disease, stages which can extend over very many years, a diagnosis was often difficult or impossible. At such a time I should have been compelled to talk at length about symptoms and signs, and at the end have left matters as they were—uncertain. We might hazard a shrewd guess, but it would have been an opinion, not an established fact. Now, owing to the introduction of iodized oil by Sicard and Forestier, we can claim to prove or exclude bronchiectasis and to localize it. The symptoms at first may be identical with those of tuberculosis—cough, sputum, haemorrhage; the physical signs do not really help, for tuberculosis may be basal, and bronchiectasis apical. The x-ray picture of both diseases may be similar, or in both cases may show nothing distinctive. If, therefore, with such symptoms there is an absence of tubercle bacilli in the sputum and faeces, a non-tuberculous condition should be thought of, iodized oil should be given, and the diagnosis established. I must confess, however, that in one or two cases I have been a little puzzled to determine whether the cavities revealed were tuberculous or bronchiectatic. In the example shown, however, I think it will be agreed that the appearance is that of lung cavitation rather than dilatation of bronchi.

In chronic *lung abscess* there are no tubercle bacilli. The x-ray appearance is suggestive. Lipiodol, as a rule, does not enter the affected area, thus differentiating it from bronchiectasis.

Malignant growth has already been discussed. *Innocent tumours*, as a rule, have a distinctive appearance on the skiagram. One great pitfall is to mistake lymphadenoma for an innocent tumour, but to discuss this would be to digress too far beyond the limits of my subject.

SOME PHARMACOLOGICAL ASPECTS OF AVERTIN.

BY

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ANY recent advances which have been made in anaesthesia have been rather those of improved methods of administration and technique than the introduction of new anaesthetics. This is due partly to the fact that anaesthetics have come to be regarded as substances to be administered by inhalation, a method which has attained popularity because it permits accurate control and regulation of the duration and depth of anaesthesia; and partly to the reliability of three volatile drugs—ether, chloroform, and nitrous oxide—introduced in the very earliest days.

The rectal administration of anaesthetics does not permit of such fine control of anaesthesia as can be obtained by inhalation. Gwathmey⁹ has shown that anaesthesia results when ether is absorbed at a constant rate from a solution in olive oil given by the rectum, and that the drug is excreted by the lungs. Obviously such considerations do not apply to non-volatile anaesthetics. Rectal anaesthesia has certain practical advantages: it is more comfortable for the patient, it does not necessarily require the presence of an anaesthetist, for the surgeon himself can administer the anaesthetic, and it is more convenient for operations about the head and neck. The main disadvantages are the risk of irritation to the intestinal mucosa and the difficulty of maintaining a constant concentration of the anaesthetic in the tissues. This second problem is intimately connected with the absorption and excretion of the drug in question, for the administration of a rectal anaesthetic is not continuous, and, once given, it is impossible to control its action further.

Some three years ago it was discovered that tribromomethylalcohol, a simple organic compound of bromine, possessed the property of producing anaesthesia. Moreover, it has been found¹⁴ that the therapeutic margin of safety is greatest with this substance when it is administered by the rectum. A quantity of experimental and clinical data has been accumulated (1-7 10 12 13 14 17-23, and others) regarding

Lymphadenoma may simulate pulmonary tuberculosis in many ways—by long-continued fever, by lung symptoms and signs, by the production of a pleural effusion. It is one of the most difficult of all causes of obscure fever, but the pattern of the temperature chart, the curious intermittent regular bouts of fever, will frequently help. If primary in the chest, the bulk of the disease is probably in the mediastinum, and will so appear in the skiagram. If an effusion is present and there is doubt of the diagnosis, replacement by gas and subsequent radiography will probably reveal masses in the mediastinum, perhaps extending into the lung. The response to treatment by arsenic and x rays may be a further help in diagnosis.

Syphilis.—Although many different syphilitic affections of the lung are described, such as massive consolidation, chronic bronchitis, bronchiectasis, etc., the only certain syphilitic conditions that I have seen are an apparent *gumma* in the lung, a gummatous mass in the mediastinum causing venous obstruction, bronchial stenosis, and the changes following pressure by an aneurysm. The history, the Wassermann reaction, the x-ray picture, and the response to treatment may give the diagnosis.

With *foreign body* in the bronchus, the history and bronchoscopic examinations are the most important points. In *bronchial stenosis* lipiodol injections and bronchoscopic examinations are essential.

To sum up, in difficult cases the routine to pursue will be as follows: A careful history, an exhaustive bacteriological investigation, lipiodol injections, x-ray examinations, and bronchoscopic examinations. In certain cases such procedures as replacement and thoracoscopy will be needed, in others even an exploratory thoracotomy. Of all these I would put first the bacteriological investigation.

this substance, which is now issued under the trade name of "avertin." The opinion has been formed that the drug represents a definite advance towards the ideal anaesthetic, largely because of the simplicity of its administration. All that is necessary is to give a definite proportion of the drug per unit of body weight in aqueous solution by the rectum. Administration is not continuous, for, once the requisite quantity of the drug has been injected, the patient becomes anaesthetized and remains so for a period depending upon the amount of avertin given. The drug is absorbed with extreme rapidity,²¹ so that, when the operation is over, it is useless to attempt to remove any which may remain in the rectum, as is the case with other rectal anaesthetics.

The pharmacology of avertin has been studied mainly in Germany, and no experimental investigations have been recorded in this country as yet. The present paper includes the main results of an investigation on these lines to confirm and extend previous observations.

Some Physical and Chemical Considerations.

Avertin is an odourless, white, crystalline powder. It has a melting point of 80° C., and is soluble in water to the extent of 3 per cent. at 37° C. Solution occurs very slowly; it takes upwards of forty-five minutes, aided by vigorous shaking, to produce a clear solution. As the solution must be freshly prepared for each anaesthesia this is a material disadvantage, and the makers have to some extent solved the difficulty by issuing the substance dissolved in amylene hydrate, itself a rectal anaesthetic, in the proportion of 1 gram of avertin in 1 c.cm. of the solvent. This solution is readily soluble in water, and avertin can thus be prepared conveniently for rectal injection.

The chloroform/water distribution coefficient of avertin is comparable with that of ether, and indicates that the two drugs have a similar anaesthetizing power. Avertin contains a high proportion, approximately five-sixths, of bromine. In aqueous solutions it is decomposed by heating above 50° C. into hydrobromic acid and dibromacetaldehyde:

Many of the earlier difficulties in the use of avertin by rectal administration were due to the presence of these decomposition products. It has been found that they are

markedly irritant to the intestinal mucosa; if a decomposed solution is injected into a cat's rectum an acute haemorrhagic proctitis results within a very short time. The solution should only be used when freshly prepared, and before injection it must be tested for its reaction by adding two drops of a 1 in 1,000 solution of Congo red to 5 c.cm. of avertin solution. If the reaction is less than $pH = 4.5$ the indicator gives a purplish or blue colour and the solution is not satisfactory for use. Although reports

ISOLATED RABBIT'S HEART
PERFUSED WITH AVERTIN 1-1250

FIG. 1.

to the contrary have been made, I have found that avertin does not decompose readily when exposed to light and air at room temperatures. Solutions have been kept for over three months under these conditions without any evidence of decomposition.

Avertin was first prepared by the action of yeast upon bromal.²⁵ Since then improved manufacturing methods, based upon the reduction of bromal, have been introduced. There is a close relationship chemically between bromal and chloral; and, further, this holds good up to a point with regard to their decomposition in the body. Chloral circulates in the blood as trichlorethylalcohol, which is excreted in the urine in combination with glycuronic acid as uro-chloralic acid. Bromal, upon reduction, is converted into tribromethylalcohol (avertin), and it has been suggested²² that this substance is excreted in the urine in combination with glycuronic acid as urobromalic acid. This is discussed fully later.

The Cardio-vascular System.

The action of avertin upon the heart and blood vessels has been studied by Straub^{21 22 23} and Skvortsov;¹⁹ their results have been confirmed and extended in the present research by experiments upon intact animals.

Perfusion of the isolated rabbit's heart with a 1 in 5,000 solution of avertin causes a slight increase, followed immediately by an appreciable diminution, in the force of the heart beat, accompanied by slowing of the rate. These effects are more marked when a 1 in 2,500 solution is used, and with a strength of 1 in 1,250 (Fig. 1) there is no initial stimulation and the beat is almost stopped, but regains its normal amplitude rapidly upon perfusion with Ringer's solution. Continuous perfusion with this strength of avertin causes arrest of the heart in systole within five minutes.

The coronary outflow is increased in all dilutions of avertin, but particularly at 1 in 2,500, when the increase may amount to 40 per cent. of the flow. Avertin therefore dilates the coronary arteries to a considerable degree.

The intravenous injection of a small dose of avertin (1 c.cm. of a 2 per cent. solution) into a cat already anaesthetized with this drug weakens and slows the heart beat and causes slight cardiac dilatation. The blood pressure falls about 30 mm. of mercury and may remain low for some time. This effect is due entirely to the cardiac action; intestinal volume and limb volume experiments

show that the peripheral vessels constrict, but this is not sufficient to maintain the blood pressure at a normal level. A normal anaesthetic dose of avertin administered per rectum has little or no effect upon the blood pressure in the cat, which remains at about 110 mm. of mercury. If the anaesthetic dose of avertin given in this way or subcutaneously is doubled, the blood pressure falls to about 80 mm.; and if it is tripled, it falls to about 50 mm. of mercury. Similar results are obtained with rabbits. These results confirm the findings of Blomfield and Shipway in man,² that "there is a slight fall of blood pressure, usually about 10 mm. Hg, which is greater in proportion as the strength of the dose is increased."

Avertin resembles chloroform in its action upon the heart, in that it weakens the force and slows the rate of the beat, with resulting cardiac dilatation and a fall in blood pressure. The great distinction between the two drugs is that there is a greater margin of safety with avertin; effects which are produced by chloroform in a dilution of 1 in 20,000 are not produced by avertin until a concentration of 1 in 1,250 is reached. Accordingly, avertin has a comparatively low toxicity upon the cardiac musculature—about one-sixteenth that of chloroform.

Respiration.

Avertin anaesthesia is accompanied by marked slowing of respiration, due in part to diminution of voluntary movement and to absence of reflex activity from the respiratory tract. It is possible that avertin is not responsible for this depression, which occurs after the administration of the normal dose, for the respiratory centre retains all its reflex effects and its response to drugs; thus inhalation of ammonia and injection of hydrocyanic acid still produce both quickening and deepening of respiration, while the stimulation of an afferent nerve, such as the vagus or sciatic, elicits the normal response.

The respiration under deep anaesthesia shows certain peculiarities which can be demonstrated by a rapid tracing of the respiratory movements. Such a tracing (Fig. 2) shows that the animal first takes a normal inspiration, which is followed, not by a normal expiration, but by five or six extremely short expirations and inspirations. A normal expiration occurs and then the process is repeated.

FIG. 2.—Cat, weight=2.35 kilos. Between 10.30 a.m. and 2 p.m., 45 c.cm. of a 2 per cent. solution of avertin were administered per rectum, with resulting anaesthesia. Between 2 p.m. and 2.50 p.m. a further 20 c.cm. of this solution were given per rectum, together with 70 c.cm. subcutaneously.

This type of breathing is strongly suggestive of that described by Lumsden¹⁶ as occurring when the brain is transected through the upper part of the pons; it is known to result from overdosage with anaesthetics. With toxic doses of avertin the respiration becomes slower and more irregular, and finally ceases. Death results from respiratory failure, for the heart continues to beat long after respiration has ceased. Nevertheless, there is a fairly large margin of safety; a cat requires four times the anaesthetic dose administered subcutaneously or per rectum, and very frequently 3 or 4 c.cm. of a 2 per cent. solution intravenously in addition, to cause death from respiratory failure.

The Excretion of Avertin.

We are indebted to Straub^{21 22 23} for our present knowledge of the excretion of avertin. This writer has established the fact that avertin is excreted entirely in the urine, except for traces in the breath and sweat, and he has expressed the opinion that the drug is excreted in combination with glycuronic acid. My experiments have confirmed certain of his results.

The main difficulty in determining the excretion of bromine-containing anaesthetics is to obtain a simple and accurate method of estimating bromine in the urine. Existing methods, such as those of von Wyss²⁴ for inorganic bromides only, Hale and Fishman,¹¹ and Lucas,¹⁵ are unsatisfactory because they involve complex manipulations for separating chlorine from bromine and the use of relatively large amounts of urine, with a resulting undesirable margin of error. In addition, in this work, organic as well as inorganic bromides had to be estimated, and for this purpose von Wyss's method is useless.

With the assistance of Mr. Palmer and Mr. Notton, the following method, depending upon the fixation of organic bromine by sodium carbonate and its subsequent oxidation by iodic acid, was devised. In this way the difficulty of separating chlorine from bromine is overcome, as chlorine is not liberated by iodic acid, except when present in a concentration that is never found in urine.

Method.

The apparatus shown in Fig. 3 was used. It consists of a 300 c.cm. flask, A, with a long neck, B, fitted with a ground-glass stopper, C, carrying a screw-clamp, E. A delivery tube, F, is fused into the neck of the flask as high as possible, and into this is blown a bulb, G, of approximately one inch in diameter. This bulb serves both as a trap and as an inspection chamber for fumes coming over. The delivery tube then passes vertically downwards through a condenser, J, into a boiling tube, H. This is fitted with a cork carrying a small tube, K, which just projects into the boiling tube, while the delivery tube reaches to the bottom. K is connected by rubber tubing to a glass tube, L, dipping to the bottom of a second boiling tube, M. This is also fitted with a small glass tube, N, similar to K.

When bromine is evolved in the flask A and carried over into the boiling tube H, there is no rubber with which it may come in contact. The design of the flask and delivery tube is such that there is no possibility of the contents of the flask splashing into the boiling tube H. Furthermore, by closing the clamp E, fluids in flask A can be boiled at atmospheric pressure. By attaching a pump to tube N boiling point can be reached at a reduced temperature, and by opening clamp E air can be drawn through the apparatus.

A convenient quantity of the urine to be tested is placed in a small nickel crucible; 5 c.cm. was found to be adequate in the case of urines passed immediately following the administration of avertin, but in other cases 10 to 15 c.cm. had to be taken. About 2 grams of solid sodium

carbonate are added to the urine in order to fix any organic bromine compounds which otherwise would volatilize, and the whole is evaporated down to dryness.

The crucible, with its contents, is then heated until the organic constituents of the urine are ashed and the sodium carbonate is fused. It is essential that no organic matter be left, because this liberates iodine from iodic acid and interferes with the estimation. After cooling, the fused mass is dissolved in the minimal quantity of N/2 sulphuric acid and is transferred, together with washings of distilled water, to the flask A; 20 c.cm. of N/2 sulphuric acid and 20 c.cm. of an aqueous solution of potassium iodate (7 grams per litre) are added to the flask, and about 15 c.cm. of a 10 per cent. solution of potassium iodide in water are placed in each of the tubes H and M.

The clamp is tightened and the flask is heated. Bromine is liberated by the iodic acid formed by the interaction of sulphuric acid and potassium iodate. The contents of the flask, which at first are colourless, turn brown as the temperature rises. Bromine passes through the delivery tube and bulb into the potassium

iodide solution, where iodine is liberated, which dissolves in excess of potassium iodide. Tube M traps any bromine which escapes tube H.

The contents of the flask are allowed to boil until they and the condensed fluid in the trap G are colourless. This takes about twenty minutes, and then air is sucked through the apparatus in order to remove the last traces of bromine from the distillation flask. The contents of the tubes H and M are titrated with a solution of sodium thiosulphate of known strength (1 c.cm. = 0.0008 gram of bromine), using starch as an indicator. The amount of sodium thiosulphate used corresponds with the amount of iodine liberated from the solution of potassium iodide, and indirectly with the amount of bromine liberated from the original material.

Duplicate estimations on urines to which known amounts of potassium bromide and avertin were added showed that 0.2 mg. of bromine could be estimated with an accuracy of 99.8 per cent.

Rate of Excretion of Avertin in Rabbits.

Experiments were made upon rabbits in order to determine the rate of excretion of avertin. Each rabbit was given a dose of avertin subcutaneously, the urine was collected at suitable intervals, and the bromine content estimated. The results obtained are given in Table I.

TABLE I.

	<i>Rabbit 1.</i> Weight 1.8 kg. Avertin given 0.4 g. Bromine content 0.346. No anaesthesia.		<i>Rabbit 2.</i> Weight 2.5 kg. Avertin given 0.8 g. Bromine content 0.692. Anaesthesia.	
	Urine (c.cm.).	Bromine (gram).	Urine (c.cm.).	Bromine (gram).
First day ...	90	0.1872	—	—
Bromine ...	...	54%	...	...
Second day ...	340	0.0566	135	0.505
Bromine ...	...	...	...	72%
Third day ...	200	0.056	90	0.0504
Fourth day ...	290	0.0232	130	0.0156
Fifth day ...	205	0.0123	120	0.0144
Sixth day ...	115	0.0055	—	—
Seventh day ...	...	...	290	0.0232
Eighth day ...	...	...	—	—
Ninth day ...	...	...	—	—
Tenth day ...	...	...	400	0.04
Eleventh day ...	...	...	—	—
Twelfth day ...	...	...	380	0.0228
Thirteenth day ...	...	...	—	—
Fourteenth day ...	...	...	400	0.008
Fifteenth day ...	...	...	160	0.0019
Sixteenth day ...	...	...	...	No Br
Total Br recovered ...	...	0.3408	...	0.6813
Total Br given ...	...	0.346	...	0.692
Percentage recovered	...	98.5	...	98.4

	<i>Rabbit 3.</i> Weight 1.55 kg. Avertin given 0.62 g. Br content 0.526. Anaesthesia.		<i>Rabbit 4.</i> Weight 1.55 kg. Avertin given 0.62 g. Br content 0.526. Anaesthesia.		<i>Rabbit 5.</i> Weight 2.5 kg. Avertin given 0.8 g. Br content 0.692. Anaesthesia.	
	Urine (c.cm.).	Bromine (gram).	Urine (c.cm.).	Bromine (gram).	Urine (c.cm.).	Bromine (gram).
First day ...	160	0.384	160	0.3328	142	0.368
Bromine ...	...	73%	...	63%	...	53%
Second day ...	170	0.0136	60	0.0128	...	...

— = No urine collected.

In the cases of rabbits 1 and 2, estimations were performed until no bromine could be detected in the urine. Rabbits 3, 4, and 5 are included to show the rate of excretion in the first twenty-four hours, and the estimations were not carried further. In the case of rabbit 2, the urine was not collected necessarily each day; upon occasions it was collected for two or three days and then estimated as a whole. Unless otherwise mentioned, the urine was collected at twenty-four hours' interval.

The main points may be summarized as follows:

1. The high figure for total bromine recovery. This was over 98 per cent. in each case in which the estimations were continued until no bromine was found in the urine; this is a much higher figure than that first obtained by Straub,²² who stated that he could only recover from the urine the equivalent of 81 per cent. of the avertin administered. At the same time, Straub could only find traces of bromine in the sweat and breath of avertinized animals; and the figures obtained here, which allow of the excretion of 1.2 per cent. of bromine by channels other than the urine, confirm this statement. Later, by using an improved technique, Straub²³ asserted that practically the whole of the avertin ingested could be recovered from the urine, thus confirming the figures given in Table I.

2. The amount excreted in the first twenty-four hours. Quantities ranging from 53 to 73 per cent. were recovered in this period. Great caution must therefore be exercised in giving a second dose of avertin before a suitable length of time has elapsed, because an average of 37 per cent. remains in the body twenty-four hours after administration. This shows that avertin is a cumulative drug within certain limits.

3. The period of excretion varies with the dose administered. In the case of the small rabbit No. 1 insufficient avertin was given to produce anaesthesia, and bromine disappeared from the urine on the seventh day. With rabbit No. 2 anaesthesia was produced, and bromine was found in the urine until the sixteenth day. The daily excretion gradually diminished from the first day after administration to a trace on the last few days.

Rate of Excretion of Avertin in Man.

I have had the opportunity, through the kindness of Mr. Arthur Cooke, to study the excretion of avertin in one of his patients. The urine was examined for bromine, with the results shown in Table II. The total bromine

TABLE II.

Man. Weight 9 st. 5½ lb. = 59.5 kilograms.

Avertin given = 5 grams = 4.24 grams of bromine.

	Urine passed, c.cm.	Bromine, Grams.
First day	426	1.43
Second day	852	1.636
Third day	738	0.389
Fourth day	1,136	0.182
Fifth day	738	0.177
Sixth day	824	0.068
Seventh day	—	No bromine
Total bromine recovered	...	3.882
Total bromine given	...	4.24
Percentage recovery = 91		

recovery was only 91 per cent., but as a small quantity of avertin solution was lost from the rectum during the operation this figure is probably too low. Excretion was somewhat erratic for the first forty-eight hours, and the amount of bromine passed in the second twenty-four hours exceeded that passed in the first twenty-four hours. This is explained by the fact that the patient experienced considerable difficulty in passing urine in the first twenty-four hours, and reference to the table shows that the quantity of urine passed on the second day was exactly double that passed on the first day; 72 per cent. of the bromine administered was recovered from the urine in the first forty-eight hours, and diminishing quantities were found until the seventh day, when no bromine could be detected.

The Mode of Elimination of Avertin.

It is necessary to remember the analogy between chloral and avertin which has been mentioned previously, and to point out that Straub²² in his experimental work obtained results which upheld the theoretical contention that avertin is excreted in combination with glycuronic acid as urobromalic acid.

There are four ways in which it is possible for avertin to be excreted: (1) as sodium bromide; (2) as unchanged avertin; (3) as urobromalic acid; (4) as an organic compound of bromine other than (2) or (3).

Avertin is not excreted as sodium bromide. The precipitate obtained by adding silver nitrate to the acidified urine of an avertinized rabbit contains only a trace of bromine, while the filtrate contains 95 per cent. As silver nitrate precipitates inorganic bromide, the conclusion is that avertin is not excreted in this form. This is confirmed by the fact that administration of sodium chloride to an avertinized animal does not alter the duration of anaesthesia or the rate of bromine excretion.

Avertin is not excreted unchanged. It forms a precipitate with silver nitrate, and, as stated in the previous paragraph, no such precipitate can be obtained with the urine of avertinized animals. Further, avertin is freely soluble in ether, chloroform, and petroleum ether, and extraction of suitable urines with these solvents gives negative results.

Glycuronic acid is found in the urine of both man and animals after the administration of avertin, and this suggests that the drug may be excreted as urobromalic acid. I have been unable to find any reference to this substance, but its chlorine homologue, urochloralic acid, is said⁸ to be soluble in ether and chloroform and to be precipitated by basic lead acetate. No bromine-containing compound can be extracted from the urine of avertinized animals by these solvents, neither can such a compound be precipitated by basic lead acetate.

Avertin can be distilled in steam, but when this process is applied to a suitable urine there is no bromine in the distillate, and we must conclude that avertin is absent from the urine. In addition, the distillate contains no bromine if the urine is first treated with concentrated sulphuric acid in order to decompose any hypothetical urobromalic acid that may be present into glycuronic acid and avertin; this affords strong evidence that the drug is excreted in some other form. In view of the presence of glycuronic acid, it is probable that this is a complex organic compound of bromine.

Summary.

1. Great care must be exercised in the preparation of solutions of avertin for anaesthesia. Decomposition products formed by the action of heat (over 50° C.), light, and air are irritant to the rectal mucosa.

2. In anaesthetic doses avertin has no appreciable effect upon the cardio-vascular system. In larger doses it slows the rate and weakens the force of the heart beat. The coronary vessels dilate and the blood pressure falls.

3. Avertin anaesthesia is accompanied by marked slowing of respiration. Toxic doses cause death by respiratory paralysis.

4. In both man and animals avertin is excreted in the urine over a period of several days. Considerably more than 50 per cent. is excreted in the first twenty-four hours.

5. The form in which avertin is excreted could not be determined. The indications are that elimination occurs in the form of an organic compound of bromine other than tribromethylalcohol or urobromalic acid.

I have to thank both Professor W. E. Dixon and Dr. J. C. Hoyle for their kind advice and criticism.

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