CHLOROFORM ANAESTHESIA

by

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CONTENTS.

CHAPTER 1.

HISTORICAL INTRODUCTION.

By nature all men desire to know.
Aristotle.

"Guthrie's Sweet Whisky".

As far back as 1796 a group of Dutch chemists produced a dense, oily liquid. This was probably ethylene dichloride $(CH_2Cl)_2$ and it was known as Dutch liquid or chloric ether, remaining for many years a chemical curiosity.

Professor Benjamin Silliman, in his Yale College Elements of Chemistry, dated February, 1831, gave a description of the physical properties of chloric ether, and ended the paragraph by stating :-

> Its medicinal powers have not been ascertained, but from its constitution and properties, it is highly probable that it would be an active diffusive stimulant. (83a).

These remarks about chloric ether prompted Samuel Guthrie to enquire into and produce an alcoholic solution of chloroform. It was undoubtedly he who made what was the forerunner of chloroform, later to be used as an anaesthetic agent throughout the world.

Who was this Samuel Guthrie, about whom so little seems to be known?

His grandfather sought security in America from religious persecution in his native Scotland. Samuel Guthrie was born in 1782, and studied medicine under his father. In 1817 he moved to Sackets Harbor, Jefferson County, New York. This part of the country was by then progressing and Sackets Harbor was a thriving village when Dr. Guthrie took up a tract of land and there established his home.

Samuel Guthrie was a medical practitioner and practised his art conscientiously and well. It is on record that he took advantage of vaccination for smallpox long before it was generally accepted as a prophylactic treatment in America (83b). A man of many parts, Guthrie's interests and talents were spread in many directions. One of his sources of income was the articulation of skeletons, which he sold to the medical schools. As time passed, he became more interested in chemistry, both pure and applied. These interests he put to practical use in the distillation of alcohol and the making of vinegar of which he produced large quantities.

Perhaps Guthrie's main interest was in experimenting with gunpowder. This work was not without hazard and entailed numerous painful accidents, some almost fatal. But Guthrie was made of stern stuff, and it was he who pioneered and perfected the percussion pellet, a great improvement on the flintlock then in use.

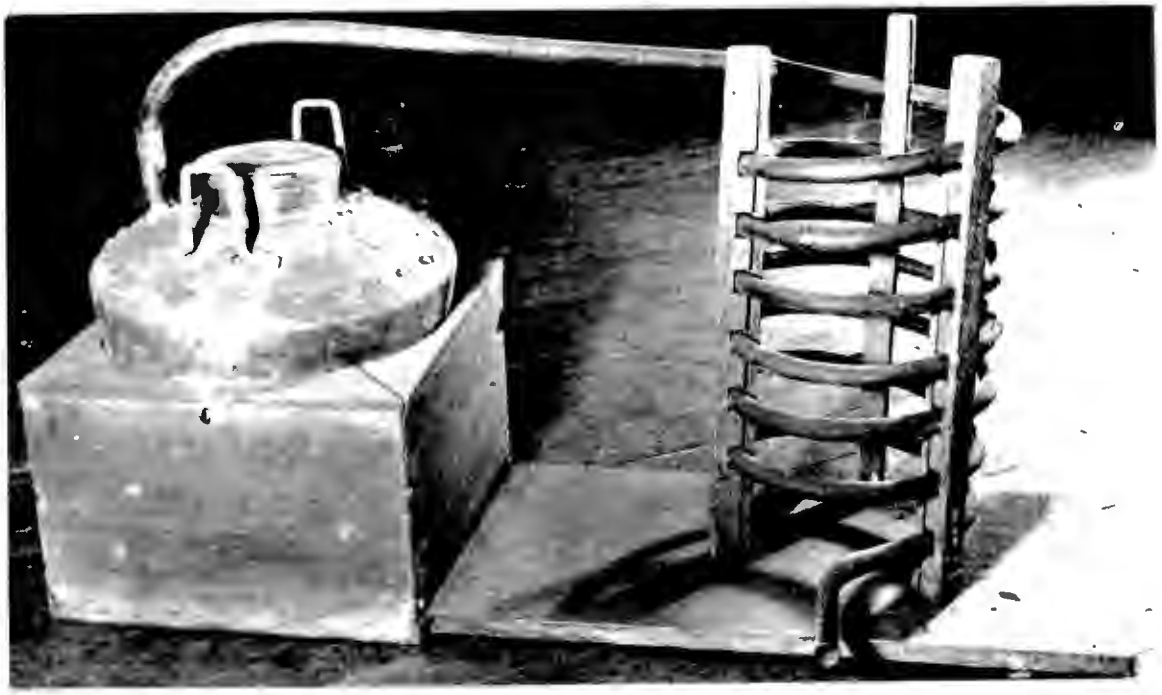


Fig. 1. Replica of the still in which Samuel Guthrie produced chloroform.

Guthrie must have led an amazingly full life in his small backwoods home, and to read the reports of his original work is a revelation of his keen and enquiring mind. The account of his first attempt at obtaining chloric ether is entertaining. It is stated that

> with the whiskey to the amount of two gallons he purchased at the tavern, Dr. Guthrie added three pounds of chlorinated lime he had been using as a disinfectant round the henhouse.

This mixture was placed in a copper still and the alcoholic solution distilled off. What Guthrie was attempting to produce was chloric ether, or ethylene dichloride. In fact, the title of his paper was"New mode of preparing a spiritous solution of chloric ether"(83c). But what he discovered was chloroform, albeit somewhat diluted by alcohol.(88a).

Guthrie remarked on the effect on men of his sweet whiskey, that it produced

> promptly a lively flow of animal spirits, and consequent loquacity; and having, after its operation, little of that depression consequent to the use of ardent spirits.

The initial production of chloroform, or chloric ether, by Guthrie, was probably made during the first half of 1831. As will be seen, the failure of Guthrie to date his original publication in Silliman's quarterly American Journal of Science and Arts led

later to controversy over the first discovery of chloroform.

Guthrie sent samples of his chloric ether to Professor Benjamin Silliman, who in turn passed it on to his colleague, Dr. Eli Ives, Professor of Medicine at Yale College. Ives and his son, reported on their clinical trials, and record the beneficial effects of chloric ether taken by mouth in cases of bronchial asthma, ulcerated throat, quinsy and scarlet fever. It was also used by inhalation in a case of pulmonic disease (83d) (pulmonary tuberculosis?).

In 1833 Dr. J. Black of Bolton, England, recommended chloric ether as a cordial in the treatment of asthma and acknowledged that this remedy had been "brought into use by our American brethren."(9).

At about the time that Guthrie made his discovery, chloroform was produced by two other men. These co-discoverers were Eugine Soubeiran, in France and Justus von Liebig, in Germany. Like Guthrie, Soubeiran distilled a mixture of alcohol and chloride of lime and obtained an impure chloroform which he called bichloric ether (ether bichlorique).(24a, 19, 88b, 83e). This was reported for the October 1831 issue of Annales de Chemie et de Physique, issue for October 1831. But owing to a revolution at the time, this issue did not appear until January 1832.

Recherches de Chimie organique ;

PAR M. J. DUMAS.

Lu à l'Académie des Sciences le 13 janvier 1834.

Dans un Mémoire que j'ai eu l'honneur de communiquer récemment à l'Académie, je suis revenu, ainsi que je l'avais annoncé, sur la question des éthers, et j'ai discuté quelques uns des argumens qui nous avaient déterminés autrefois à publier sur ces corps une théorie qui a soulevé tant de discussions, qu'on peut s'étonner qu'elle ait pu résister à des attaques si vives et si répétées.

0,699 de matière ont fourni 0,260 d'acide carbonique et 0,061 d'eau. Ces résultats donnent en centièmes :

Carbone.....	10,29
Hydrogène.....	0,97
Chlore.....	88,74
	100,00

Tous ces résultats s'accordent entr'eux et s'accordent fort bien aussi avec les résultats calculés d'après la formule $C^2\ H\ Ch^3$; celle-ci donnerait en effet :

C^2.....	76,52	10,24
H.....	6,25	0,83
Ch^3....	663,96	88,93
	746,73	100,00

Ces résultats s'accordent également bien avec ceux qui seraient tirés de la même formule relativement à la densité de la vapeur. On a, en effet,

C^2.....	=	0,8432
H.....	=	0,0688
Ch^3....	=	7,3150
		8,2270

$$\frac{8,2270}{2} = 4,113$$

Il me paraît donc certain que la substance que j'ai analysée, substance qui possède tous les caractères que M. Liebig assigne à celle qu'il a soumise à l'analyse, mais que je ne saurais assurer être parfaitement identique avec elle, possède pour formule $C^4\ H^2\ Ch^6$.

Cette composition assigne à la substance que je viens

Fig. 2. Extracts from J.B.A. Dumas' article.

Liebig published a note in November 1831,(88b) and a more complete annotation in 1832. He obtained a purer form of chloroform by distillation and called it liquid chloride of carbon (chlorique de carbone liquide).

In his original report, estimated to have been in the publisher's hands between May and July, 1831,(16), Guthrie reports that

> during the last six months a great number of people have drunk of the solution of chloric ether in my laboratory. (83f).

This seems to indicate that chloroform was probably produced by Guthrie in January or February of 1831.

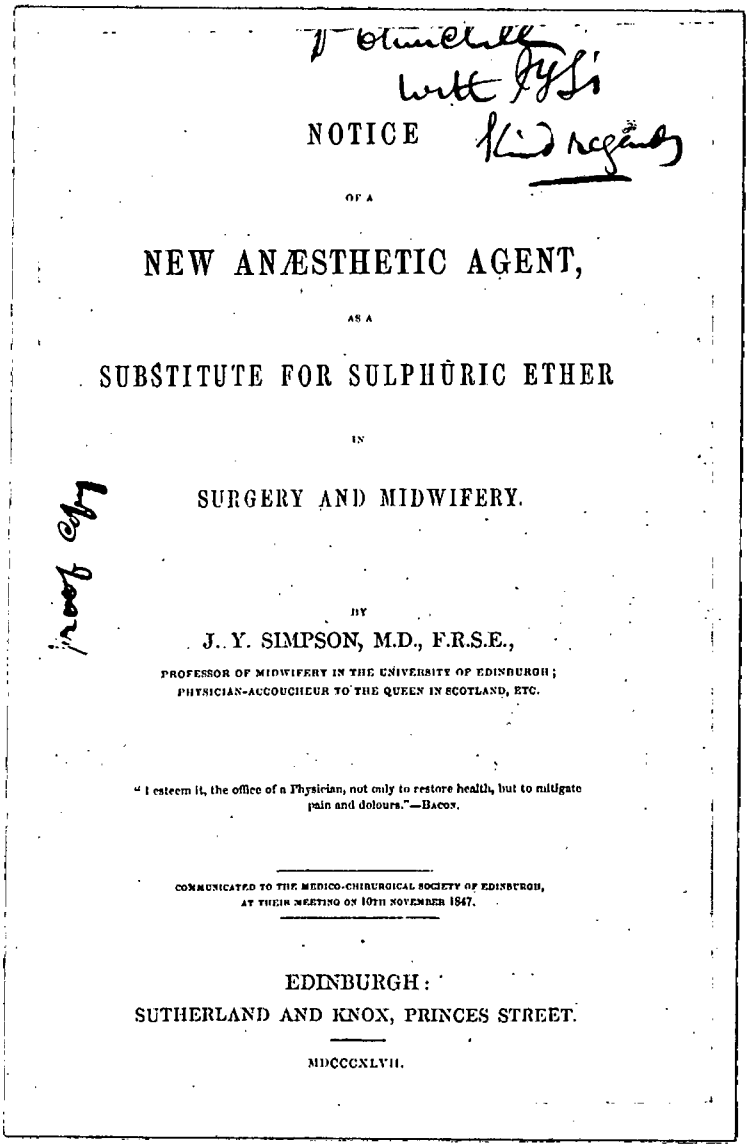
It is probable that all three, Guthrie, Soubeiran and Liebig, discovered chloroform independently at practically the same time, with Guthrie leading by a few months. The efforts of Guthrie are all the more remarkable when it is appreciated that by comparison with his continental co-discoverers, he had practically no formal training, worked in the most primitive conditions and lacked the stimulus of academic colleagues.

In 1834 J.B.A. Dumas obtained pure chloroform and gave it its name. His analysis of its empiric formula was not quite correct - he alloted it two carbon atoms - but was nevertheless a close approximation (see Figure 2).

To us it may seem extraordinary that the anaesthetic properties of chloroform should have remained a secret so long

after the discovery of the drug. In fact, it is on record that Guthrie's daughter, whilst playing with a tub of chloroform, fell down and was found by her father in a stuporous slumber (110). In those days of course, surgical anaesthesia was practically unthought of and certainly unheard of.

And so it was that the true worth of this drug was not discovered for another sixteen years, and on another continent in the land of Guthrie's forefathers.



NOTICE

OF A

NEW ANÆSTHETIC AGENT,

AS A

SUBSTITUTE FOR SULPHURIC ETHER

IN

SURGERY AND MIDWIFERY.

BY

J. Y. SIMPSON, M.D., F.R.S.E.,

PROFESSOR OF MIDWIFERY IN THE UNIVERSITY OF EDINBURGH;
PHYSICIAN-ACCOUCHEUR TO THE QUEEN IN SCOTLAND, ETC.

"I esteem it, the office of a Physician, not only to restore health, but to mitigate pain and dolours."—BACON.

COMMUNICATED TO THE MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH,
AT THEIR MEETING ON 10TH NOVEMBER 1847.

EDINBURGH:
SUTHERLAND AND KNOX, PRINCES STREET.

MDCCCXLVII.

Fig. 3. Title page of Sir J.Y. Simpson's first publication on chloroform.

The barefoot baker's boy from Bathgate.

-275. June 7. Simpson, David, baker, Bathgate. Wife, Mary Jarvey, Aet. 40. Lab.nat., easy, rapid. 8th child. Son. Natus 8 o'clock. Uti veniebam natus. Paid 10s. 6d.(98).

This is the first note of James Simpson. It is taken from the notebook of a Dr. Dawson, local practitioner in the village of Bathgate, West Lothian, where Simpson was born in 1811.

It was soon recognised that young James Simpson was a boy of more than average ability. Although the family income was meagre, the older members scraped together the means to secure the education that would obviously benefit him. And so, at the age of fourteen, Simpson enrolled as a student at the Edinburgh University (88c, 35_a). He attended the lectures of the notable teachers of his time - Robert Knox, the anatomist, later to be implicated in the activities of the notorious Burke and Hare; Robert Liston and James Syme, surgeons; and James Hamilton, Professor of midwifery, during whose lectures Simpson seemed to have been for the most part asleep (35b).

By the time he was 18, Simpson had obtained the diploma of the Royal College of Surgeons, and three years later, in 1832, his Doctorate in Medicine. He devoted his attention to obstetrics, and in 1840, at the age of 28, was elected to the chair of midwifery at Edinburgh University.

Surgery in those days was a brutal trade, and Simpson's

humanity and compassion was probably more highly developed than that of his contemporaries. It is evident that the horrors and miseries of the operating theatre distressed him greatly, and it is not surprising that he actively searched for some way of preventing suffering of patients during surgery. So it was that Simpson was the first to use ether in obstetrics within a month of its introduction into surgical practice in England in January 1847.

As we have seen, chloroform was used in England for medicinal purposes as far back as 1833. David Waldie relates how he improved the making and purifying of chloroform when he was head chemist at The Apothecaries Hall, Liverpool. Whilst in Scotland in October, 1847, Waldie met Simpson, who was then searching for an anaesthetic with fewer hazards and drawbacks than ether. Waldie suggested that chloroform might be tried and promised to send a sample (113). Before the promise could be fulfilled Simpson obtained a sample from an Edinburgh chemist. On the night of November 4th he and two colleagues discovered for themselves the anaesthetic effect of chloroform vapour.

Simpson wasted no time in informing the world of his discovery. The agent was used by him in clinical practice on November 8th, anaddress on its use was made to the Medico-Chirurgical Society of Edinburgh on November 10th, and the first publication on the use of chloroform was on November 12th (89). (See Figure 3). A more detailed report is to be found in the Lancet of 1847(96).

There are some who think that Waldie has not received his rightful due for his part in the discovery of chloroform (77). John Snow states .....,

> for when he informed Dr. Simpson of the existence and nature of chloroform, he was able to give him, not merely an opinion, but an almost certain knowledge of its effects. (105a).

This emphasis on Waldie's contribution is not endorsed by the chemist himself, who wrote

> Some of my friends have considerably over-rated the importance of my share in the discovery, but this I have uniformly discountenanced(24b).

Two historical facts are certain though. Simpson "discovered" the anaesthetic properties of chloroform very shortly after his meeting with Waldie; and he gave Waldie scant recognition in the announcements of his "discovery".

The Lancet of November and December 1847 teems with articles on the use of chloroform (115) in obstetrics (103, 13, 97, 75), surgery (68), dentistry (46) and veterinary surgery (112). No less direct and robust are the criticisms of Simpson, not only in respect of his new form of anaesthesia (6), but also of his methods of midwifery (54).

It is common belief that James Young Simpson was the first man to use chloroform for anaesthesia, and no doubt this was the belief held by Simpson himself. I was surprised to find that this was not the case. Dr. Furnell, writing in the Lancet in 1877 (29) and 1871 (3), pointed out that chloric ether (a mixture of chloroform and spirits) was used by Dr. Holmes

Coote of St. Bartholomew's Hospital about six months before Simpson's publications. The use of this drug had been suggested to Coote by Furnell, then a medical student. It is not surprising to find that Holmes Coote was one of the early users of chloroform in England. He records his use of it at St. Bartholomew's Hospital tendays after the first publication of the news from Edinburgh - that is, on November 20th 1847 (20).

Within a few months of Simpson's publications, chloroform had practically displaced ether as an anaesthetic agent in Britain and on the Continent. But in America things were different. In the Northern States chloroform was tried, but as the result of several fatalities the use of ether was resumed. At the Massachusetts General Hospital chloroform was prohibited not long after its introduction (24c). In the Southern States, however, chloroform was preferred, possibly due to the influence of New Orleans, where, it was stated,

> one could scarcely practice surgery unless one had been to Paris, and in Paris the anaesthetic of choice was chloroform (24d).

The first verified use of chloroform anaesthesia in South Africa occurred at the Cape in 1850. It was administered by Dr. F.L.C. Biccard to a young woman for the disarticulation of the humerus at the shoulder joint. Dr. Biccard also performed the operation, and the patient recovered (15).

Fatalities from chloroform anaesthesia soon occurred in England, France, America, though allegedly not in Scotland.

Simpson and his colleagues attributed this to the fact that chloroform was perfectly safe as long as the Edinburgh technique was adhered to; namely, the dropping of liquid chloroform on to a handkerchief or towel held over the patient's face (60). This legend of the infallibility of chloroform north of the Tweed is questioned by Sykes. He points out that owing to the absence of coroners' inquests in Scotland at that time, deaths were far more unlikely to be reported in the press. He also makes the point that deaths certainly did occur following chloroform anaesthesia in Scotland but they were conveniently overlooked.

It must also be emphasized that the population of London was approximately fourteen times that of Edinburgh. So that it was to be expected that mortalities in England would be greater by comparison (107). Nevertheless, Scottish surgeons stoutly adhered to chloroform for the remainder of the nineteenth century. On the Continent, with the exception of one or two isolated districts, the trust in chloroform remained unshaken until the eighteen-nineties. The French used the Edinburgh method, or else the cardboard cone, which contained lint in the apex to absorb the chloroform (24e).

By 1863 the increasing number of fatalities occuring during chloroform anaesthesia made it evident that something would have to be done about the matter. The Royal Chirurgical Society (now the Royal Society of Medicine) appointed a committee to investigate and advise about

chloroform anaesthesia, and a report was published in 1864. Many of the committee's conclusions had been reached by John Snow before, and were, in essence, that whilst chloroform was easy to give and pleasant to take, it frequently killed. Ether, on the other hand, was slow in action, unpleasant to take and caused greater excitement. In order to obtain the best of both worlds, the committee advised the use of mixtures of chloroform and ether. Many of these were tried, amongst them the famous ACE mixture, suggested originally by George Harley in 1860. This mixture was constituted of one part of alcohol, two parts of chloroform and three parts of ether. Another renowned mixture was C_2E_5 - chloroform, two parts, ether, three parts - a mixture well known to many a senior doctor in practice to-day (70).

The most important aspect of the committee's report was that it ended the overwhelming supremacy of chloroform in England. Although chloroform was used extensively (31) well into the present century, it was realised that other agents had much to offer. In not many years ether became the serious rival of chloroform and was soon to practically displace it.

CHAPTER 2.

THE EFFECTS OF CHLOROFORM ANAESTHESIA ON VARIOUS ORGANS AND TISSUES.

> "Contrariwise", continued Tweedledee, "if it was so, it might be; and if it were so, it would be; but as it isn't, it ain't. That's logic."
>
> Through the looking-glass.

It is not my intention to reproduce here a list of the physical properties of chloroform. This information is available in textbooks of pharmacology or anaesthesia. Relevant material in connection with the physical properties of the drug will be mentioned in passing, and in connection with the matter under discussion.

1. Blood.

The solubility of chloroform in blood is estimated at 1.42 cc. per 100 cc. whole blood (40a). It is generally agreed that the larger part of chloroform is taken up by the red corpuscles. Nicloux estimated the red cell capacity for chloroform to be seven or eight times that of the serum (76) and Adriani states that 65 per cent is transported by the red cells (1b). Chloroform does not effect the oxygen carrying power of the blood. This matter will be discussed in the section on respiration.

2. Nervous Tissue.

Chloroform first depresses the higher centres, then the motor areas and lastly the vital centres of respiration and circulatory control (59a).

The highest centres and special senses are quickly depressed and conscious control is lost rapidly. In common with most inhalation anaesthetics, there is a stage of excitement or second stage associated with muttering and struggling. The degree of excitement is influenced by such factors as the patient's psychological state, his physique and the degree of pre-medication. It is my experience that the second stage of chloroform anaesthesia is neither as violent nor as prolonged as that experienced during comparable ether anaesthesia.

Levy states that vomiting occurs in protracted light chloroform anaesthesia, due to excitement of the vomiting centre (59a). This has not been observed to any degree locally, and analysis of 707 cases of chloroform anaesthesia record only two incidents of vomiting during anaesthesia. Levy also remarks that during recovery from anaesthesia, vomiting is almost invariable. This has certainly not been the experience locally, where immediate post-operative retching or vomiting has occured in 3 per cent of cases. This compares with a similar figure given by Gillespie in 1947, who observed in addition that vomiting and retching occurred in 35.5 per cent

of cases when agents other than chloroform were used (30a).

It may be of interest to note that 6 of the 33 local chloroform cases that vomited post-operatively had respiratory obstruction and cyanosis at some stage. It is possible that the high incidence of vomiting that Levy noted was a result of hypoxia and hypercarbia that occured with the methods of anaesthesia in use at that time.

3. Respiratory System.

Coughing. Given in gradually increasing dosage, chloroform does not cause undue irritation of the pulmonary tree. Coughing during induction is occasionally seen in the heavy smoker or the patient with pulmonary infection.

Mucous Secretion. This is rarely troublesome during chloroform inhalation. I cannot recall an instance of difficulty in this respect in a patient who has had hyoscine or atropine pre-operatively.

In my experimental work on dogs which were given chloroform anaesthetics, it was unnecessary to give atropine pre-operatively and mucous secretion was absent. On the other hand, when dogs were given ether, under similar circumstances, mucous literally poured out, and pre-operative atropine was essential to prevent this.

. Rate and depth of respiration.

In light chloroform anaesthesia, the respiratory rate (59b, 84)

and the depth (1a) are increased.

The deeper the anaesthesia, the more is the respiratory rate and excursion depressed and this is due to the suppression of the respiratory centre. It is the result of overdosage and often is soon obvious after premedication with opiates (70), when complete apnoea may occur.

Table 2 (see Appendix) taken from 707 cases of chloroform anaesthesia from Groote Schuur Hospital, shows that in 48 per cent of the short anaesthetics, tachypnoea was observed. In operations lasting up to two hours, this figure had decreased to 25 per cent. This bears out the statement made at the beginning of this paragraph - that respiration is stimulated in light chloroform anaesthesia.

Gaseous exchange.

It is thought that about 65 per cent of chloroform is carried in the erythrocytes. Buckmaster and Gardner found in animal experiments, that in deep chloroform anaesthesia the arterial oxygen saturation was depressed and the blood carbon dioxide content was increased (14). They proposed that this was due to the drug interfering with the function of haemoglobin, and denied that it was the effect of underventilation. This view has persisted for fifty years and is quoted as fact in modern text-books (53, 118a).

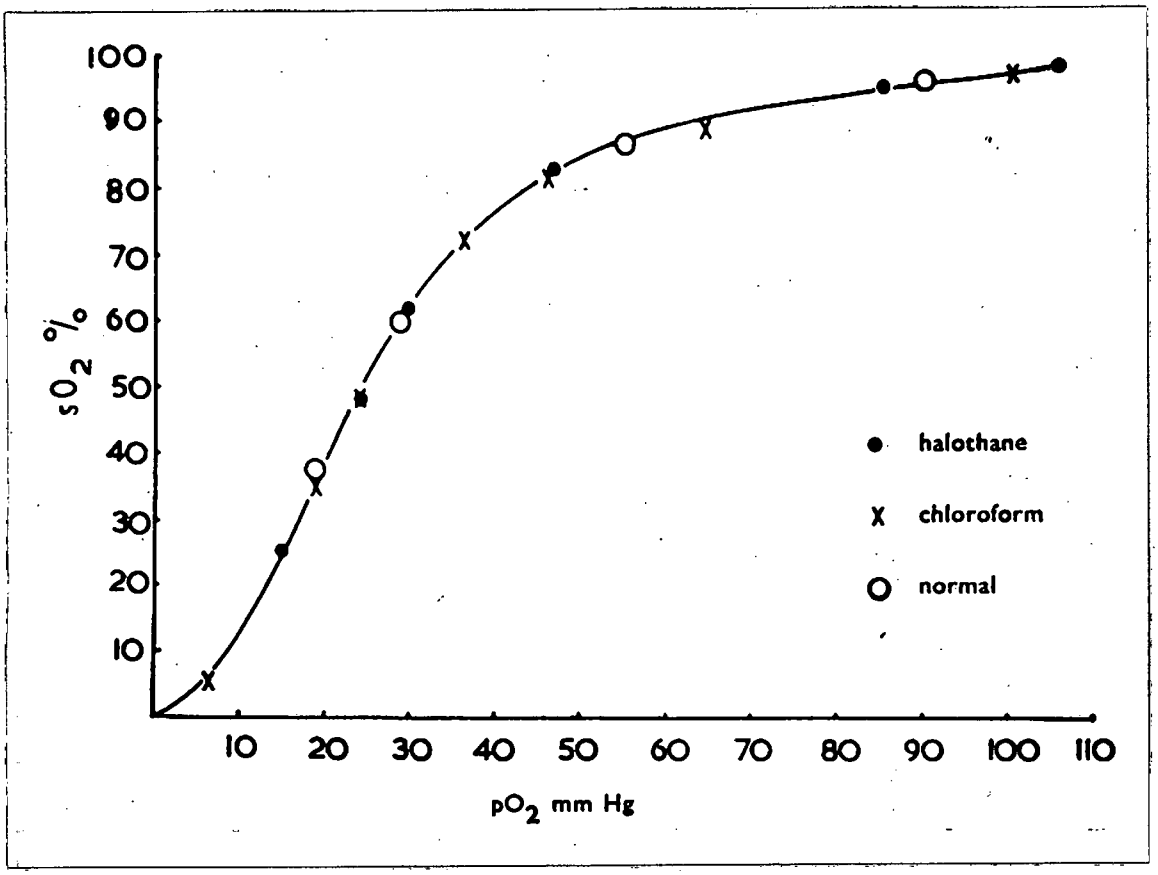


Fig. 4. Oxygen dissociation curve for human blood.

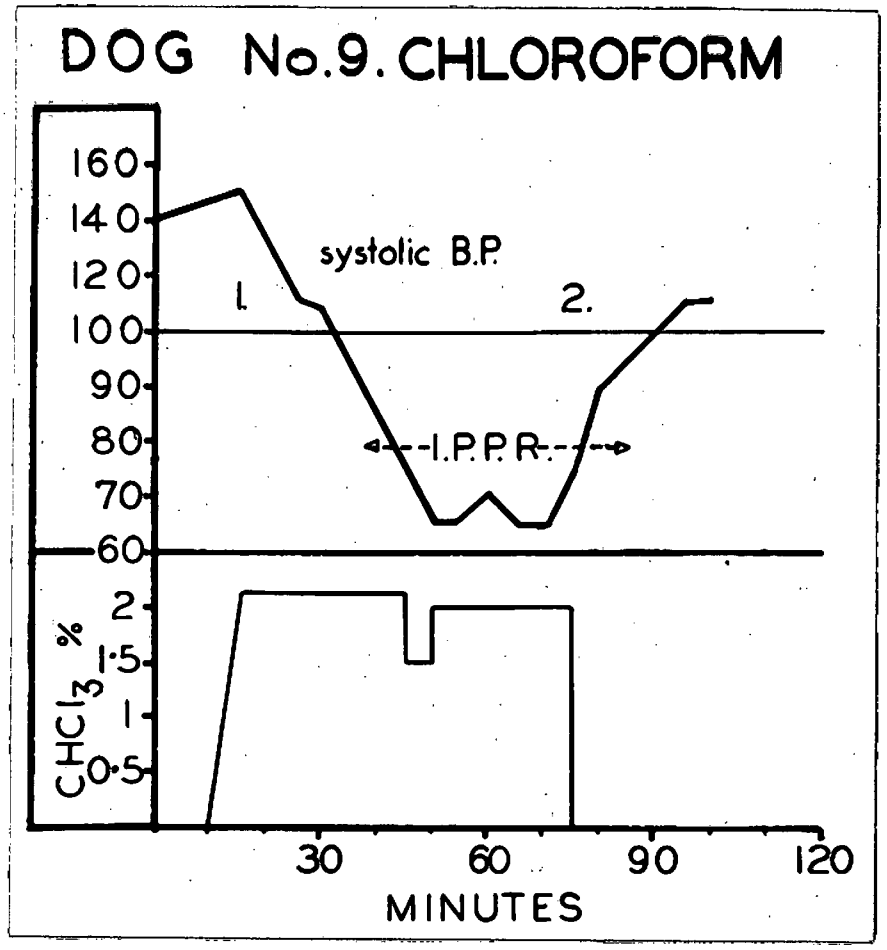

DOG No.9. CHLOROFORM
160
140
120
100
90
80
70
60
systolic B.P.
1.
2.
I.P.P.R.
2
1·5
1
0·5
CHCl3 %
30
60
90
120
MINUTES

Fig. 5.

Yet this fallacy was disproved before it was uttered. In 1902 Tissot administered chloroform to a dog and at the same time assisted respiration artificially. He found that an arterial blood sample taken at the time of death from chloroform overdosage contained a normal oxygen saturation and, as one would expect, the carbon dioxide concentration was lower than normal (111).

More recent work confirms Tissot's results. Dobkin and his colleagues, using chloroform and artificial respiration on human beings, found that the anion-cation balance was not disturbed and that chloroform had no depressant effect on the oxygen saturation of the blood (23). It has been found that the oxygen dissociation curve for human blood is unaltered by chloroform (102) (See Figure 4). This could not be if the oxygen combining power of haemoglobin was diminished by the drug.

This matter of arterial oxygen saturation during deep chloroform anaesthesia is well demonstrated in Figure 5. This is the record of a dog in which I produced hypotension by means of chloroform overdosage. It will be seen that at (1), during spontaneous respiration and during moderately light anaesthesia, the oxygen saturation of arterial blood was 90 per cent (14.9 c.c. Oxygen per cent). During the period when intermittent positive pressure respiration (IPPR) was used, the oxygen saturation improved to 95 per cent (2) (15.7 c.c. Oxygen per cent), not withstanding the fact that

the dog was saturated with chloroform nearly to the point of vasomotor collapse. For this animal the inspired air had an oxygen concentration of at least 30 per cent.

Conclusions.

1. It would seem that in deep or prolonged chloroform anaesthesia, assisted or controlled respiration is desirable.
2. A high concentration of oxygen (30 per cent or higher) in the inspired air is also necessary. It is probable that the triad of high oxygen concentration, controlled respiration and a non-rebreathing valve is the method of choice in deep chloroform anaesthesia, but more work on this subject is required.

4. Renal Tissue and Renal Function.

A reduction of urine secretion is seen during all forms of general anaesthesia. The administration of morphine or barbiturates have a similar antidiuretic effect (4, 22, 38). Urine output is related, though not constantly, to renal blood flow (109), and reduced renal blood flow is the result of renal vasoconstriction. Renal blood flow and urine output fall rapidly during anaesthesia and recover rapidly as anaesthesia is lightened.

The systemic blood pressure appears to have a paradoxical effect on renal blood flow. Hypotension, either drug induced or from haemorrhage, does not reduce renal blood flow immediately.

Conversely, hypertension resulting from injection of a vasopressor reduces renal blood flow. This control of renal vasomotor tone is thought to be an intrinsic one. In prolonged hypotension this renal vasoconstriction cannot be maintained, and the renal blood flow will eventually fall (22).

Another likely factor responsible for the suppression of urine during and after surgery is the antidiuretic hormone of the posterior pituitary (117a). The action of this hormone is probably transient after anaesthesia (82), but it is active and evident (25) for a variable time after the stimulation of surgery.

On the other hand , Habif and his colleagues have demonstrated quite convincingly (38), that most operations produce minimal changes in renal blood flow.

So much for what might be called a summary of the physiological effects of anaesthesia on renal function. But what of chloroform as a so-called nephrotoxic agent? Work on this subject is sparse and thinly spread over the last fifty years. Three methods of investigation are available; namely urinalysis, renal function tests and histologic examination of the kidney.

Urinalysis. This has failed to throw any light on the matter and in both man and animals no significant alterations have been detected. Transient albuminuria occurred in roughly equal

water, given by stomach tube. He found that oliguria and anuria occurred more rapidly in the chloroformed dogs. Histologic sections of the kidneys of the etherized dogs were essentially normal, but in the dogs that had had chloroform and in those which had undergone periods of hypercarbia, changes in the tubules were evident (64).

MacNider experimented again in 1935 on dogs which were given an acute nephritis by the use of uranium nitrate. Again he found oedema and necrosis of the tubular epithelium following administration of chloroform or Gerhant's anaesthetic. MacNider therefore stated that chloroform produced not only a functional depression in the kidney,

> but the action went further and established a cytological basis for its existence by induced cell degeneration and death (65).

Conclusion.

Schmaman stated that chloroform anaesthesia had an adverse effect on kidney function and based this statement mainly on the work of MacNider (91). Like many workers of yesteryear MacNider failed to distinguish between the toxic effects of respiratory depression and those of the drugs under test. In fact the renal changes in MacNider's etherized dogs which had respiratory depression and hypercarbia, as indicated by raised blood pressure

proportions after ether and chloroform anaesthesia; on microscopic examination occasional casts, erythrocytes and leucocytes were seen (109, 80, 82). It is suggested (109) that stasis in the glomerular vessels rather than the toxic effects of the drugs is responsible for these abnormal constituents.

Renal Function Tests.

The excretion of urea is one of the chief functions of the kidney and involves the activity of both the glomeruli and the tubules in filtration and re-absorbtion. The urea clearance test is therefore a reliable index of the functional state of the kidney (117b). This test was first used experimentally by Orth and Stutzman to study the renal effects of cyclopropane, ether and chloroform, and their results indicated that none of the agents interfered with kidney function (82). More recently controlled experiments were conducted in man by Orth and Cohen, using urea clearance tests, non-protein nitrogen determinations and phenolsulphonthalein excretion tests, amongst others. This work showed that although renal function was slightly depressed in the first two or three postoperative days, this depression was a common factor of all the anaesthetics used.

Histologic examination of the Kidney.

In 1920 MacNider anaesthetized dogs with ether, chloroform and Gerhants anaesthetic, a mixture of chloroform and alcohol in

and changes in the alkali reserve, were similar to those seen in the chloroform group, which were all hypercarbic. More recent opinion states that anaesthetic drugs have little specific direct action on renal tissue (38), and this probably applies to chloroform when administered properly.

More investigation is required in this field before the question can be finally settled.

5. Cardio-Vascular System.

About two months after the introduction of chloroform anaesthesia, the first fatality was reported. This death and the many subsequent disasters, exercised anaesthetists and physiologists for many years to come.

In the case of Hannah Greener four different causes of death were postulated by four eminent men. Sir John Fife, distinguished Newcastle surgeon, who performed the autopsy stated that

> .....he attributed the fatal result in this young woman's case to some peculiarity of her constitution - not to be detected beforehand - either in the lungs or in the nervous system (24f).

John Snow thought that she died of cardiac paralysis due to overdosage (105b).

The redoubtable Sir James Simpson's contribution was the assertion that the girl died from inhaling the brandy used in

attempting to revive her (99).

Francis Sibson, in his analysis of the first four chloroform deaths, seems to have come nearest the truth. Like Snow, he thought that death was due to paralysis of the heart; that

> there is indisputably the direct action of the poison on the muscular tissue of the heart. The poison penetrates to the heart from the lungs in a single pulsation, and at the beginning of the next systole, the blood is sent through the coronary artery to the whole muscular tissue of the heart. The blood passing into the coronary artery is ..... more strongly impregnated with chloroform ..... than is the blood in any other part of the system except the lungs (94).

That chloroform can and does cause death through cardiac arrest cannot be denied. But by what mechanism? Examination of the work of our predecessors takes us a long way in attempting to answer this question.

Ten years after Sibson's observation, John Snow, in his book On Chloroform and other Anaesthetics, gave an account of the first fifty recorded deaths under chloroform anaesthesia (105c). He agreed with Sibson that death was due to the harmful effect on the heart of overdosage. Many of the cases analysed by Snow show that the patients did, in fact receive an overdose of chloroform. For example, in case 19, the conventional vaporizer being found too slow a method of induction,

> witness directed that a napkin should be folded into the shape of a cone which was applied with chloroform (105d).

This was all too effective, and in ninety seconds the patient was dead.

In case twenty, one drachm plus another thirty drops of chloroform was poured onto lint. This was held within a sponge over the patient's nose, his mouth being closed (105d). In this case, not only was the volume used excessive, but the warming of the apparatus by the anaesthetist's hand must have produced an extremely high concentration of chloroform.

In case twenty-four, a debilitated patient with advanced cancer was under anaesthesia for eight to nine minutes (105e), during which time 10½ drachms (37 ml.) of chloroform was used.

In 1864 The Royal Medical and Chirurgical Society (now the Royal Society of Medicine) appointed a committee to investigate and report on chloroform anaesthesia (24g). This committee concluded that concentrations of chloroform above four or five per cent were likely to lead to cardiac syncope, a finding that Snow had published some years before. Subsequent committees and opinions served only to confirm this view.

As a result of 430 experiments on a variety of animals, the Second Hydrabad Chloroform Commission concluded that cardiac syncope only occurred after cessation of respiration. Edward Lawrie, instigator and president of the commission, drew some rather odd conclusions from the experiments. One of these was that the fall of blood pressure and the bradycardia

seen during chloroform anaesthesia was a safeguard. He stated,

> The failure of the heart, if such it can be called, instead of being a danger to the animal, proved to be a positive safeguard, by preventing the absorption of the residual chloroform and its distribution through the system (52).

This and one or two other strange ideas tend to mar what was an excellent investigation. Critics of Lawrie have tended to abstract the few obvious absurdities and ignore the good. It is my opinion that Lawrie and his staff owe their successful use of chloroform to the fact that they adhered strictly to rules laid down in the Hydrabad report - rules that are based on common sense and which we now realize must be observed for the safe giving of any "open" anaesthetic. Also, the "Hydrabad cone" used by Lawrie resembled an ice-cream cornet, in that its vertical height was greater than its diameter. The surface area of this cone was greater than that of the contemporary Skinner or Esmarch masks, thus giving a greater dilution with air of a given quantity of chloroform.

In the same year, 1890, MacWilliam reported that, in cats, cardiac failure occured as a result of depression of the myocardium, leading to dilatation of the ventricles (66). In fact, sudden cardiac failure was the result of sudden overdosage.

Embley believed that he had demonstrated that vagus inhibition was the prime factor in the cause of death in chloroform anaesthesia (26). His experiments were performed

on heavily morphinized dogs, and his contention was that chloroform raised the excitability of the vagus mechanism, particularly during the early phase of anaesthesia. He maintained that section of the vagi or atropinization prevented cardiac arrest from chloroform - the reverse of the opinion expressed by the Hydrabad Commission. The moral of his work was that low concentrations of chloroform should be used in the early stages of anaesthesia until the critical stage of vagal sensitivity had been passed.

Goodman Levy criticized Embley's work on the grounds that the dogs were very heavily dosed with morphine, thus nullifying the conclusions about the vagal phenomenon (59 c, 58). Levy also maintained that "vagal escape" occured before cessation of the heart beat. In his articles and his book, Levy expounded his thesis on the cause of cardiac arrest during chloroform anaesthesia. In his experiments on cats, Levy found that during light anaesthesia the heart was in an "irritable" condition, with a tendency to exhibit premature or extra beats. Stimulation at this stage by surgical stimuli, intermittent administration of the anaesthetic, struggling (58) or the injection of adrenaline (57), resulted in ventricular fibrillation and cardiac arrest.

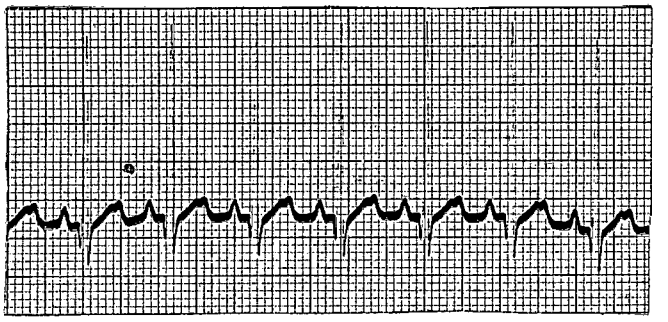
Levy correlated his experimental findings with clinical reports of fatalities, including those of his own experience and cases chronicled by John Snow. Many of these deaths had occured in the early phase of the anaesthetic, in fact, before

the start of the operation. To Levy this seemed to lend weight to his contention that ventricular fibrillation as a cause of death under chloroform anaesthesia was probably the only cause.

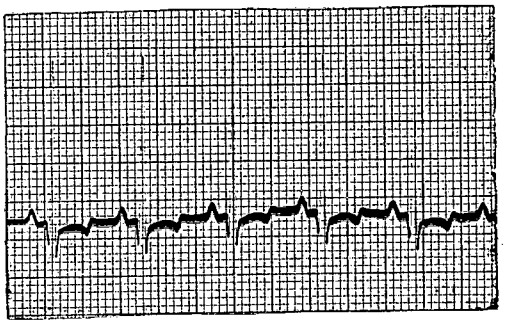
So far we have three hypotheses as to the cause of cardiac arrest under chloroform - overdosage, vagal inhibition and ventricular fibrillation during light anaesthesia. Before attempting to reach any conclusion, it is as well to review some of the more recent work. Orth and his colleagues perfused isolated turtle and rabbit hearts, exposing the perfusates to varying tensions of chloroform vapour. They showed that chloroform had a direct depressive effect on the hearts and that the rapidity of the depression was related to the concentration of the drug. Ventricular fibrillation occured twice (81a).

Similar experiments were performed with a heart-lung preparation of the dog and similar cardiac depression was observed, without ventricular fibrillation. It must be mentioned here that all anaesthetic agents cause myocardial depression, and that the isolated heart is rapidly depressed by that time-honoured, safe anaesthetic - ether (118b).

Orth then tested the effects of chloroform on intact dogs taking frequent electrocardiographs. In over three hundred inductions there was one recorded case of ventricular tachycardia during light anaesthesia, but no instance of ventricular fibrillation. Overdosage resulted in several cases of depression of ventricular and sinus automaticity,



(a)



(b)

Fig. 6. E.C.G. of dog No.9, both lead II.
(a) Systolic blood pressure, 110 mm.Hg.
(b) Systolic blood pressure, 65 mm.Hg. Note inversion of T-waves.
This E.C.G. was typical of the three recordings.

but recovery was prompt with removal of the anaesthetic and full oxygenation.

Electrocardiographs (ECG.) were made of three dogs used in my experiments with chloroform. The object of the experiments was to secure hypotension for surgery by using large, but controlled, dosage of chloroform. During deep anaesthetic little change has occured on the ECGs, and this I attribute to the fact that the animals were well ventilated and oxygenated (See figure 6).

An interesting point arising from Orth's work is concerned with vagal control. He found that if, after cardiac arrest from chloroform overdosage, the vagus trunks were infiltrated with procaine, the heart restarted very rapidly, in six or seven seconds. This seems to support Embley's work reported nearly fifty years before (26), and to refute Levy's statement that

> the heart always escapes from the vagus reflex, however long the stimulus be applied, and such a condition as permanent arrest of the heart through a vagal reflex is unknown in experimental physiology. (59d).

What about the matter of ventricular fibrillation during light chloroform anaesthesia? It will be remembered that Goodman Levy found that stimulation of the lightly anaesthetized cat caused ventricular fibrillation. This, he postulated, was caused by release of endogenous adrenaline. Likewise, injection of adrenaline into the animal caused ventricular fibrillation. Levy assumed that deaths in lightly anaesthetized humanbeings was caused

by the mechanism.

It should be emphasized that Levy's work was done entirely on cats. Meek and his co-workers conducted experiments on dogs similar to Levy's. They make the point that Levy's results could not be duplicated in the dog, probably due to a marked species difference. Injection of 0.01 mg. per kilogram of adrenaline (equivalent to about 0.7 mg. adrenaline for an average sized adult) produced ventricular extrasystoles or nodal rhythm, but not ventricular tachycardia (69).

Orth and colleagues agree that ventricular fibrillation is rare (81b).

The absorbtion coefficient of the heart for chloroform is greater than that of the brain. In consequence, the nervous conducting tissue of the heart, which has a particularly liberal blood supply, reaches equilibrium with chloroform sooner than the cardiac centre in the medulla, or any other part of the brain. While the chloroform concentration is high in the heart, the brain, and particularly the hypothalamus, is unsuppressed. The posterior hypothalamic nuclei control sympathetic response and stimulation of these nuclei promote secretion of adrenaline. It is suggested that the coincidence of a high level of chloroform in cardiac nervous tissue, plus an excessive adrenaline secretion, is responsible for arythmias leading to ventricular fibrillation. Singly, either factor is relatively harmless; together, the effect may be catastrophic.

This view, propounded by Harris (40b), is really a more involved version of the judgement of Francis Sibson about a century earlier. (See page 23).

It seems that the experimental evidence on the cardiovascular effects of chloroform is equivocal. It is now pertinent to consider recent clinical work.

Orth and his colleagues studied 52 patients under chloroform anaesthesia on whom E.C.G. tracings were made (81c). The techniques used were to-and-fro-absorbtion, open mask with air, and open mask with oxygen under the mask. The results are shown in Table 1, and it will be seen all but seven patients showed some form of arythmia. The commonest being ventricular extrasystoles and premature contractions.

TABLE I

THE CARDIAC IRREGULARITIES RECORDED IN FIFTY-TWO PATIENTS DURING CLINICAL CHLOROFORM ANESTHETIZATIONS.

Number of cases	52
No irregularities	7
Sinoauricular block	4
Sinoauricular extrasystoles	11
Auricular fibrillation	4
Auriculoventricular block	22
Auriculoventricular extrasystoles	14
Auriculoventricular rhythm	32
Ventricular extrasystoles and premature contractions	36
Slow ventricular rhythm	6
Bundle branch block	2
Ventricular tachycardia	20
Cardiac arrest	4

Since many of the patients exhibited several types of irregularities the total exceeds the number of cases.

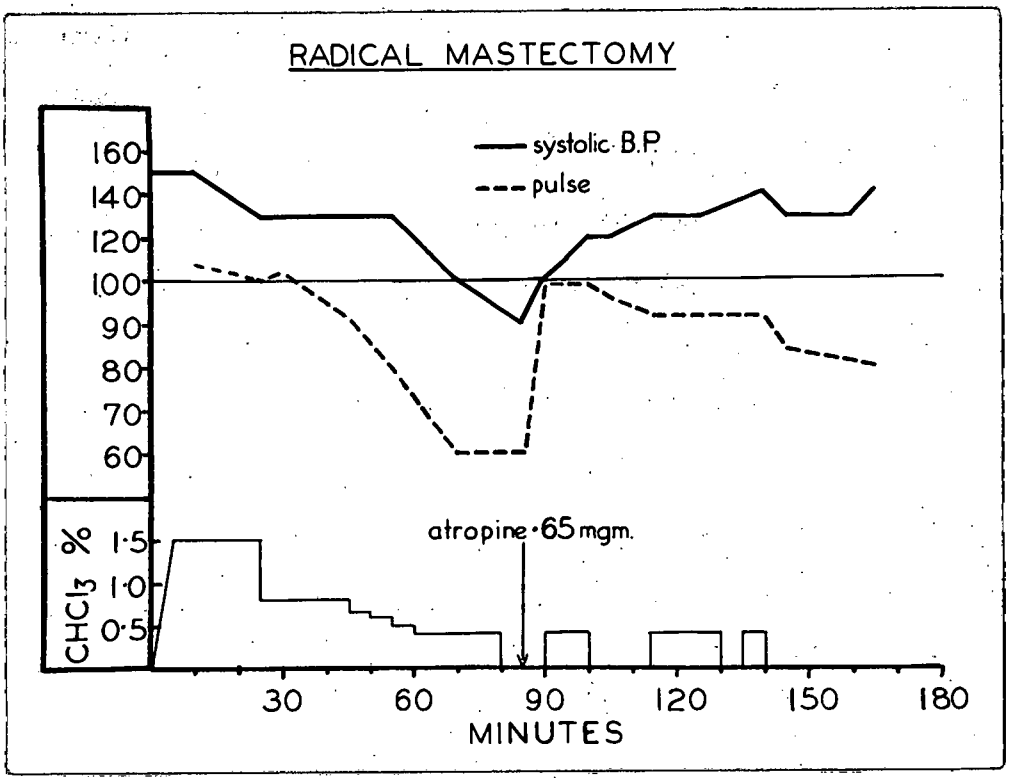

RADICAL MASTECTOMY
systolic B.P.
pulse
160
140
120
100
90
80
70
60
CHCl3 %
1·5
1·0
0·5
atropine·65 mgm.
30
60
90
120
150
180
MINUTES

Fig. 7.

In this review of 1,111 chloroform anaesthetics, four cases of cardiac arrest occurred, all probably due to overdosage. These arrests were of short duration, one case requiring cardiac massage. No case of ventricular fibrillation was noted in this series.

Hill conducted an E.C.G. survey of 16 patients under chloroform anaesthesia and his findings were similar to those of Orth, namely, gross and varied disturbances of rhythm in half his patients (44). These irregularities were not usually clinically obvious, occurred in the second stage, particularly in association with struggling and anoxemia. They were transient and were generally abolished by deepening the anaesthesia. Hill suggests that these deviations of rhythm correspond to the "pre-fibrillation" stage observed by Levy during light chloroform anaesthesia in the cat; that they could, in fact, be the precursors of ventricular fibrillation in man.

In the local series of chloroform anaesthetics, from Groote Schuur Hospital, E.C.G. monitoring was not done and we have relied on clinical signs. It will be seen from Table 3 (see appendix), that of the 707 cases reviewed, bradycardia of less than sixty beats per minute occurred in 63 patients, or 9 per cent of the total. It is also interesting to note that the frequency of occurrence of bradycardia seems to be related to the length of operation. Figure 7 shows a typical gradual decline of pulse rate and the prompt correction caused by injection of atropine.

A more exact representation of this phenomenon is demonstrated by Bamforth and his colleagues, who estimated the relative fall in pulse rate (5). They found that 22 per cent of their patients under chloroform anaesthesia sustained a bradycardia of 10 - 20 per cent less than the starting pulse rate. What is more significant, an equal number had a decline in pulse rate of between 21 to 40 per cent. These authors affirm that slowing of the pulse is often a guide to the depth of anaesthesia, but with this I cannot agree. It seems more likely that chloroform has a "vagus inhibition" effect on the heart, but this is not confined to chloroform (5).

Johnstone has shown that in patients not premedicated with atropine, cardiac inhibition to the point of standstill may occur when cyclopropane or ether is used. He stated that the inhibition varied directly with the irritancy and concentration of the vapour; that the anaesthetic stimulated sensory nerve endings in the lungs with resulting cardiac inhibition through the pulmo-cardiac reflexes. Atropine prevented vagal inhibition, but arythmias were pronounced when carbon dioxide was allowed to accumulate (50).

Although Johnstone did not use chloroform in his work, there is no reason to doubt that the same would occur with that drug. In fact, the local experience cited in the preceeding paragraphs shows that chloroform is particularly vagomimetic.

It would seem that chloroform could cause cardiac arrest through the mechanism described. Premedication with atropine did not come into general use until the turn of the century (7, 101), and till recently chloroform anaesthesia was associated with under-ventilation and carbon dioxide accumulation. It is not difficult to suppose that these two factors can and did lead to fatalities (87, 84).

As regards cardiac irregularities other than bradycardia, we have found these to have occurred in 1.5 per cent of all cases. (Table 4, see appendix). An analysis of the eleven cases recorded shows that in five of these there was pre-disposing cause for the irregularity.

In our series, the sum of bradycardias and other irregularities that were clinically detectable was 10.5 per cent of the total.

Blood Pressure.

Arterial blood pressure varies as the product of the cardiac output and the peripheral resistance. Chloroform has a direct depressant effect on cardiac muscle and conducting tissue and also on the smooth muscle of the peripheral vessels. During inhalation of moderate concentrations of chloroform - 1.5 - 2 per cent - the cardiac output (10) and the peripheral resistance are progressively decreased (118c, 114a, 81b).

There is little doubt that a fall in blood pressure during chloroform anaesthesia is due to relative overdosage, and it is this fact that has led some anaesthetists to state dogmatically

that chloroform should not be used for more than one hour (53).

Table 5 (see appendix) is an analysis of the patients in the Groote Schuur Hospital series who showed a fall of blood pressure of 10 mm.Hg. or more. This occured in 156 patients, or 22 per cent. It will be noticed that 45 of these patients who had a drop in blood pressure were given sodium pentothal. The inference is obvious but it is uncertain whether the fall of blood pressure was due to pentothal or to excess chloroform, or to both. In the fifth column of Table 5 are recorded clinical notes. It will be seen that in four cases chloroform was used specifically to secure hypotension, whilst in others there were complicating factors calculated to cause hypotension. It will also be noted that a blood pressure drop occured in 21 per cent of patients when anaesthesia lasts less than one hour, but this figure was nearly doubled in operations of over an hour.

Table 6 is a more detailed analysis of the patients who had a fall of blood pressure. The values are reported as a percentage change from the preanaesthetic systolic blood pressure reading. It will be seen that 10 per cent of all patients had a fall of blood pressure of 20 per cent or less, whilst 12 per cent had a fall in blood pressure of more than 20 per cent of the starting level. The figures agree very closely with those of the much smaller series of Bramforth and his colleagues (5). The figures in Table 6 also show the relationship between the

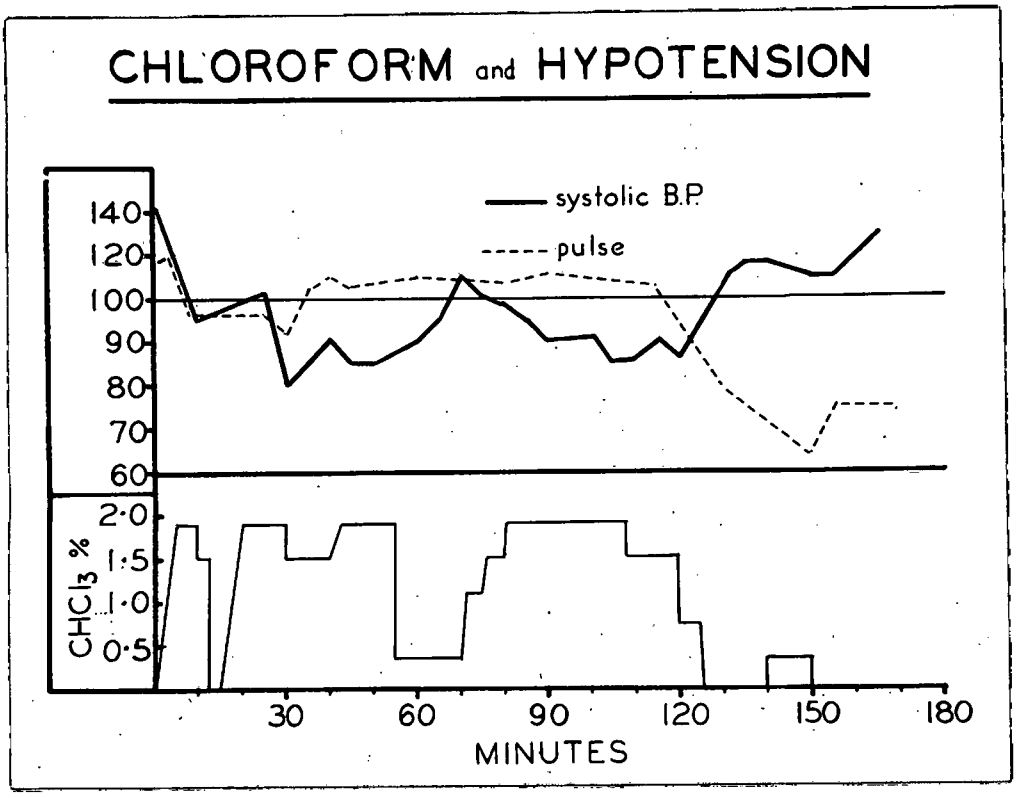

CHLOROFORM and HYPOTENSION
systolic B.P.
pulse
140
120
100
90
80
70
60
2·0
1·5
1·0
0·5
CHCl3 %
30
60
90
120
150
180
MINUTES

Fig. 8.

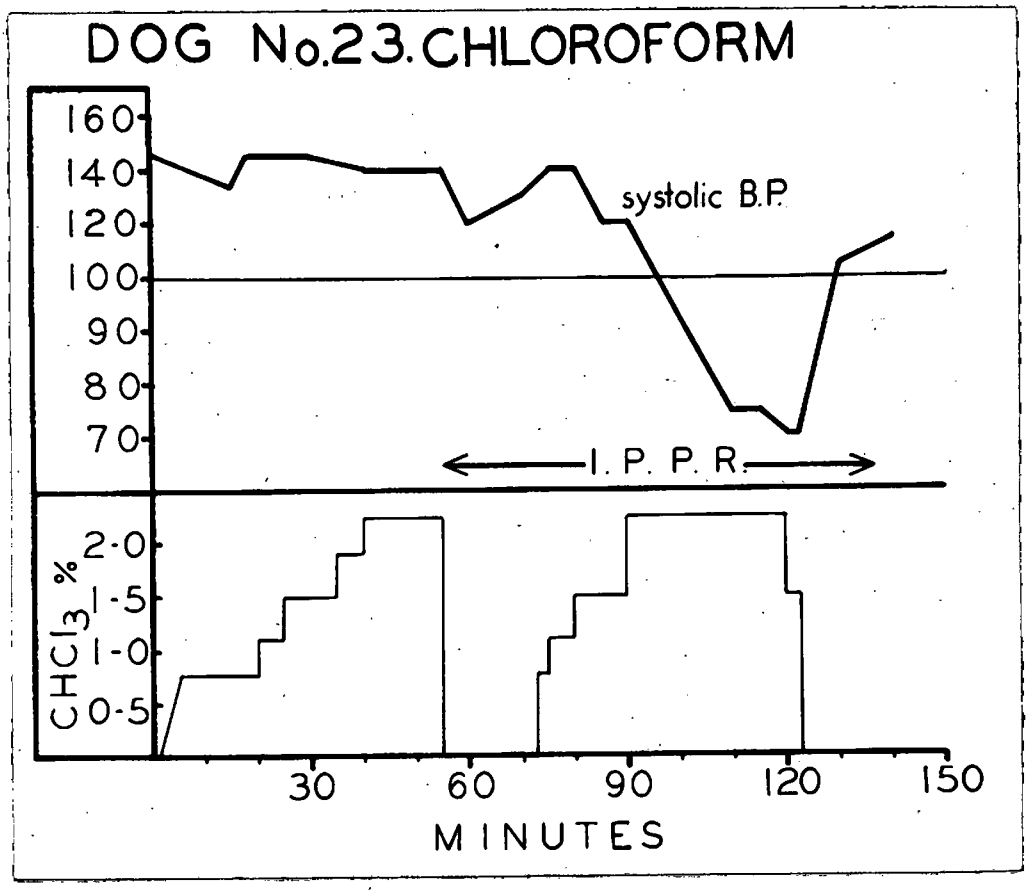

DOG No.23. CHLOROFORM
160
140
120
100
90
80
70
systolic B.P.
I. P. P. R.
2·0
1·5
1·0
0·5
CHCl3 %
30
60
90
120
150
MINUTES

Fig. 9.

duration of anaesthesia and fall of blood pressure.

In nine patients chloroform was used successfully to produce hypotension and reduce bleeding.

Case History K.G., aged 42, weight 120 lbs.
Operation : amputation of penis and block dissection of inguinal glands.
Premedication: morphine, 10 mg, atropine 0.65 mg.
Agents : sodium pentothal 2.5 per cent, 250 mg. Nitrous oxide, 70 per cent, Oxygen 30 per cent., and chloroform through a precision vaporizer.
Spontaneous respiratory, and Magill circuit.
Approximately 650 ml. of blood was given during the operation.

It will be seen that the systolic pressure record is a "mirror image" of the chloroform concentration record (See Figure 8). When the concentration of chloroform vapour was increased, the blood pressure declined, and vice versa.

This method of producing hypotension seemed to have two distinct advantages. It was rapidly reversible, and no additional drugs were used. On investigating the matter experimentally, I found that in thirteen of the fourteen dogs used, hypotension could be secured satisfactorily. The dog's vasomotar control appeared to be more robust than that of the humanbeing and it was necessary to use intermittent positive pressure respiration (IPPR) and moderate hyperventilation in order to reduce the blood pressure satisfactorily (See Figure 5, Dog 9, page17). In dog 23, the same rapid fall of blood pressure was seen coincidental with increase in chloroform (See Figure 9). It is interesting to observe in this and

other experiments that IPPR and hyperventilation with nitrous oxide and oxygen only did not cause a decline in blood pressure. Dog 23, in fact, woke up during this manoeuvre.

My experimental work on dogs showed that

(1) hypotension could be produced by using chloroform in concentrations up to 2.2 per cent;

(2) the level of blood pressure could be controlled by altering the concentration of chloroform;

(3) hypotension could be produced and controlled by using ether or fluothane in the same way;

(4) when using chloroform under the conditions described, ECG changes were minimal, being depression of T-wave, a sign of myocardial insufficiency - dog 9 see Figure 6. There was no alteration in ventricular complexes as described by Orth;

(5) liver damage was marked when chloroform was used for hypotension, but did not occur when hypotension was not secured. This aspect is discussed more fully in the relevant section.

Chloroform and adrenaline.

Case History: A.D., a woman, aged 59. For nasal polypectomy. This patient was in good health : her pre-operative blood pressure was 160/90 mm.Hg. Premedication : pethidine 75 mg., atropine 0.65 mg. given two hours previously. The nose had been packed with gauze soaked in adrenaline and cocaine. Immediately before operation the pulse rate was 104 per minute, and systolic blood pressure

200 mm. Hg. The patient was induced with nitrous oxide, oxygen and chloroform, the concentration of the latter being gradually increased to 2 per cent.

After about ten minutes pulsus alternans was observed. This developed into a tachycardia (probably ventricular) of about 200 beats per minute. The chloroform was turned off and pure oxygen given. The sequence of arythmias was reversed - normal sinus rhythm rapidly ensued. Recovery was complete and subsequent ECG was normal.

It is seen that cardiac function deteriorated in stages to ventricular tachycardia and at this stage circulation was failing. Had the anaesthetic not been stopped and oxygen given, ventricular fibrillation would have been a distinct possibility.

The normal human physiological response to an injection of adrenaline is well known. Recently in South Africa a death has been reported following local infiltration of as little as two minims of 1:1000 adrenaline during a thyroidectomy (51).

Oliver and Schafer were the first to note that the injection of adrenal extracts into experimental animals caused inhibition of nodal rhythm together with tachycardia or fibrillation of the ventricles (78).

Ventricular fibrillation depends on increased sympathetic activity and an increased blood level of adrenaline or no adrenaline. There is a probable increase in the irritability of the ventricular muscle itself.

The adrenaline may be liberated by the adrenal medulla, or may be introduced artificially.

Death from ventricular fibrillation is associated with cardiac anoxia. If fibrillation persists until the cardiac reserve of oxygen is depleted the heart will fail to contract again. If fibrillation passes off before the oxygen in the cardiac tissue is used up, normal activity may be resumed (36).

Clinical evidence of deaths following the use of adrenaline during chloroform anaesthesia are not lacking (36, 59e, 28), and we have already seen that ventricullar fibrillation can be produced in cats by this means, though not so easily in dogs (69, 72). What is the position with regard to endogenous adrenaline?

Goodman Levy maintained that it was this brisk release of adrenaline during excitement or stimulation which had such a detrimental effect on a heart made "irritable" by chloroform. Other workers have shown that in the human patient ventricular tachycardia occurs early in chloroform anaesthesia (43, 44) or may occur at rest in the nervous patient (41). Others believe that the anxiety of the patient leads to increased adrenaline secretion, sensitizers the myocardium and is one of the conditions predisposing to cardiac arrest (90).

The vital question is, how much adrenaline can a human patient secrete? Cannon has estimated this amount to be between 0.001-0.005 mg. per kilogram per minute (17). If these figures are reliable it would mean that sympathetic stimulation for one

minute in a 70 kilogram patient would produce at least 0.07 mg of adrenaline, not very much. At most, 0.35 mg. which is a large amount in a short time.

The adrenaline which supposedly appears in the heart comes from two sources - the sympathetic excitor cells and the adrenal medulla. These structures are reputedly controlled by hypothalamine nuclei via efferent sympathetic fibres. Theoretically, then, any interruption of the efferent sympathetic fibres should abolish cardiac irregularities. Experimental work shows this to be so. Removal of the stellate ganglion from cats in which irregularities had developed under chloroform abolished those irregularities. On the other hand, stimulation of the ganglia brought on the irregularities. Section of the second, third and fourth thoracic nerves likewise abolished arythmias. Section of the cord at the fifth thoracic segment - whence arises the sympathetic outflow to the adrenal - prevented the production of extrasystoles on stimulation of the sciatic nerve. Finally, when the hypothalamic region was isolated, extrasystoles which had developed during chloroform anaesthesia were abolished. Conversley, stimulation of this hypothalmic area produced extrasystoles when they were not present before. When the suprarenals were removed, stimulation of the hypothalamus still produced irregularities (12).

This experimental work is a practical verification of the views of Harris, stated earlier in this essay. Namely, that

due to the rapid uptake of chloroform by cardiac tissue, excess of that drug and of adrenaline are in the same place and acting at the same time, and before the "sympathetic tap" - the hypothalamus - has been "turned off", or depressed by anaesthesia.

Conclusions.

This chapter is the backbone of the essay, and there are several conclusions to be drawn.

1. Chloroform has a vagomimetic effect. Adequate atropine should be given with premedication.
2. Adrenaline should not be used in the presence of chloroform anaesthesia. Nevertheless, I have given a number of chloroform anaesthetics during which a small amount of a weak solution of adrenaline 1:300,000 has been infiltrated for haemostasis. There have been no untoward effects.
3. Chloroform can be used successfully to obtain hypotension, but carries its own risk of liver damage in addition to the risks pertaining to hypotensive techniques in general.
4. It cannot be stated with certainty which is the most likely cause of cardiac arrest during chloroform anaesthesia. My view is that overdosage is probably the main offender, with vagal inhibition coming second. I do not think that ventricular fibrillation is as frequent a cause of death as was supposed (3). As far as cardiac irritability goes, the

human heart occupies a position intermediate between the cat and the dog (106). Injection of adrenaline during chloroform anaesthesia may well cause ventricular fibrillation; and hypoxia or hypercarbia, by increasing adrenaline production, may well predispose to the condition.

6. The Liver.

Pharmacologists state that chloroform is a powerful hepatotoxin and that repeated doses can cause altered liver function, or liver failure and death (34).

Casper is reputed (108, 118d) to have been the first to report on delayed chloroform poisoning, in 1850. However, perusal of Casper's work (18) shows that what he was most probably reporting were the delayed effects of and death from cerebral anoxia. In addition, two of his three cases were complicated by severe infection.

More precise accounts of delayed chloroform poisoning were given by Guthrie (37) in 1903 and Telford and Falconer in 1906 (108). Willcox, in 1931, delivered the Lumleian Lectures on toxic jaundice and presented an excellent illustration of the histologic changes in the liver of a case of delayed chloroform poisoning (116).

The deaths occurred mainly after operations on children and followed a similar clinical pattern ; namely vomiting, cerebral irritation, pyrexia, collapse and deepening coma.

An almost constant finding at autopsy was a yellowish-brown discolouration of the liver with an abundance of visible fat. Microscopically, central cellular necrosis was seen, and perilobular fatty infiltration.

Beesley made the important observation of the coincidence of persistent postoperative acetonuria and delayed chloroform poisoning (8). The patients described by him died in a state of extreme acidosis, with a marked smell of acetone on the breath. The children described in these papers were operated on for the correction of the deformities of rickets or tuberculosis, or the scraping and draining of tuberculous abscesses. The acute infective condition predominating then was acute appendicitis, and it must be remembered that in those days laparotomy was not performed for this condition before abscess formation had occurred - at least, not in Europe. All these conditions presuppose either a state of malnutrition or chronic ill health, or toxicity and temporary starvation.

In starvation the stress of metabolism falls on the fat in the depots and, as lipotropins are not available in adequate amounts, fat accumulates in the liver (117d). This excess of fat directly depresses the functional activity of the liver cells, and the swollen cells compress the sinusoids, reducing the blood supply. This explains why the necrosis seen in liver poisoning is central; that is, becomes more marked nearer the central hepatic vein.

It would appear that a liver depleted of protein and carbohydrate and consequently loaded with fat, is susceptible to damage by an agent like chloroform. For not only has chloroform a high fat solubility but the liver cells are at the time partially anoxic.

It has been shown experimentally that this is the case and that the sulphur containing amino-acids, methionine and cystine afford most protection. Miller and Whipple showed that protein-depleted dogs submitted to chloroform anaesthesia succumbed to liver failure; those given methionine shortly before anaesthesia survived (71). These workers also showed that methionine given within four hours after chloroform anaesthesia protected the liver.

Goldsmith and his co-workers have shown that in rats a high carbohydrate diet will also protect the liver to a certain degree against chloroform poisoning, probably by its protein sparing action (33).

It is pertinent to consider at this stage the blood supply of the liver. The organ receives blood from two sources, the hepatic artery and the portal vein. The hepatic artery is small in relation to the size of the organ it supplies, conveying as it does about 20 per cent of the volume of blood passing to the liver (117e, 67, 55). It has been estimated experimentally that the portal vein supplies from 62 to 72 per cent of the oxygen taken up by the liver (67,61,93).

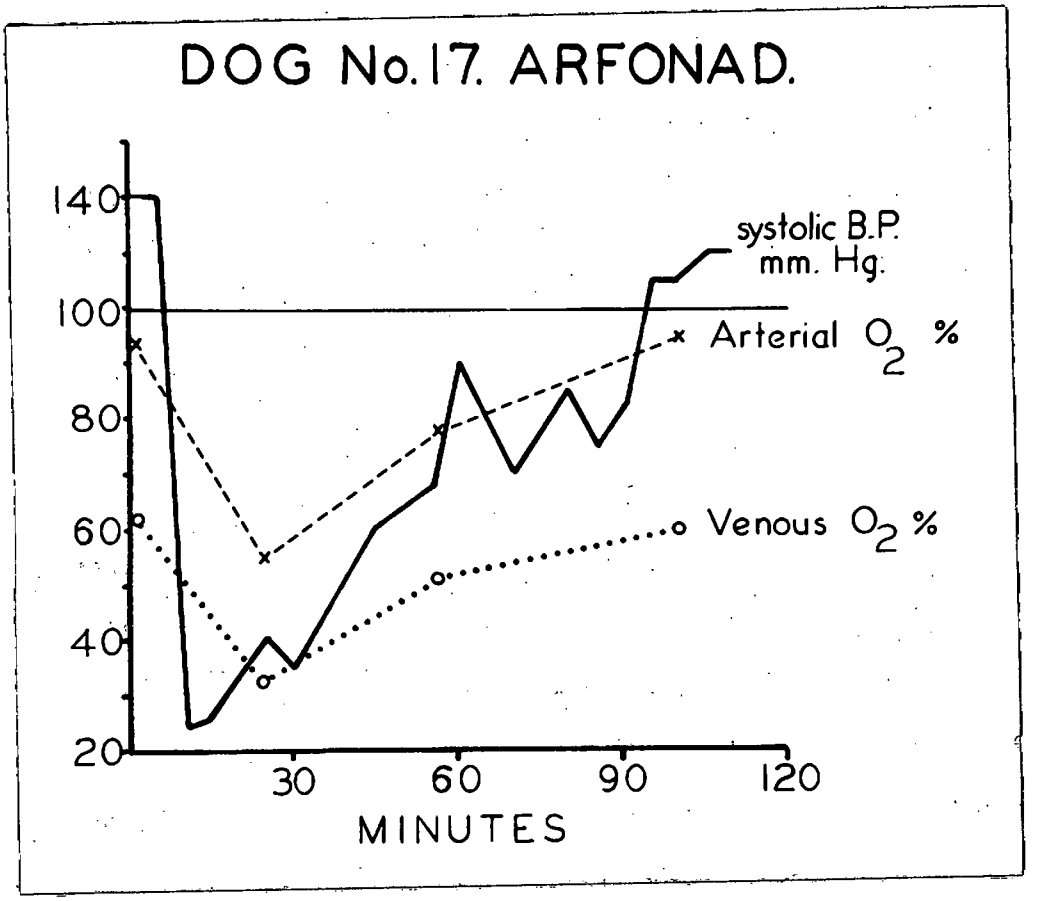

DOG No. 17. ARFONAD.
140
100
80
60
40
20
30
60
90
120
MINUTES
systolic B.P.
mm. Hg.
Arterial O_2 %
Venous O_2 %

Fig. 10.

The figures are dependent on the blood pressure and oxygen saturation. It will be seen, then, that the liver depends mainly on venous blood for its supply of oxygen. So that any reduction in oxygen tension, caused either by hypoxia or hypotension, will reduce oxygenation of liver cells and cause liver damage (2).

Goldschmidt and his colleagues have demonstrated that the necrotizing effect of chloroform is largely prevented by volatilizing the anaesthetic with oxygen (32). These workers found that when oxygen was used as a vehicle for chloroform, as opposed to air, the arterial oxygen saturation increased from 87 per cent to 100 per cent, and the portal vein oxygen saturation from 59 per cent to 81 per cent.

I have shown experimentally that in dogs a severe degree of hypotension drastically decreases both the arterial and venous oxygen saturation. A glance at Figure 10, Dog 17, will show that the curves for blood pressure, arterial and venous oxygen saturation follow a similar pattern. In this experiment hypotension was induced with trimetaphan (Arfonad) and the animal was breathing spontaneously through a Ruben non-breathing valve. Venous blood samples were taken from the inferior vena cava close to the right atrium. The coefficients of utilization of oxygen of the four samplings were 27, 43, 35 and 26 per cent respectively. The normal is about 26 per cent.

DOG No. 6 - CHLOROFORM

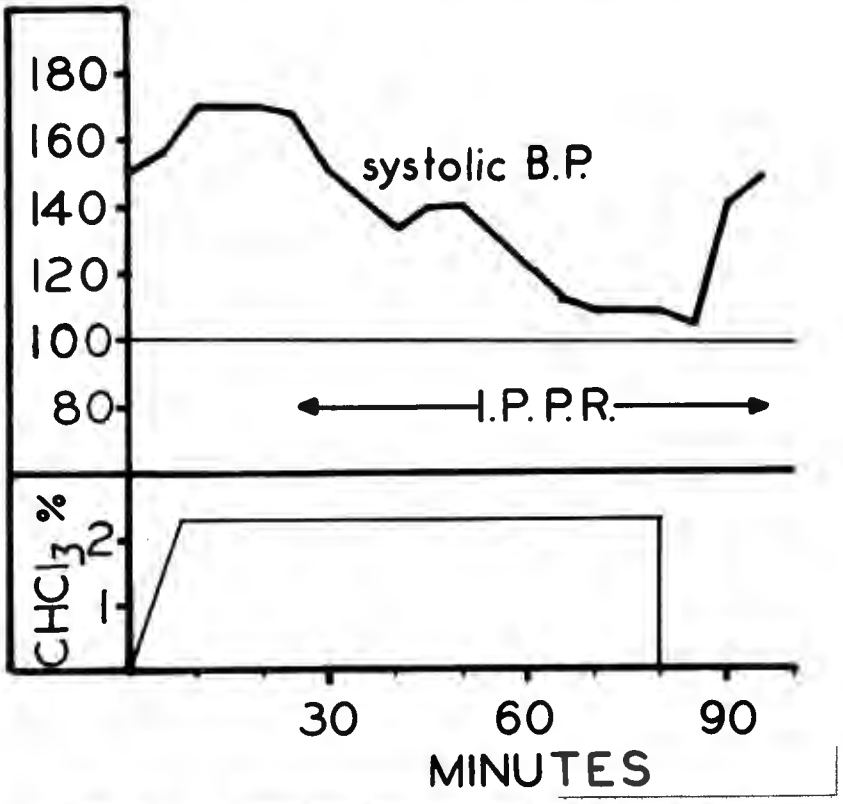


Fig. 11. Hypotension was not obtained in this animal.

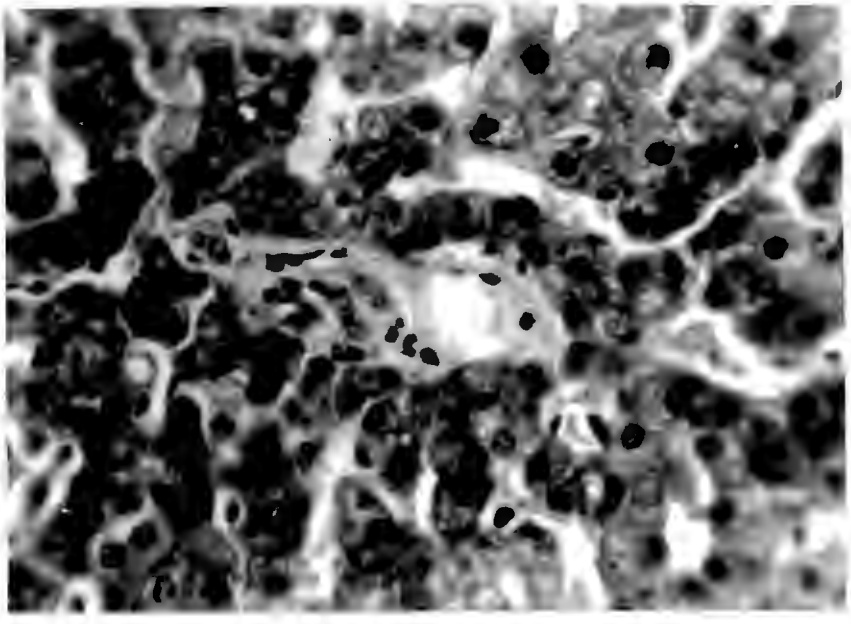


Fig. 12. Liver of Dog No. 6. Cellular structure is normal. x400.

Under the conditions demonstrated in this animal it must be supposed that the liver underwent a considerable degree of stagnant anoxia. A biopsy of Dog 17's liver taken two days after the experiment shows no histologic change. A biopsy taken on the ninth day was likewise normal.

Further work showed that dogs rendered hypotensive by overventilation with ether or halothane, or by injection of arfonad, suffered no liver damage as shown on histologic examination.

But the dogs in which hypotension was induced by hyperventilation with chloroform we see a different picture. Fourteen such experiments were performed, and hypotension was induced thirteen times. The last eleven consecutive dogs underwent post-anaesthetic liver biopsies. Every liver, with the exception of that belonging to the dog who had not sustained hypotension, showed signs of central necrosis ranging from 90 per cent to 30 per cent distruction. The liver of the dog in which hypotension could not be induced was virtually normal (See Figures 11 and 12). One dog died within 24 hours of anaesthesia, showing signs of early and severe liver damage.

The blood pressure record of a chloroformed dog is illustrated in Figure 5, Dog 9. A histologic section of this dog's liver is shown in Figure 13. It will be seen

that the organ sustained central necrosis of about 30 per cent, in addition to hydropic changes. There is also evidence of mitotic activity, indicating cell regeneration. Liver biopsy made on the ninth day shows restitution to normal, with suspicion of early fibrosis (see Figure 14). The necrosis of liver tissue seen in this example is typical of the other chloroformed and hypotensive dogs, but is less severe than most.

Clinical evidence of the harmful hepatic effects of chloroform in the presence of hypoxia and hypercarbia is seen in a report on seven open thoracic operations under chloroform anaesthesia. In four of the patients described, marked hepatic damage developed, severe enough to cause the death of two. In these four cases there was evidence of hypoxia and hypercarbia during operation (95).

The early reports of delayed chloroform poisoning should now be scrutinised in the light of recent work. Many of these deaths occurred in children who were in poor nutritional state, toxic or temporarily starved. Beesley was on the right track when he drew attention to the fact that the majority of deaths occurred in patients who were acidotic (8), that is, in those who were depleted in carbohydrate and protein, and whose livers were loaded with fat. The anaesthetics were given by the open drop or draw-over methods, without additional oxygen. Intravenous therapy with glucose or protein was not

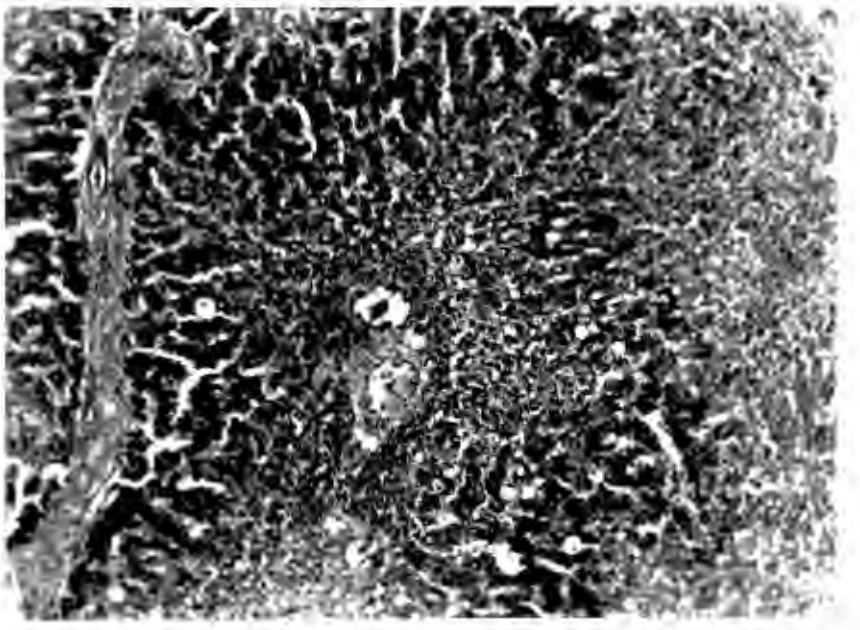


Fig. 13. Liver of Dog. No. 9., second post-anaesthetic day. Note central necrosis and cell infiltration. x100.

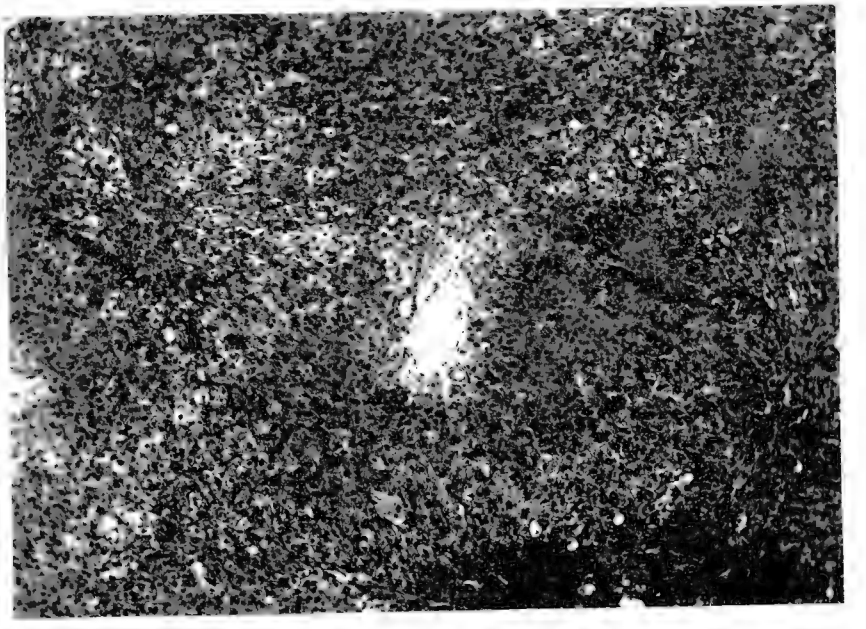


Fig. 14. Liver of Dog No. 9., ninth day. Restitution to normal is almost complete. Signs of early fibrosis. x100.

available at that time. Under these conditions, is it to be wondered at that profound liver damage occurred?

With modern anaesthetic methods, control of chloroform concentration and avoidance of hypoxia, gross derangement of liver function should not occur. Hepatic damage, as estimated by liver function tests, occurs in approximately 50 per cent of all patients who undergo major surgery (100). When optimum gas concentrations are maintained in the tissues there is little to choose between hepatic damage occurring after chloroform or any other form of anaesthesia (86, 85, 74, 79).

Himsworth observed that subclinical cases of hepatitis have been noted, and, as hepatitis is usually a transient condition, liver damage is rarely suspected in man in the absence of jaundice. It is therefore likely that in man liver damage after exposure to hepatotoxins is commoner than is realized (45).

In the series of cases of chloroform anaesthesia from Groote Schuur Hospital one case of postoperative jaundice occurred. In retrospect this patient was judged to have been in the pre-icteric stage of infective hepatitis before the anaesthetic. The outcome was satisfactory (47).

Chloroform anaesthesia can be eminently suitable for obstetric operations. The question arises whether or not the agent can cause liver damage in the foetus. It has been

shown that while chloroform anaesthesia will kill a protein depleted pregnant bitch, the livers of the pups remain quite unaffected (71). The biological law that the needs of the foetus take precedence over those of the mother is observed in this instance, for apparantly the foetus in utero extracts sulphur from the mother's liver in the same way that it extracts iron. Up to the fourth week after birth, pups have an extraordinary liver tolerance to chloroform. In early life the liver is a blood-forming organ and blood islands are present in the liver lobules. It is thought that this endogenous protein also protects the liver in the foetus and pup, but the true explanation is not yet known for certain.

Conclusions:-

Chloroform is a potential hepatotoxin. It should not be used under the following circumstances :-

1. When there is liver damage or the possibility of liver damage.
2. In cases of carbohydrate or protein depletion, such as marked malnutrition, starvation or prolonged vomiting. For example the patient with obstructing neoplasm of the oesophagus or one who has hyperemesis gravidarum would be unsuitable subjects for chloroform. A knowledge of the patient's condition over the previous few days will warn the anaesthetist of the possibility of liver damage (92).

3. In the presence of tissue anoxia such as caused by hypotension or severe haemorrhage.

In the presence of liver hypoxia chloroform has a marked necrotizing effect on the liver which is not seen under similar circumstances when ether or halothane are used.

CHAPTER 3.

METHODS OF ADMINISTERING CHLOROFORM.

> Is there any thing whereof it may be said, See, this is new? It hath been already of old time, which was before us.
>
> Ecclesiastes, Chap.1., 10.

The invention of anaesthetic apparatus has always been the delight of the gadgeteer and experimenter. Chloroform has been the inspiration of an incredible number of inhalers, some intrigueing and many bewildering. But it is beyond the scope of this work to describe these in detail, interesting though they may be. Instead the three main types of chloroform inhaler will be mentioned and it will be seen that the basic principles of the past are still applied in the administration of chloroform to-day.

The Mask Inhaler.

The earliest example of this type was that described by Sir James Simpson. Several drachms of chloroform were poured onto a cloth folded into layers, this being laid over the patient's face. Simpson modified this method in 1860 by dropping the chloroform slowly onto a single layer of cloth held so as to form a mask over the face.

Snow's criticism of the "folded cloth" method was that it was quite impossible to control the amount of chloroform inhaled (104) and he made the point that sudden death could occur before the patient became insensible. Nevertheless, it was by dropping chloroform onto a handkerchief that Snow induced analgesia for Queen Victoria during the birth of Prince Leopold in 1853.

In 1862 Thomas Skinner introduced his wire framed mask. This was the forerunner of many similar masks, including Esmarch's chloroform mask (1879) and the famous Schimmelbusch mask, designed in 1890 and still in active service.

The quantity of chloroform vapour inhaled from a mask is uncertain as it depends on many variables - the area of the cloth, the nature of the material, the amount of chloroform applied, the temperature, and the size of the breath taken by the patient.

Yet this method of administering chloroform, now over one hundred years old, is still in use to-day, particularly in domiciliary midwifery. It is doubtful if a more satisfactory way has been found of relieving the discomfort of the crowning head.

The Percentage Inhaler.

This type of inhaler is designed to deliver chloroform vapour of known strength, regulated by mechanical means. The

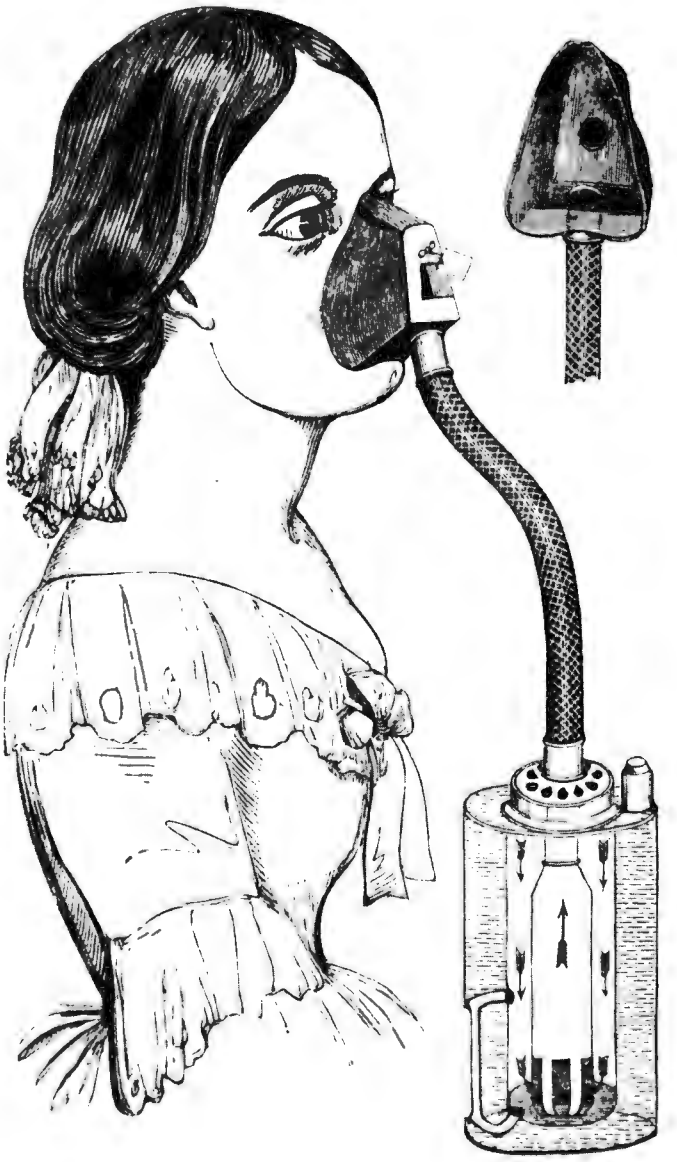


Fig. 15. Snow's chloroform inhaler.

carrier gas is either air or nitrous oxide and oxygen, the last two being supplied from cylinders under pressure. Until recently none have been entirely satisfactory.

The percentage inhaler may be divided into two types:-

1. "Suction" or "draw over" types.

One of the more satisfactory early vaporizers of this type was that designed by John Snow in 1848. It consisted of two cylinders, the outer one a water jacket. The inner cylinder contained a measured amount of chloroform which was evaporated from coils of blotting paper. The apparatus communicated with the patient by means of a rubber tube and mask (see Figure 15). This vaporizer was designed to give a maximum of five per cent chloroform (42a).

One of the most accurate of the percentage inhalers must have been that invented by Clover. This historic apparatus was really a "draw over" type of inhaler in reverse, as a calculated amount of chloroform vapour and a measured amount of air were mixed in a bag, from which the patient inhaled. The apparatus delivered chloroform vapour of up to four per cent (62). Despite its bulk, Clover used his machine constantly for six or seven years and it was adopted by several of the larger London hospitals (24h).

At the turn of the century, Vernon Harcourt introduced his inhaler (see Figure 16). His machine was fitted with

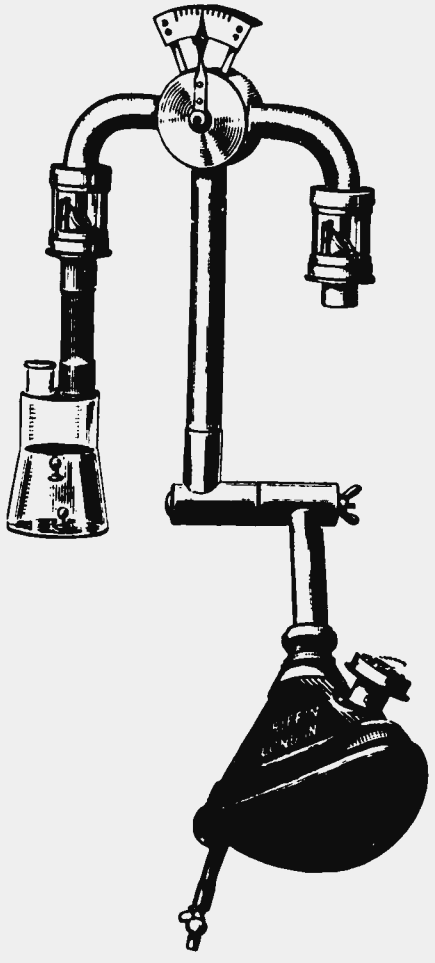


Fig. 16. Vernon Harcourt's chloroform inhaler.

Fig. 17. E.M.O. inhaler.

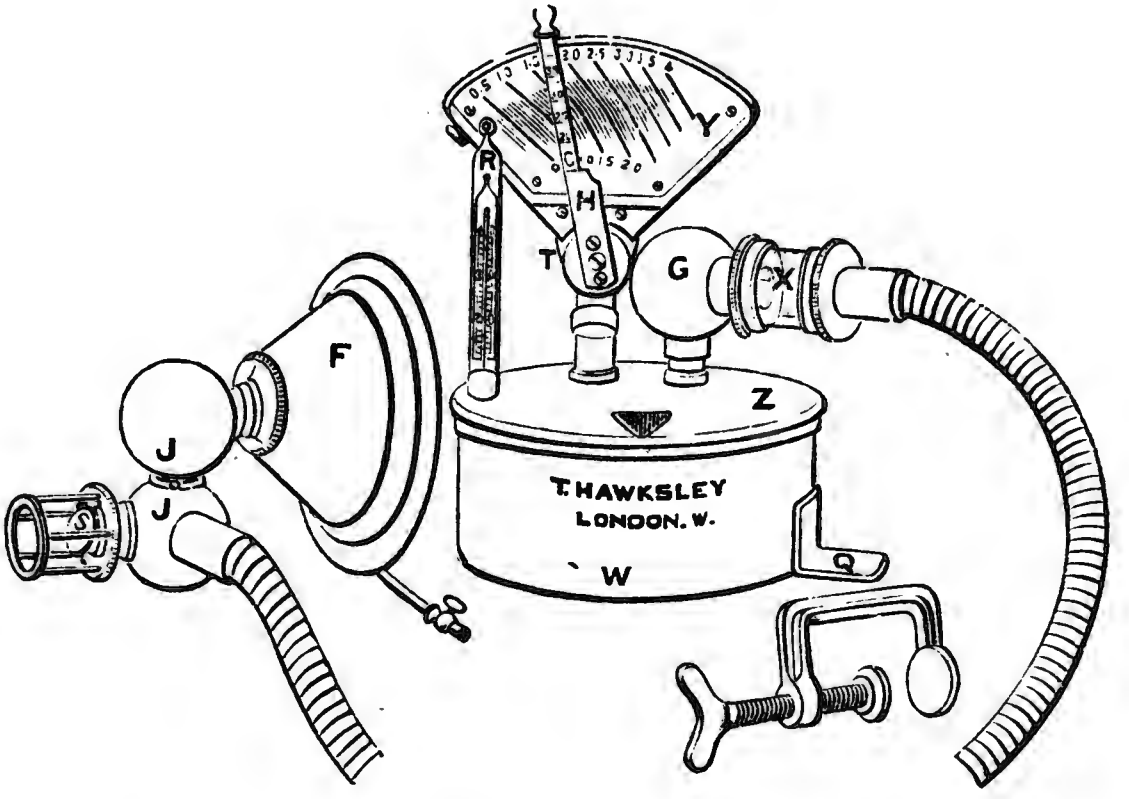


Fig. 18. Levy's regulating chloroform inhaler, 1905.

many ingenious gadgets, including a stopcock with reciprocal apertures to control the amount of the inhaled air passing over the surface of the chloroform. The temperature was estimated and regulated by two small specific gravity beads floating in the chloroform. To compensate for evaporation, the chloroform bottle was conical so that as the chloroform level sank the surface area presented to air was increased (39). This vaporizer was supposed to limit chloroform to two per cent, but inaccuracies undoubtedly occurred especially if it was agitated (59f).

The modern counterpart of these early draw over inhalers is the E.M.O. inhaler. In this machine the concentration of anaesthetic vapour is controlled by a thermostat. Originally designed for ether, it is also available calibrated for chloroform. Except for the thermostat the E.M.O. inhaler is similar in design and function to Levy's chloroform inhaler, invented in 1905 (56) (see Figures 17 and 18).

2. "Blow over" or "ad plenum" type.

In this type of inhaler air, or a mixture of gases is forced by pressure through a chloroform vaporizer. The Junker's inhaler, which appeared in 1867, is the best known early example. A hand bellows pumped a stream of air through a length of tubing into a graduated chloroform flask. Another tube led the mixture from the flask to the patient. One of the drawbacks was that if the afferent and efferent tubes were

Fig. 19. Hewitt's modification of Junker's inhaler.

wrongly connected, the patient was likely to receive a squirt of liquid chloroform. This led to several fatalities and Hewitt modified the inhaler to obviate this (42b). He led the efferent tube back through the afferent tube, as shown in Figure 19.

An ingenious but involved "anaesthetizing machine" was described by Raphael Dubois in 1891. A measured volume of air was drawn through an evaporating chamber containing a measured volume of chloroform. The vapour was stored in a "gasometer" and blown to the patient. The drawing and pumping components, worked by crank, were mounted on the "gasometer". The machine was graduated to supply 1.2, 1.6 and 2 per cent of chloroform vapour (see Figure 20). One of the disadvantages of the early "blow over" inhaler was that a high flow of anaesthetic vapour had to be maintained - about 30 litres per minute. If the flow rate fell off, the patient breathed a large proportion of fresh air. The anaesthetist using the Junkers or Dubois inhaler had to pump or crank with great vigour and without pause during the induction. These two machines were, of course, forerunners of the familiar Boyle's machine. Until the advent of Boyle's machine, with its reservoir attachment, the open mask method must have been the easiest and most practical way of administering chloroform.

Since the introduction of chloroform anaesthesia, one of the obstacles to its use was the lack of reliable and delicate

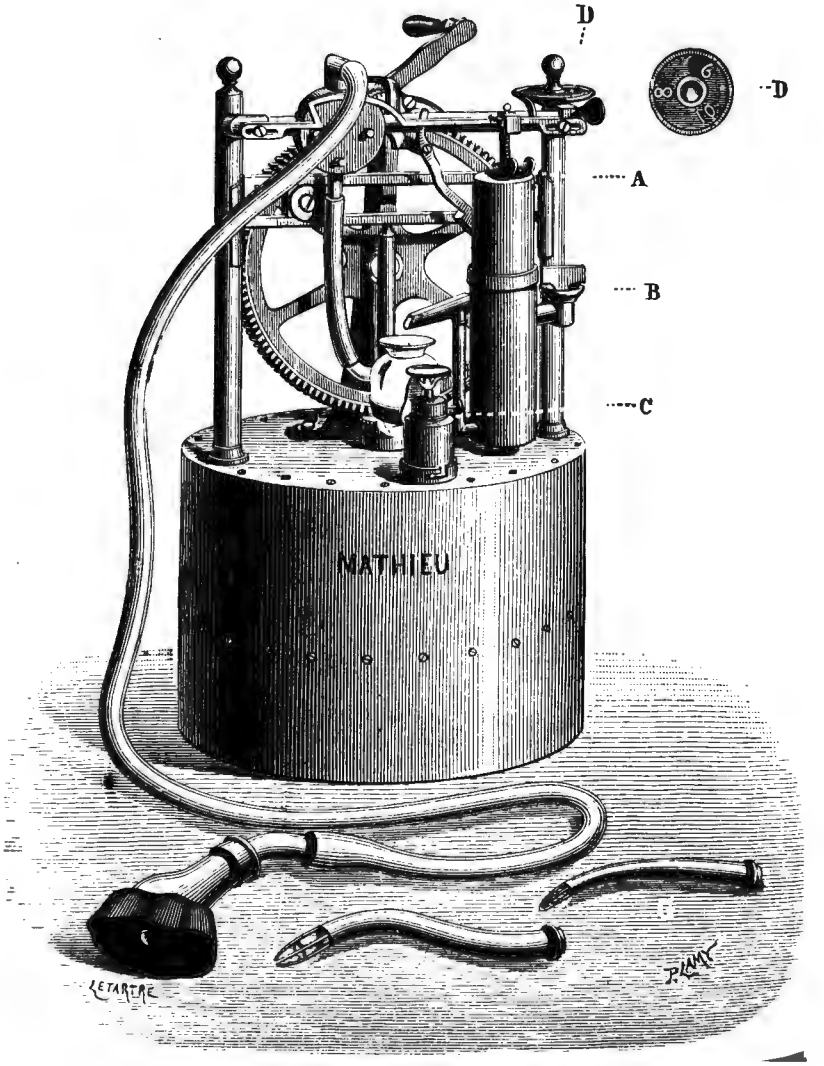


Fig. 20. Dubois' anaesthetising machine.

control of vapour concentration. With the introduction of modern temperature compensated vaporizers, this problem has been overcome. The method of giving chloroform anaesthesia with precision apparatus is described in the appendix.

CHAPTER 4.

THE SUMMING UP.

> Techniques are discovered, utilized for a time and then discarded, only to be rediscovered, and in the light of increased knowledge these again find a place in surgical practice.
>
> Howard Dittrick, M.D.

The majority of the opinions expressed in this chapter are personal and the result of clinical and experimental experience in chloroform anaesthesia.

Potency. Morris rates chloroform as the most potent inhalation agent available, but I feel that this may not be so. As regards respiratory depression, the effect of chloroform does not seem to be as rapid or profound as halothane or cyclopropane. Morphine and chloroform are not good bedfellows (70, 27) and I have frequently noticed that patients premedicated with morphine exhibit a rapid and complete apnoea Pethidine or a barbiturate in normal dosage seem to be satisfactory as premedicants.

Circulatory and cardiac depression occur clinically and experimentally as a result of overdosage (114b).

Chloroform has a powerful vagomimetic effect. In the event of a decline in pulse rate and blood pressure, an injection of atropine almost invariably results in a salutary response.

As will be seen in the Appendix, slightly more than 20 per cent of the patients had a fall of blood pressure during anaesthesia and 10 per cent showed bradycardia or other arythmias.

Liver Damage.

Chloroform is potentially more hepatotoxic than other anaesthetic agents in common use. It is inadvisable to give chloroform to patients in a poor nutritional state or to those who have, or are likely to have liver derangement. In any situation which leads to tissue anoxia chloroform causes marked liver necrosis.

Renal Damage.

It appears from the literature that chloroform causes no greater renal damage than any other anaesthetic agent. As yet this aspect has not been thoroughly investigated.

Death.

No deaths due to chloroform have occurred in the Groote Schuur Hospital series. It is possible that deaths due to the drug occur primarily from overdosage, causing cardiac depression or vagal inhibition. Hypoxia or hypercarbia increase the chances of death from such causes.

Injection of adrenaline during or immediately before chloroform anaesthesia is highly dangerous.

Post-operative vomiting.

The incidence of immediate post-operative vomiting after

chloroform was recorded locally and found to be less than after halothane anaesthesia (48). As regards "long term" vomiting, Gillespie found that the incidence with chloroform was 46 per cent, as against 35.5 per cent when other agents were used (30a).

Post-operative analgesia.

This is prolonged and satisfactory after chloroform anaesthesia. The patient dozes quietly, can be easily roused and will answer intelligently, and will drop off to sleep again. This compares favourably with the postoperative "ether" patient who is frequently restless and who has to be restrained physically or with analgesics and sedatives. Halothane appears to have no postoperative analgesic effect worth mentioning.

Subjective feelings after chloroform are pleasant but somewhat strange. For about a day the patient feels completely detached and quite willing to lie quietly in blissful mental isolation.

Administration of chloroform.

Control: The anaesthetist must have complete and accurate control of the concentration of the agent. This is now possible with the method described in the Appendix.

John Snow wrote

> The rigidity and struggling are less marked when chloroform is given slowly than when quickly given (105f).

With a precision vaporizer it is easy to give chloroform slowly.

The tendancy to hurry a chloroform anaesthetic must be resisted.

Oxygen: Any volatile anaesthetic acts as a diluent to atmospheric oxygen, thus decreasing the alveolar and arterial oxygen tensions. It has been shown experimentally that low oxygen tension is an aggravating factor in post-chloroform liver damage, and it is probable that undetected anoxia in chloroform anaesthesia has caused cardiovascular depression. An oxygen tension greater than atmospheric is therefore desirable. In local work a minimum oxygen concentration of 30 per cent has been used. I feel that a higher concentration of oxygen should be used during deep or prolonged anaesthesia.

Controlled respiration: When chloroform anaesthesia is taken to a depth that gives good relaxation, the respiratory minute volume is drastically decreased. To avoid hypercarbia at this stage I think it necessary that controlled or assisted respiration be used. I have found the Ruben non-breathing valve suitable for this purpose and a concentration of from 0.3 to 0.5 per cent of chloroform all that is required to maintain satisfactory conditions in a fit adult.

I have no experience of using chloroform in a soda-lime absorbtion system and can find only one recent reference to this technique (84).

Specific Operations: Rapid recover, relative absence of complications and low cost make chloroform a particularly suitable agent for out-patient operations (49). Its non-inflammability,

smooth induction and early paralysis of the eye muscles, make it an ideal anaesthetic for opthalmic surgery, particularly for squint correction. Likewise, in any operation where cautery is used, as in otorhinolaryngeal or intracranial operations, chloroform given by controlled methods has a useful place.

Chloroform has not been used in recent years for intrathoracic or intracardiac operations at Groote Schuur Hospital.

The Anaesthetist: The vast majority of accidents that occur in any walk of life are due to the human element, and this applies in particular to anaesthesia. Any anaesthetic is as safe or as dangerous as the man giving it. An anaesthetist who will use chloroform must be alert all the time, including the time before the start of his anaesthetic. Assessment of the patient is vital and the advice of John Snow is as valid to-day as when he wrote,

> It is advisable, however, to pay attention to every circumstance connected with the health and constitution of the patient before exhibiting chloroform, as many circumstances influence its effects (105g).

In order to give chloroform with safety it is obligatory that the anaesthetist keep a constant note of the pulse rate and blood pressure, recording these data at intervals of not less than five minutes. At the same time a constant check must be kept on pulmonary ventilation and chloroform concentration.

If the merits and hazards of the drug are properly understood, and if it is administered with the meticulous care it warrants, chloroform has a useful part to play in the Art of Anaesthesia.

APPENDIX.

A brief summary of 707 chloroform anaesthetics given at Groote Schuur Hospital in 1959-1960. The page numbers in brackets refer to the text.

Method. A "Fluotec" temperature compensated vaporizer (11) is placed between the Boyle's machine outlet and the Magill attachment (see Figure 21). The vaporizer is calibrated to deliver 0.5 to 3.0 per cent halothane vapour by volume, in increments of 0.1 per cent (63). It is charged with chloroform and the dial reading is multiplied by 0.75 to give the vapour concentration of the substituted agent (21). The highest concentration of chloroform obtainable is approximately 2.25 per cent, which was found quite adequate.

The chloroform concentration is increased gradually from the 0.5 dial reading by one notch per breath until the desired concentration is reached.

This system may be used in conjunction with a Ruben's or similar non-rebreathing valve.

Figures 22 and 23 summarize age distribution and duration of anaesthesia.

Table 2 shows the tendency to increased respiratory rate during light anaesthesia (page 16).

Table 3 illustrates the incidence of bradycardia in relation to the duration of anaesthesia (page 31).

Table 4 summarizes the cases of aythmia, other than bradycardia, which were detected clinically. Colume 4 records individual cases in whom factors other than the anaesthetic probably influenced cardiac rhythm. (page 33).

Table 5 is an analysis of those cases in whom a fall of blood pressure of more than 10 mm.Hg. was observed. Colume 5 records those cases in whom factors other than the anaesthetic would cause a fall of blood pressure. Overall, it will be seen that there is a relationship between the length of anaesthesia and the percentage of cases in which a drop in blood pressure occurred (page 34).

Table 6. This reports the fall of blood pressure as a percentage of the preanaesthetic systolic blood pressure reading. (Page 34).

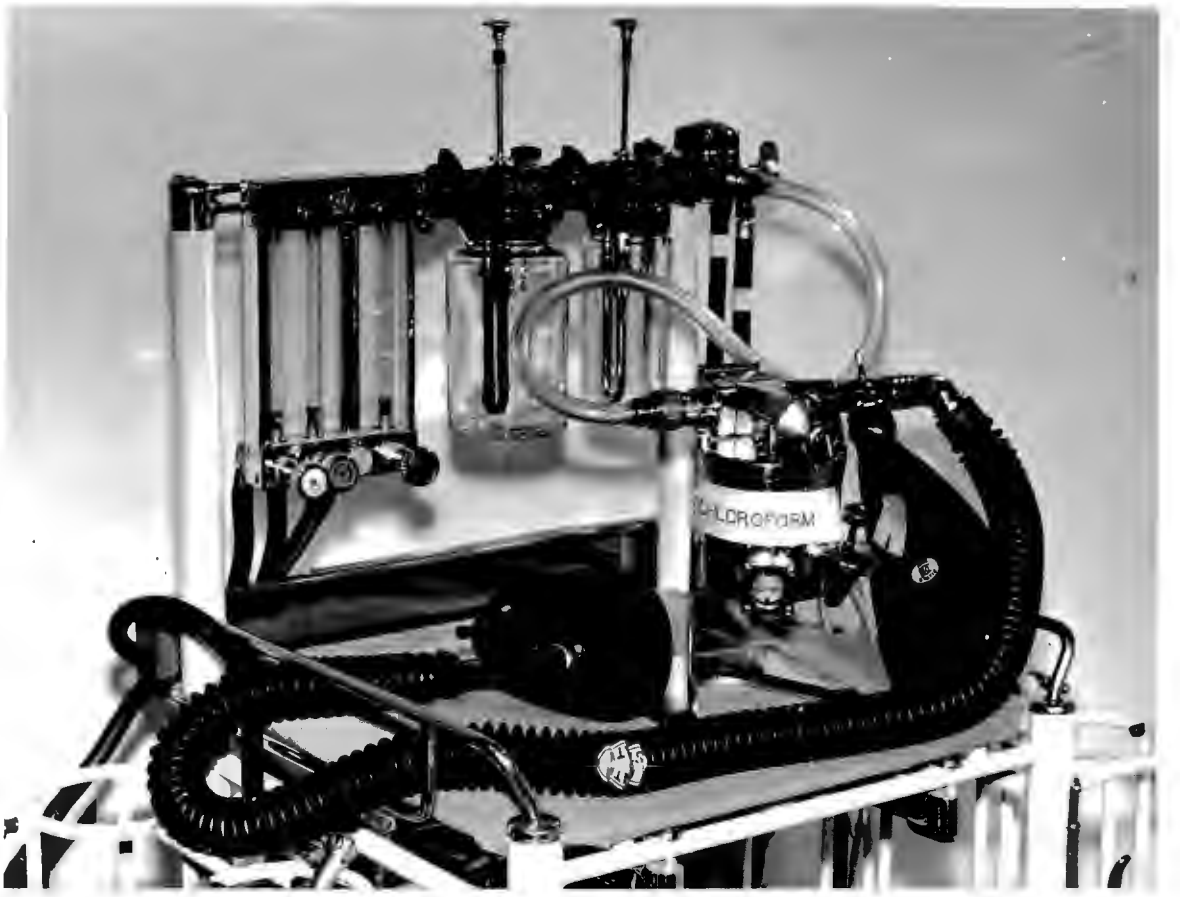


Fig. 21

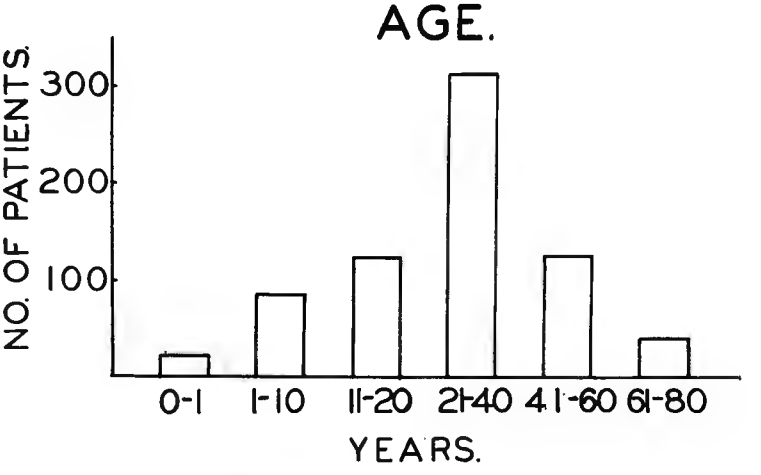

AGE.
NO. OF PATIENTS.
300
200
100
0-1
1-10
11-20
21-40
41-60
61-80
YEARS.

Fig. 22

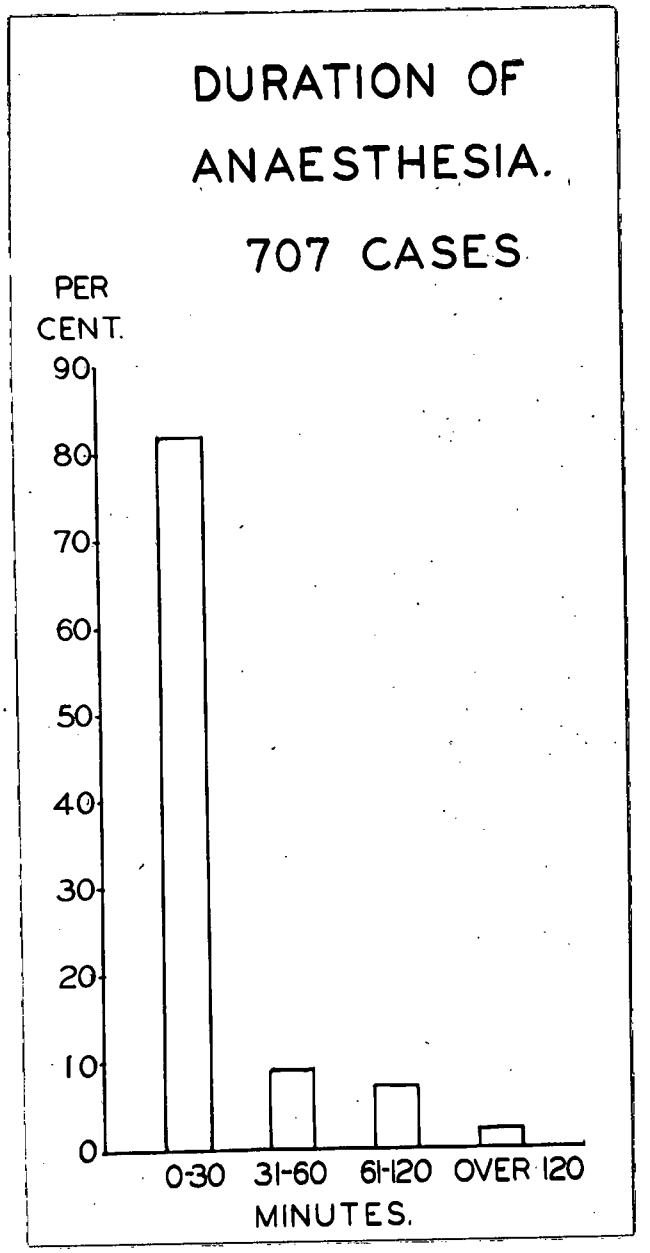


Fig. 23.

RESPIRATORY RATE

duration minutes.	No. of cases.	RATE / MIN. per cent over 30.	RATE / MIN. per cent less than 30
0-30	579	48	52
31-60	63	35	65
61-120	53	25	75
over 120	12	33	67

Table 2.

BRADYCARDIA

duration minutes.	No. of cases.	PULSE RATE less than 60 / minute.	
		No. cases.	per cent.
0-30	579	42	7
31-60	63	6	9·5
61-120	53	11	21
over 120	12	4	33
TOTAL	707	63	9

Table 3
Bradycardia during anaesthesia

Duration in minutes.	Arrythmias	
No.of cases	Cases	%
0-30 / 579	a,b 6	1
31-60 / 63	-	-
61-120 / 53	c,d,e 5	9·4
over 120 / 12	-	-
TOTAL -707	11	1·5

a. History of angina pectoris.
b. Adrenaline nasal plug; ventricular tachycardia.
c. Chloroform used for hypotension.
d. Previous pulmonary infarct.
e. Hypertensive heart disease.

Table 4
Arythmias during anaesthesia.

FALL OF BLOOD PRESSURE

Duration in minutes.	Fall of blood pressure over 10mm			
No. of cases	Cases	%	Pent.	
0-30 / 579	107	18	8	< 60 mins. – 21 %. > 60 mins. – 37%
31-60 / 63	25	40	18	3 Caesarean sections. 3 very toxic. 1 severe haemorrhage.
61-120 / 53	18	34	14	3 - $CHCl_3$ for hypotension. 3 severe haemorrhage.
over 120 / 12	6	50	5	1 - $CHCl_3$ for hypotension.
TOTAL / 707	156	22	45	

Table 5

Duration in mins.		0 - 30	31 - 60	61-120	>120		
No. Patients with hypotension		107	25	15	5	Total. 152	
%Fall in Blood Pressure	<10	8	2	1	-	11	70 (10%)
	11-20	50	6	2	1	59	
	Sub-Total %	54%	32%	20%	20%		
	21-30	32	9	6	4	51	82 (12%)
	31-40	13	4	3	-	20	
	41-50	3	4	3	-	10	
	>50	1	-	-	-	1	
	Sub-Total %	46%	68%	80%	80%		

<20% fall in blood pressure - 10% of all patients
>20% fall in blood pressure - 12% of all patients

Cases of deliberate hypotension excluded.

Table 6

Detailed analysis of Table 5

My thanks are due to the following colleagues:
Dr. C.S. Jones, Head of the Department of Anaesthesia, Groote Schuur Hospital, who started the local chloroform investigation.
Professor J.H. Louw and Dr. C.N. Barnard for allowing me the use of the Surgical Research Laboratory.
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Miss Tina Morrison and Mr. G. MacManus, who produced the photographs.

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