter he stated that he had secured a small tank of cyclopropane from the Ohio Chemical Company and, after testing it on a dog, he had used it in the hospital on three patients. One operation was a simple appendectomy (35 min.; Fig. 5); one an inguinal hernia (40 min.; Fig. 6); a third on a fat woman, her tenth operation, for the removal of a gall bladder previously drained and the repair of a recurrent inguinal hernia (1 hr. 28 min.; Fig. 7). Dr. Waters had included a copy of the operating room charts for each patient. Analysis showed that about 40 per cent cyclopropane was essential for anaesthesia.

He states in his letter, "I believe that further investigations on this are distinctly indicated because the thing which anaesthesia needs more than anything

THE UNIVERSITY OF WISCONSIN
STATE OF WISCONSIN GENERAL HOSPITAL
MADISON

DIVISION OF SURGERY

August 20, 1930

Professor V. E. Henderson
University of Toronto
Ontario, Canada

Dear Doctor Henderson:

At your suggestion, I secured from the Ohio Chemical Company a small tank containing ten gallons of Cyclopropane. This, by means of the absorber technique, I found sufficient to anesthetise one dog, forty minutes, and being then satisfied that I need not harm the patients, I have used the remainder of the tank for three complete clinical anesthesias. One simple appendectomy--thirty-five minutes, one inguinal hernia--forty minutes, and one fat lady (her tenth operation) for the removal of a gall bladder, reviously drained, and the repair of a recurrent inguinal hernia, the latter operation lasting one hour and twenty-eight minutes. An attempt to use the tank again this morning gave me an incuotion, but during the insertion of the pharyngeal airway, the small amount of cyclopropane was lost so that the one dog anesthesia and three clinical were all I could secure from ten gallons.

The gall bladder case described above was distinctly obese, and of the type most difficult to relax with any other method than spinal, and I believe that the results, so far as relaxation goes, were better than could have been secured in any other way than spinal. Whether it was as good as we would have secured with spinal, I doubt. The first case, ap endectomy, was the type of individual in whom I would expect postoperative disturbances, a young Jewess, who had had some vomiting previous to operation. She vomited more than we would have expected postoperatively and complained of a "dizziness". The hernia case also vomited, although not excessively. The gall bladder and hernia were done this morning.

The blood pressure variations as a result of this agent, observed in three cases, were suprisingly stable it seems to me. I am asking my secretary to make copies of the operating room charts of these three cases for your information. The pulse rate in the first case was quite variable, but was extremely rapid before the anesthesia was begun due, I presume, to fright. There was a suprising lack of respiratory stimulation even during induction in the first case and we therefore didn't insert the soda lime during induction in the other two. The pulse in each case showed a slight irregularity when too great a concentration was reached, with some tendency to arhythmia, but the arhythmia was used by me as an indication for more oxygen. We made gas analyses of the oxygen-carbon dioxide content of bag at the end of each operation, and in the case of the hernia, did so as soon as anesthesia was well established. These gas analyses are at extreme variance with your laboratory results, and it is for this reason I am sending you them today. The first two cases, as you will see, were run on percentages in excess of 40 of cyclopropane. The gall bladder-hernia case had 23% cyclopropane at the end of operation it is true, but during the gall bladder procedure, I am sure the concentration was very much higher. We estimated that a 50-50 mixture was placed in the bag at the beginning and that it was replaced with a 40-60 mixture at the time the abdomen was opened.

FIGURE 4 Facsimile of a letter from Dr Ralph Waters t Professor V E Henderson concerning the first use of cyclopropane in clinical surgery

A constant delivery of oxygen, probably more than sufficient to cover the metabolic demand for oxygen was flowing throughout most of the operative time, so that the 23% found in the bag at the end of the hernia operation was probably much weaker than that used at the height of the operative procedure. I shall be glad to have your reaction to my discrepancies in cyclopropane concentrations as compared to your experience. We tried the addition of decidedly more oxygen with the idea of dropping back to such percentages as you had found necessary in animals, but retching resulted when we did so. I regret having been unable to complete more clinical cases with the gas supplied me, and in case any more is manufactured, I should be very glad to give the gas a further trial clinically. The Ohio Chemical Company stated that they might make up more of the gas late in the fall. This ten gallons was all they had at the present time.

I believe that further investigational in this gas is distinctly indicated because the thing which anesthesia needs more than anything else at the present time, it seems to me, is a quick acting gaseous agent which will produce reasonably extreme relaxation of abdominal muscles with reasonably rapid recovery therefrom. This, it seems to me, cyclopropane shows some possible evidence of doing.

Trusting that my notes may be of some interest to you, and with kindest personal regards, I am,

Sincerely,

Ralph W. Waters

Ralph W. Waters, M. D.
Department of Anesthesia

RWW:VH

FIGURE 4 (continued)

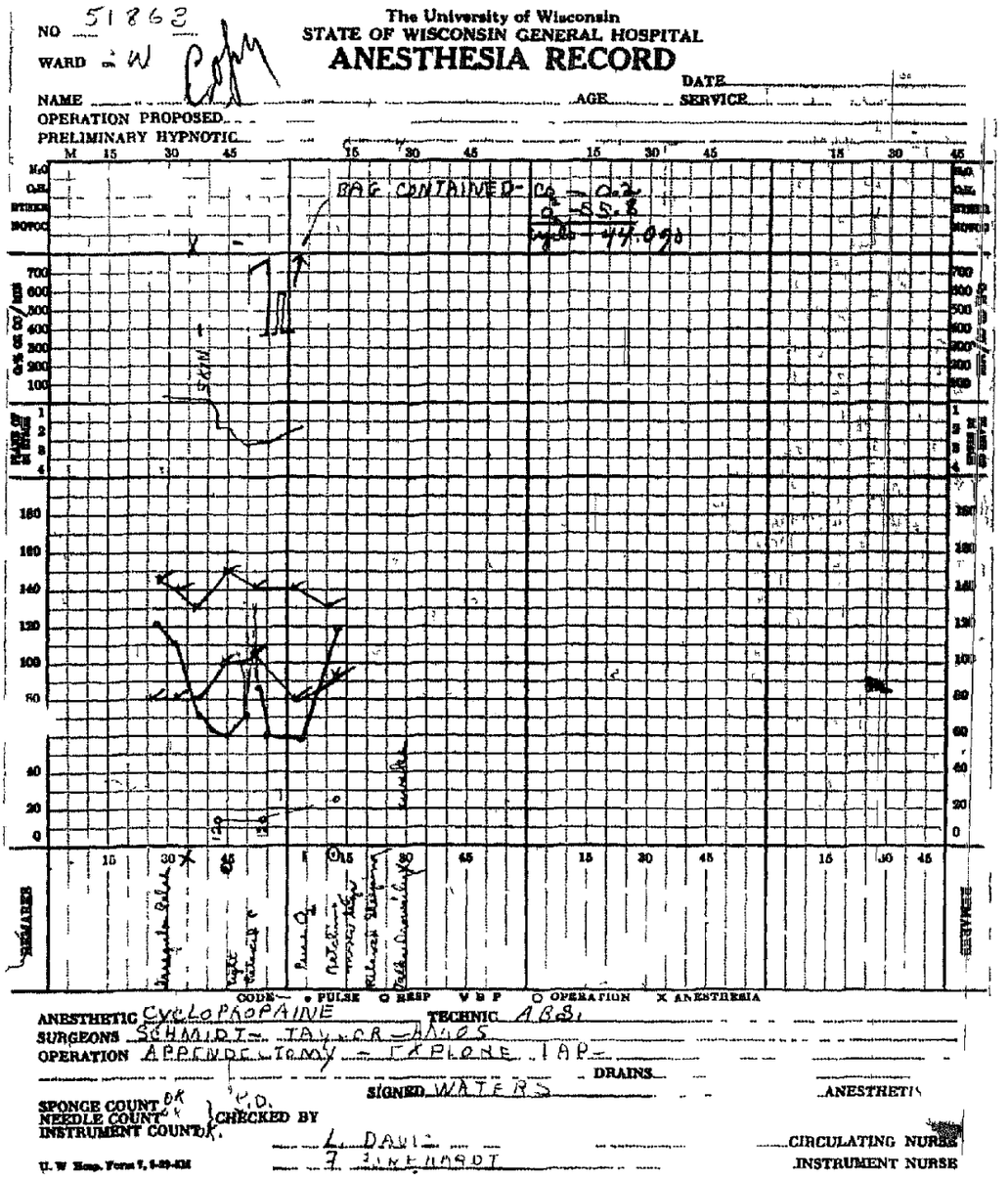

FIGURE 5 Facsimile of a copy of the anaesthetic record of the first patient anaesthetized with cyclopropane for a surgical operation supplied by Dr Waters to Professor Henderson

PREOPERATIVE NOTES

NAME .....

SEX 7, AGE 22, WT 110, HT ....., COMPLEXION .....,

AIRWAY ....., MOUTH .....,

T. P. R. RATE 19.8 - 88 - 24, VITAL CAPACITY ....., BREATH H. ....., B. M. R. .....

LUNGS Cl.

HEART Cl. B. P. { BEFORE B. H. ..... AFTER B. H. .....

BLOOD: HB 72, R. B. C 5,800, W. B. C 9,200, COAG. TIME .....

N. P. N. ....., CHLORIDES ....., SUGAR .....

URINALYSIS UK.

MISCELLANEOUS Sickle Cell. DIAGNOSIS CHRONIC APPENDICITIS

ANESTHETIC HISTORY APPENDECTOMY

PROPOSED OPERATION APPENDECTOMY

EVALUATION: PRESSURE RATIO ....., SHOCK INDEX .....,

ENERGY INDEX ....., CORNELL TEST ....., McINTYRE TEST ....., RISK { A ..... B ..... C ..... D .....

SPECIFIC TOXEMIA .....
HYPERPYREXIA .....
HYPERMENTATION .....
HYPERSTHENIC .....
HYPOMETABOLIC .....
HYPOSTHENIC .....
HABITUAL DRUGS .....
.....

POST OPERATIVE NOTES: VOMITED SOME - COMPLAINED OF DIZZINESS HEADACHE NEXT DAY, GAS PAINS UNTIL THIRD NIGHT ... DOING PT WELL & T. P. R. - NOT UNUSUAL POST OP.

FINAL COMMENT: .....

SIGNED ..... ANESTHETIST.

FIGURE 5 (*continued*)

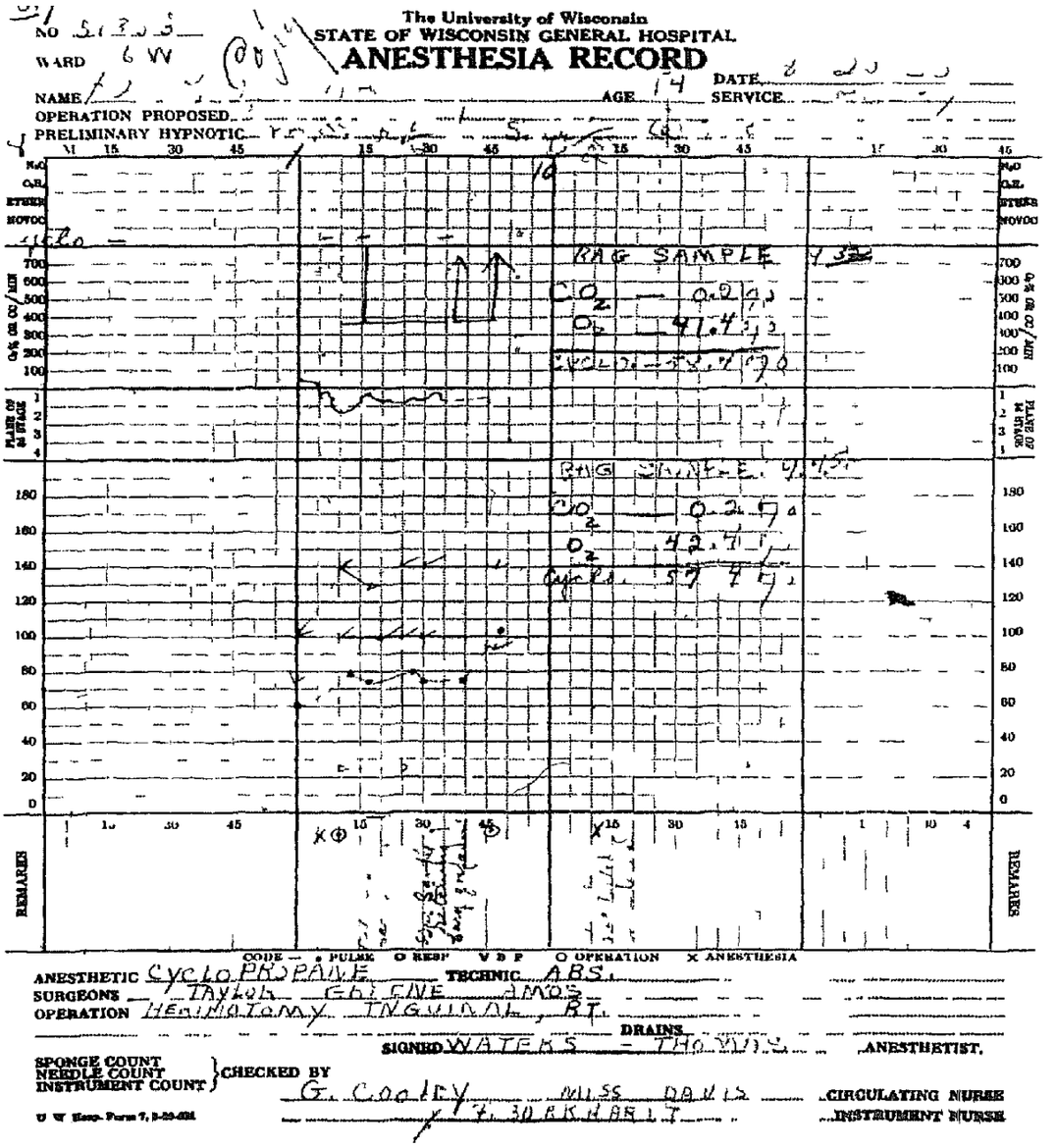

FIGURE 6 Facsimile of a copy of the anaesthetic record of the second patient to be anesthetized with cyclopropane for a surgical operation supplied by Dr Waters to Professor Henderson

PREOPERATIVE NOTES

NAME .....

SEX ..., AGE ..., WT. ..., HT. ...; COMPLEXION .....

AIRWAY ..., MOUTH ...,

T. P. R. RATE ..., VITAL CAPACITY ..., BREATH H. ... B. M. R. ...

LUNGS .....

HEART ..... B. P. { BEFORE B. H. ... / AFTER B. H. ...

BLOOD: HB. ..., R. B. C. ..., W. B. C. ..., COAG. TIME ...

N. P. N. ..., CHLORIDES ..., SUGAR ...

URINALYSIS .....

MISCELLANEOUS .....

ANESTHETIC HISTORY .....

PROPOSED OPERATION .....

EVALUATION: PRESSURE RATIO ..., SHOCK INDEX ...

ENERGY INDEX ..., CORNELL TEST ..., McINTYRE TEST ... RISK { A ... / B ... / C ... / D ...

{ SPECIFIC TOXEMIA ... / HYPERPYREXIA ... / HYPERMENTATION ... / HYPERSTHENIC ... / HYPOMETABOLIC ... / HYPOSTHENIC ... / HABITUAL DRUGS ...

POST OPERATIVE NOTES: ...

FINAL COMMENT: ...

SIGNED ..... ANESTHETIST.

FIGURE B (*continued*)

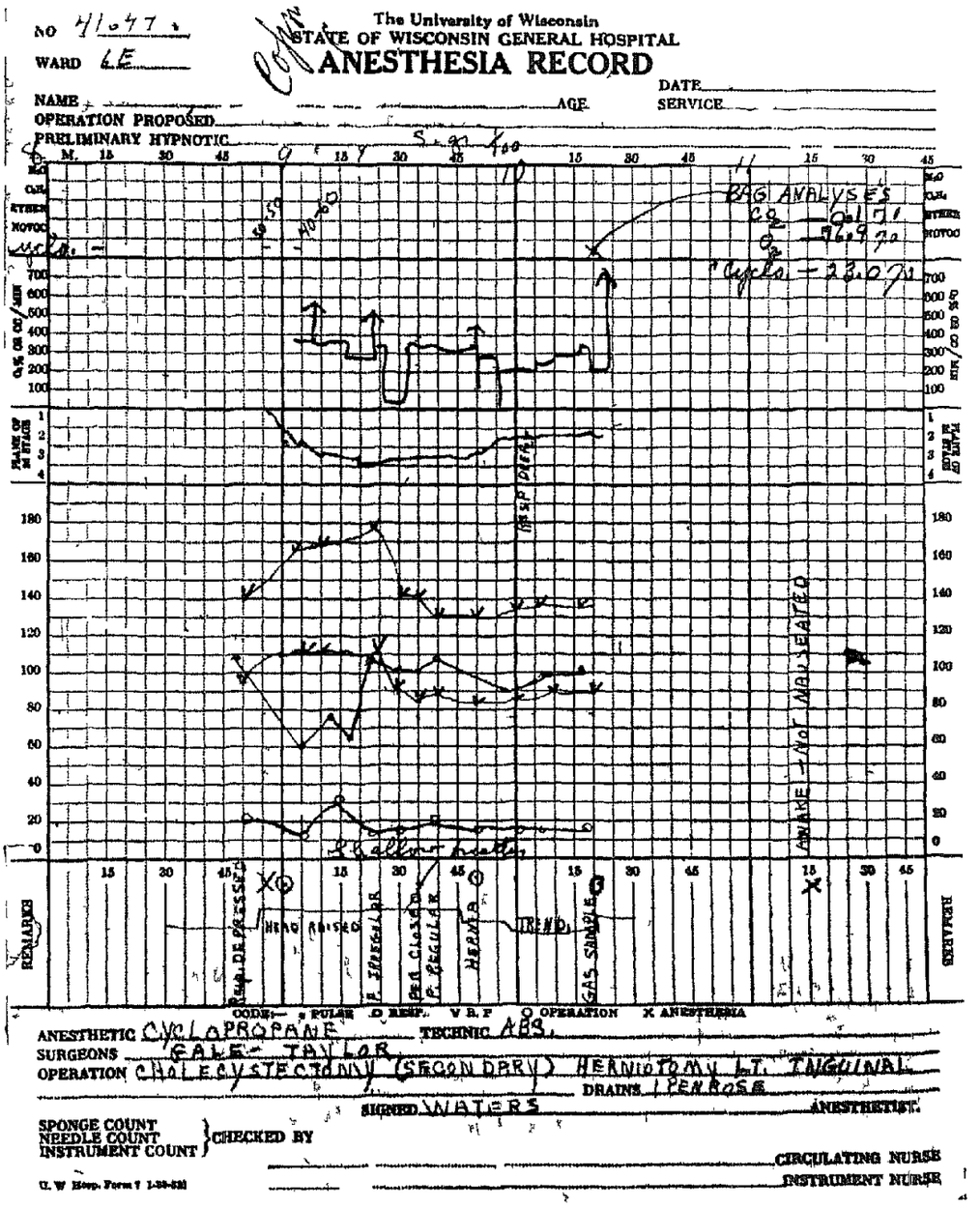

FIGURE 7 Facsimile of anesthetic record of the third patient [illegible] with [illegible] by Dr. Waters to Professor Henderson

PREOPERATIVE NOTES

NAME

SEX F. AGE 23 WT 161 HT 5'4 COMPLEXION

AIRWAY OK. MOUTH OK.

T. P. R. RATE. VITAL CAPACITY. BREATH H. B.M.R.

LUNGS OK.

HEART OK. B.P. 96/65 Before B. H. / After B. H.

BLOOD. HB 68 R.B.C. 3,680 W.B.C. 11,550 CLOT. TIME

N.P.N. CHOLESTEROL SUGAR 98 (9-19-33)

URINALYSIS negative

MISCELLANEOUS OBESE, SLIGHT COLD

ANESTHETIC HISTORY multiple previous operations in the lumbar region and cholecystotomy.

PROPOSED OPERATION cholecystectomy and herniotomy

EVALUATION PRESSURE RATIO SHOCK INDEX

ENERGY INDEX CORNELL TEST MCINTYRE TEST

Specific Tension / Hypertension / Hypersensitivity / Hypotension / Hypometabolic / Hypertrophic / Habitual Drugs

RISK A / B / C / D

POST OPERATIVE NOTES: NAUSEA AND VOMITING 5 TIMES IN 1st 24 HRS. PERIODIC SLIGHT DYSPNOEA

URINE NEXT DAY TRACE OF ALBUMEN, NO SUGAR NOR ACETONE.

FINAL COMMENT

SIGNED ANESTHETIST.

FIGURE 7 (continued)

else at the present time, it seems to me, is a quick-acting gaseous agent which will produce reasonable extreme relaxation of the abdominal muscles with reasonably rapid recovery therefrom. This, it seems to me, cyclopropane shows some possible evidence of doing."

Professor Henderson, in answer to this letter, wrote (Fig. 8) pointing out that Dr. Waters should estimate the cyclopropane content of gaseous mixtures by dissolving it in sulphuric acid and should not assume that all the gas remaining after the removal of oxygen and carbon dioxide was cyclopropane (Fig. 5). I recall that Dr. Waters reported later that the analyses made by the Toronto method showed that the anaesthetic concentrations of cyclopropane were about half that reported in his first three cases.

The friendship, interest, and co-operation of two doctors outside of Toronto were largely responsible for the employment of cyclopropane clinically. Dr. Ralph M. Waters and Dr Harold R. Griffith were present in Montreal at the meeting of the Canadian Medical Association in June, 1929, when Professor Henderson announced our discovery of cyclopropane as a general anaesthetic. They were much interested in the gas and followed our progress with it. Dr. Griffith became interested in Dr. Waters' success in the Wisconsin General Hospital and a paper presented by Stiles, Neff, Rovenstine, and Waters at the 12th Annual Congress of Anaesthetists in Chicago, October, 1933 (12), convinced him of its clinical value and led him to begin using it as a general anaesthetic in the Homeopathic Hospital of Montreal in 1933. He thus became the first anaesthetist in Canada to employ cyclopropane.

Pharmacology of Cyclopropane

Cyclopropane (trimethylene) was prepared in 1882 by Von Freund. It was made from trimethylene bromide plus zinc dust. Later it was made from 1-3-dichlorpropane plus zinc. This latter method is known as the Haas method. The anaesthetic potency of cyclopropane was determined in 1928–9 by Lucas and Henderson (10). Its molecular weight is 42.05; its specific gravity 1.46 (air—1). It liquefies at 5 atmospheres pressure at room temperature; the boiling point is −34.4° C. It is rapidly absorbed by sulphuric acid, a property which makes it easy to analyse when in combination with other gases. It is stable when stored in liquid form in steel alloy tanks at room temperature. The impurities occurring in it may be propylene, propane, allene, organic halides, and cyclohexane. Some of these are formed during its manufacture. The solubility in oil as compared to water is 34.4; oil as compared to blood 15.3. The flash point of this material is below 0° C. The minimum ignition temperature is 927° F. in air and 849° F. in oxygen.

It is a colourless gas, non-irritating to the respiratory tract. It has a sweetish odour and taste. It is inflammable and, according to my notes, forms an explosive mixture in anaesthetic concentrations (Fig. 9); in air, mixtures of 2.4 to 10.3 per cent and oxygen 2.5 to 60 per cent are explosive. It is not altered in the body. The major portion is eliminated from the body in 10 min., but for complete desaturation of the tissues a number of hours are required. No histological changes occur in any of the organs.

September 8, 1930.

Dr.R.M.Waters,
Dept. of Anesthesia,
State of Wisconsin General Hospital,
Madison, Wis.

Dear Dr.Waters:

I am sorry to have delayed in acknowledging your letter of August 20th, which came while I was away on holidays, and not easily reached.

Your experience is extremely interesting and valuable to us. Our experiments with the human anesthetics have not proceeded very far, owing to various delays and holidays. Consequently, we cannot give you very intelligent criticism on your findings. We are, however, extremely doubtful if such a high percentages are required.

As far as we can judge from your letter and charts, you estimate the amount of cyclopropane by analyzing for oxygen and carbondioxide and considering the residue of cyclopropane. We are quite sure that this will not give you accurate results. Any gas unabsorbable by pyrogallol will then be counted cyclopropane. Cyclopropane can be absorbed by strong sulphuric acid, and all our calculations of anesthetic concentration have been based on such an analysis. We find in one sample of cyclopropane a considerable amount of unabsorbable gas, either a saturated hydrocarbon which is apt to be present in small amounts, or nitrogen.

We will let you know when we have tried some more experiments.

Yours sincerely,

FIGURE 8 Facsimile of a letter from Professor Henderson to Dr Waters

x

8.6 ... not very violent

5.9 ... to be not active

Gas + Oxygen

11.2 cc Cyclop. + O₂ to 100 cc very explosive

5.0 % cycl + O₂ 100 — "

not 30 minutes 10

2.5 — 100 — explosive

1.4 % — no explosion.

16% Pole all [illegible]

... on the explosability of cyclopropane in oxygen

On inhalation laryngospasm may develop during induction or during very light anaesthesia, possibly owing to the parasympathomimetic action of the gas; atropine and scopolamine medication ordinarily inhibit this effect. Laryngospasm may occur if high concentrations are inhaled.

During cyclopropane anaesthesia, dreams do not occur as they do when nitrous oxide or ethylene is administered.

Analgesia occurs when concentrations of 3 per cent to 5 per cent of the gas are inhaled. Plane II requires from 11 to 14 per cent; plane III, 14 to 23 per cent; plane IV, 23 to 40 per cent. At this high concentration respiration may fail. The gas is administered in a closed circuit and is not altered by alkaline absorbants or carbon dioxide. The kidneys, liver, spleen, and uterus are little affected during anaesthesia. The activity of the intestine is depressed in deep anaesthesia, but recovery is rapid when the gas is withdrawn. Blood-clotting time is unchanged although oozing and capillary bleeding are encountered owing to vasodilation and to some elevation of the blood pressure. Metabolic processes and blood chemical patterns are not disturbed significantly.

Relaxation of skeletal muscle is adequate for many surgical operations. The gas may be administered with muscle relaxants such as curare to gain greater relaxation.

The most serious disadvantage of cyclopropane lies in the fact that the irritability of the automatic tissue of the heart is increased, causing arrythmias from the displaced pacemaker. Vagus escape, atrioventricular block, ventricular tachycardia, and ventricular fibrillation may occur spontaneously. The mechanism by which this anaesthetic adversely influences cardiac automaticity is not completely understood, although much research has been directed to the solution of the problem and a voluminous literature exists. There is some evidence that sympathetic reflexes arising in abdominal receptors play a role in the production of these cardiac disorders.

It has been known for a long time that epinephrine and some related amines enhance the production of the arrythmias, but the mechanisms involved are subject to much debate. In the opinion of some workers both the rise in blood pressure and the direct effect of epinephrine must be considered.

Epinephrine is lost from the adrenal gland during cyclopropane anaesthesia but less so than with ether. Ether, however, protects the heart from cyclopropane arrythmias when it is administered with the gas.

The proper choice of drugs for premedication may play an important role in the incidence of cyclopropane arrhythmias. There is some support for the belief that they arise more frequently with morphine than with barbiturates. The content of potassium in the myocardium may also play some role in the occurrence of arrhythmias in cyclopropane anaesthesia. It has been shown that an increase of the potassium in the myocardium follows the injection of epinephrine. Anoxia, an excessive rise in carbon dioxide, alkalosis, and a rise in blood sugar may also contribute to such irregularities.

Atalectasis, partial or massive, may occur, it is claimed, if the anaesthetist does not watch his patient carefully to be sure of adequate respiration and to see that some inert gas such as nitrogen or helium is left in the inspired air after cessation

of the operation. Cyclopropane and oxygen are rapidly absorbed and unless some less soluble gas is in the lungs, areas may collapse.

Following long operations, postoperative hypotension may occur (cyclopropane shock). This condition appears to be associated with a severe respiratory acidosis. It is believed that the proper prophylaxis to prevent this syndrome may be achieved by maintenance of a normal alveolar carbon dioxide tension.

Experimentally on dogs, employing the cyclopropane-epinephrine test, investigators have reported that procaine amide, prbcaine, meperidine, quinidine, atropine (large doses), ergotamine, dibenamine, and tolazoline afford partial or complete protection against cardiac arrhythmias.

I have taken considerable time to discuss the early history of the research on anaesthesia in the Department of Pharmacology and to show how the pioneer investigations of the late Dr. Velyien E. Henderson and the late Dr. W. Easson Brown led to our discovery of cyclopropane. It was my good fortune to be associated with them in this work.

It is fortunate, also, that my notes on the preparation and first use of the gas experimentally on animals have been preserved, together with some of the apparatus used in the experimental investigations, and that I found Dr. Waters' letter to Professor Henderson, along with copies of the hospital records of Dr. Waters' three patients, and the copy of Dr. Henderson's reply.

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