cessation of the inhalation it rises considerably. I have not determined the cause of this after-rise.

The rise in pressure seen in an animal with intact vagi is due, I think, to the removal of the inhibitory vagal impulses, the rise being usually accompanied by an acceleration of the heart. The subsequent fall is due to the direct action of the drug on the heart.

Effect on the Vagal Nerve Endings in the Heart.

I find that during the inhalation of somnoform or of ethyl bromide, the endings of the vagus in the ganglia of the heart are paralysed. I have observed this in 2 cats and 7 rabbits, in every case in fact in which I have looked for such an effect.

In the frog I have found that the post-ganglionic endings in the heart itself are not paralysed by ethyl bromide, stimulation of the sino-auricular junction by a weak interrupted current producing marked inhibition, whilst stimulation of the trunk of the vagus is entirely without effect. This is shown in Fig. 5.

Effect on the Cardio-inhibitory Centre.

Owing to the depression of the vagal nerve endings I have been unable to ascertain the effect of the drug on the cardiac centre in the medulla. And owing to this peripheral depression it seemed unnecessary to investigate this point, for any impulses that would be originated in the medulla could not affect the heart's action.

Effect on the Vasomotor Functions.

I have performed two experiments on cats with an intestinal plethysmograph to ascertain the effect on the blood vessels, using somnoform and ethyl bromide. I was quite unable to detect any alteration. The intestinal volume increased with a rise in blood pressure, and decreased with a fall. I found this to be the case even with a very large dose, and am therefore unable to agree with Ginsberg, who states that ethyl bromide paralyses the peripheral vaso-constrictor fibres.

Effect on the Skeletal Muscles.

A striking effect of the drug is the peculiar rhythmic movements of the limbs, jaws, and tail that nearly always supervene with somnoform and ethyl bromide inhalation. The muscles are quite firm, even during deep coma. The struggling movements occur when it is quite impossible to obtain the corneal reflex, and are due to an excitation of the cord or higher centres. They cease immediately on section of the motor nerves to the parts.

Effect on the Non-skeletal Muscle.

In the case of the bladder I have observed a most distinct and rapid rise of pressure in a cat that was being experimented on by Mr. T. R. Elliott, of Trinity College, Cambridge. Since the increase in pressure could only be obtained when the pressure in the bladder was high, we concluded that it was due to a direct effect on the musculature of the viscus.

Effect on the Pupil.

It is difficult to estimate the action on the pupil owing to the effect of the previous anaesthetic. Whenever the pupil was small under the influence of ether, somnoform caused a dilatation, passing into a constriction with large doses.

Conclusions.

The chief indications that my experiments afford as to the use of somnoform as an anaesthetic are:

1. The chief danger being a paralysis of respiration; careful watch must be kept over the respiratory movements.
2. Owing to the depression or paralysis of the peripheral endings of the cardio-inhibitory fibres, and the comparative slight action on the heart itself, there is no danger of heart failure provided respiration has not ceased.
3. After cessation of the respiratory movements it is easy to restore the animal by artificial respiration.

I am of opinion that the paralysis of the cardio-inhibitory fibres by ethyl bromide renders that drug a very valuable anaesthetic. Embley⁹ has recently shown that the sudden death that not infrequently occurs in chloroform anaesthesia is due to inhibition of the heart through stimulation of the cardio-inhibitory centre. This is usually only seen in the early stages of chloroform administration, the danger passing off when the medullary centres are exhausted.

I venture to suggest that a valuable anaesthetic for pro-

longed operations could possibly be obtained by combining ethyl bromide with chloroform. During anaesthesia produced by ethyl bromide the vagi are paralysed; chloroform would then be deprived of one of its great dangers. It might be possible to get well past the stage of excitation into that of depression of the medulla before ceasing to give ethyl bromide and maintaining anaesthesia by chloroform alone, ethyl bromide being discontinued owing to its paralytic effect on respiration. I hope shortly to give an account of experiments I am performing to test this possibility.

REFERENCES.

- ¹ Nunneley, BRIT. MED. JOURN., 1849. ² Williams, BRIT. MED. JOURN., 1884, 1, 402. ³ Hartmann and Bourbon, Rev. de Chir., 1893, 701. ⁴ Ginsburg, Inaug. Diss., St. Petersburg Imp. Med. Acad., 1893. ⁵ Thornton and Meixell, Annales des Maladies de l'Oreille, 1893, 382. ⁶ McCardie, Lancet, 1901, 698. ⁷ Quoted from Richet's Dictionnaire de Physiol., v, 888. ⁸ Roy and Adams, Trans. Roy. Soc., 1892. ⁹ Embley, BRIT. MED. JOURN., 1, pp. 817, etc., 1902.

THE INFLUENCE OF ETHER ADMINISTRATION ON NITROGENOUS METABOLISM.

By HORACE JAMES PECHELL, M.B., C.M. (EDIN.),

Late Anaesthetist, Derbyshire Royal Infirmary.

[From the Clinical Laboratory of the Westminster Hospital.]

THE question upon which the following research was made has already received a certain amount of attention. In the larger number of cases chloroform has been the anaesthetic employed, but since my own observations have been conducted with ether as the anaesthetic that work does not strictly come within the scope of the present paper.

It may be incidentally remarked, however, that the results of Terrier¹ (whose work on the nitrogen excretion of rabbits and man after chloroform is careful and exhaustive) bear a general resemblance to the results to be detailed below.

Thompson,² working with the human subject, found that ether anaesthesia produces diuresis and an increase in the total nitrogen and urea excretions.

Haig³ found, under similar circumstances, that "the rise of urea was enormous."

I have been unable to find any literature dealing with the excretion of uric acid and xanthin bodies under similar circumstances. Previous writers have for the most part been contented with estimating variations in urea, few of them entering even into the question of total nitrogen excretion.

METHODS.

The patients whose urine was investigated were in the wards of the Westminster Hospital. It will be seen that in most cases the patient were young adults suffering from surgical ailments which did not greatly interfere with their general health, and whose kidneys were, with one exception, absolutely healthy.

Below are given short details of the cases themselves:

CASE I.—J. G., female, aged 17. Laparotomy for tuberculous peritonitis. Temperature raised irregularly. Milk diet before and after the operation.

CASE II.—Mrs. K., aged 50. Removal of deltoid bursa. Fish before operation; milk to twenty-four hours after, then fish. No temperature.

CASE III.—R. T., male, aged 18. Radical cure of varicocele. Temperature to 100° on third day after operation, then normal. Diet ordinary before, milk to third day after, then fish.

CASE IV.—T. G., male, aged 18. Radical cure inguinal hernia. Temperature 99.8° third day after, then normal. Ordinary diet before, water to twelve hours after, then milk.

CASE V.—S. M., male, soldier, aged 24. Bilharzia. No cutting operation, only cystoscopy. No temperature. Ordinary diet before anaesthesia, and from twelve hours after. The complete table of estimations of this case is quoted in Tables I and II.

CASE VI.—K. W., female, aged 23. Tuberculous abscess of breast. No temperature. Ordinary diet before; water twelve hours after, then milk.

CASE VII.—T. H., male, aged 28. Wiring of fracture. No temperature. Ordinary diet before; milk and beef-tea to third day, then fish.

CASE VIII.—C. C., male, aged 25. Radical cure of inguinal hernia. Ordinary diet before; milk and beef-tea after operation.

CASE IX.—R. T., male, aged 18. Removal of sequestrum. No temperature. Ordinary diet before operation; fish after.

CASE X.—A. S., male, aged 22. Removal of sequestrum. No temperature. Ordinary diet before; milk and beef-tea afterwards.

CASE XI.—T. S., male, aged 15. Removal of tumour from sphenoid. Much haemorrhage. Temperature 100° second day, after then declined. Ordinary diet before operation; milk and beef-tea after.

CASE XII.—Mrs. P., female, aged 30. Radical cure femoral hernia. No temperature. Fish diet to day before, then milk.

CASE XIII.—Mrs. H., female, aged 25. Dilatation of cervix uteri under

anaesthetic. No cutting operation. No temperature. Ordinary diet before; resumed 8 hours after operation.

The operations were thus of all types of severity, but, speaking generally, were followed by little or no pyrexia; the haemorrhage was slight, and the diet was by no means of a highly nitrogenous nature. It may be mentioned that the mean total nitrogen of three separate estimations of average hospital beef tea was 2.46 grams per litre, and that in no case was this quantity of beef-tea exceeded in twenty-four hours. Tested similarly, milk gave an average 4.95 grams total nitrogen per litre, and not more than $1\frac{1}{2}$ to 2 litres would be given in twenty-four hours.

The urine of the twenty-four hours was collected, and mixed, and measured, and a sample was used for the various estimations. In all cases the total nitrogen, urea, and uric acid were estimated directly; the xanthin bases were estimated by subtraction.

The total nitrogen was estimated by Kjeldahl's method, urea by the sodium hypobromite method in Dupré's apparatus, and uric acid by Hopkins's method. With regard to the estimation of urea, it must be noted that I have indicated in another place⁴ that the addition of 10 per cent. glucose to the urine increases the amount of urea nitrogen by about 9 per cent. In the results given below correction has therefore been made for this factor, and for the error in the particular apparatus employed, as determined by estimating a 2 per cent. watery solution of chemically pure urea.

Examination was made of the urine passed by the patient on the day before the operation and the three days succeeding the operation. These four periods are hereinafter denoted by the Roman figures I, II, III, IV the operations thus occurring between I and II.

In some instances it was unfortunately impossible to obtain the full twenty-four hours urine, as some was lost with the faeces; but cases in which this source of error could be definitely excluded agree so well with the others in their essential points that it is probable that no serious source of error has been introduced thereby.

RESULTS.

It will be convenient if at the outset tables are given (Tables I and II) of the entire series of estimations made in a typical case, and (Tables III and IV) of the condensed and combined results in the 13 cases.

In the selected case (No. 5, S. M., in list) anaesthesia was produced for the purpose of cystoscopy, nothing further was done and the total administration of ether lasted about 20 minutes. The patient preserved a normal temperature, and resumed full diet twelve hours after the administration.

TABLE I.—S. M., 24 years Case 5.

Day in Roman Figures as noted above.	Amount of Urine in 24 hours in cubic centimetres.	Percentage of Total Nitrogen (Kjeldahl).	Percentage of Urea.	Percentage of Uric Acid.	Percentage of Nitrogen Passed as Xanthin Bodies.	Total Nitrogen Excretion in 24 hours.	Total Urea in 24 hours.	Total Uric Acid in 24 hours.	Total Nitrogen Passed as Xanthin Bodies in 24 hours.	Remarks.
I	1077	1.54	3.50	0.05	0.02	16.58	34.46	0.54	0.32	Anaesthetic
II	1256	0.91	1.60	0.07	0.15	11.44	30.09	0.88	1.77	
III	877	1.56	2.81	0.07	0.22	13.69	24.64	0.61	1.99	
IV	1559	1.15	2.24	0.02	0.09	17.93	34.92	0.31	1.54	

TABLE II.*

Day.	Total Nitrogen Excretion.	Total Nitrogen Passed as Urea.	Total Nitrogen Passed as Uric Acid.	Total Nitrogen Passed as Xanthin Bodies.	Percentage of Total Nitrogen Passed as Urea.	Percentage of Total Nitrogen Passed as Uric Acid.	Percentage of Total Nitrogen Passed as Xanthin Bodies.	Remarks.
I	10.58	16.08	0.18	0.32	97.90	1.09	1.01	Anaesthetic.
II	11.44	9.38	0.29	1.77	81.90	2.53	15.48	
III	13.69	11.50	0.26	1.99	84.00	1.46	14.54	
IV	17.93	16.29	0.10	1.54	90.85	0.56	8.59	

* Summary of nitrogen excretion in above case, with percentages deduced from total nitrogen per cent., urea per cent., and uric acid per cent. The "xanthin" columns are in every case estimated by subtraction from the total nitrogen of the group in which they are placed, and hence are probably not strictly correct with one another beyond the first place of decimals. This, however, is immaterial.

TABLE III.*

Case.	Day.	Total Nitrogen in 24 hours in grams.	Total Urea. Ditto.	Total Uric Acid. Ditto.	Total Xanthins. Ditto.	Percentage of Total Nitrogen Passed as Urea.	Ditto as Uric Acid.	Ditto as Xanthins.
I	1	8.85	13.68	0.24	2.40	71.90	0.90	27.20
	2	10.62	19.50	0.80	1.26	85.66	2.40	12.00
	3	9.78	15.93	0.22	2.29	74.80	0.70	23.50
	4	15.85	22.65	0.46	5.20	66.00	0.90	33.10
II	1	8.92	16.08	0.43	1.29	83.90	1.50	14.60
	2	5.40	10.15	0.44	0.57	87.00	2.50	10.50
	3	10.24	18.48	0.17	1.44	85.40	0.49	14.11
	4	6.42	12.70	0.19	0.57	90.30	0.70	9.00
III	1	6.54	8.28	0.25	5.61	28.80	1.20	40.00
	2	7.47	14.72	0.45	0.48	91.80	2.00	6.20
	3	10.33	30.93	0.57	1.72	88.20	1.10	10.70
	4	17.25	25.87	0.79	4.95	69.70	1.50	28.80
IV	1	8.27	17.13	0.23	0.22	97.30	0.84	1.86
	2	8.79	16.80	0.71	0.71	89.10	2.60	8.30
	3	18.33	35.69	0.33	1.63	90.50	0.60	8.90
	4	6.35	13.39	0.14	0.08	98.10	0.60	1.30
V	1	16.58	34.46	0.54	0.32	97.90	1.09	1.01
	2	11.44	20.09	0.88	1.77	81.90	2.53	15.48
	3	13.69	24.64	0.61	1.99	84.00	1.46	14.54
	4	17.93	34.92	0.31	1.54	90.85	0.56	8.59
VI	1	7.16	13.30	0.27	0.98	85.00	1.20	13.80
	2	8.54	14.57	0.40	1.65	79.50	1.50	19.00
	3	17.16	21.36	0.72	6.98	52.00	1.30	46.70
	4	Specimen lost						
VII	1	11.88	24.42	0.20	0.44	95.40	0.50	4.20
	2	6.07	10.05	0.40	1.42	73.90	2.60	23.50
	3	10.88	19.40	0.68	1.63	83.40	2.02	16.50
	4	22.99	41.99	0.23	3.30	84.90	0.30	14.80
VIII	1	19.32	35.18	0.23	2.87	84.70	0.30	15.00
	2	3.25	6.61	0.18	0.13	96.00	1.40	2.60
	3	24.74	40.72	0.44	5.63	76.60	0.50	22.90
	4	18.06	25.61	0.38	6.04	65.80	0.60	33.60
IX	1	12.08	21.10	0.14	2.67	77.60	0.30	22.10
	2	3.84	6.33	0.24	0.82	76.50	2.08	21.42
	3	8.8	15.13	0.20	1.18	85.90	0.90	13.02
	4	8.7	9.58	0.42	4.15	50.80	1.60	47.60
X	1	13.08	16.01	0.84	5.38	56.70	2.10	41.20
	2	5.29	8.61	0.37	1.18	75.40	2.20	22.40
	3	18.57	31.15	1.03	3.78	78.00	1.60	20.40
	4	25.77	35.25	0.81	9.05	63.70	1.04	36.26
XI	1	12.85	17.37	0.36	6.99	44.70	0.90	54.40
	2	4.49	7.39	0.26	0.98	76.30	1.70	22.00
	3	8.83	14.86	0.33	1.79	78.40	1.20	20.40
	4	12.65	24.73	0.36	1.05	90.70	0.90	8.40
XII	1	6.33	14.24	0.31	0.00	97.20	1.40	1.40
	2	2.83	5.89	0.04	0.15	96.40	0.30	3.30
	3	12.32	23.03	0.68	1.24	88.00	1.80	10.20
	4	4.89	6.99	0.18	1.57	66.60	1.20	32.20
XIII	1	9.93	16.51	0.43	2.09	77.50	1.40	21.10
	2	5.53	9.06	0.33	1.20	76.30	1.90	21.80
	3	7.64	14.87	0.35	0.59	90.70	1.50	7.80
	4	8.75	13.96	0.44	2.09	74.40	1.70	23.90

* Totals of nitrogen, urea, uric acid, and xanthins passed on each "day" by the 13 cases. Also percentages of total nitrogen accounted for by urea, uric acid, and xanthin bodies. For the purposes of this paper the term "xanthins" must be considered as equivalent to "nitrogen passed as xanthin bodies."

TABLE IV.—Composite Table of all Cases in Table III.

Case.	Day.	Average of Total Nitrogen in Grams.	Ditto of Urea.	Ditto of Uric Acid.	Ditto of Xanthins.	Average Percentage of Total Nitrogen Passed as Urea.	Ditto as Uric Acid.	Ditto as Xanthins.
Composite of Nos. I to XIII	1	10.87	17.12	0.34	2.49	79.00	1.06	21.4
	2	6.43	11.52	0.45	0.95	83.70	1.04	14.6
	3	12.71	23.57	0.49	2.45	81.40	1.17	16.6
	4	22.14	22.22	9.41	3.29	70.91	0.91	37.0

TOTAL NITROGEN EXCRETION.

The most striking result with regard to the total nitrogen excretion (Table IV) are: (1) That there is a marked fall

on the day after etherization; (2) and a considerable rise on the two subsequent days.

So much is this the case that according to this table, on the day after the operation the total nitrogen excretion is little more than half the excretion on the day before the operation, whereas on the fourth day the total nitrogen excretion is practically double the normal. In only four cases was the rule of a fall on the day after the operation not observed. With reference to the subsequent rise, although Table IV. shows that the maximum occurred on the fourth day, this was not absolutely true in the individual cases, for in six cases the maximum occurred on day 3. It may therefore be concluded that a rise in total nitrogen excretion may be expected on days 3 or 4.

EXCRETION OF UREA.

In spite of the dogmatic assertions that have been made as to the behaviour of urea excretion after anaesthesia, it has been impossible in this set of experiments to speak with absolute certainty.

The total urea columns in Tables III and IV show that there is a general tendency for urea to fall on the day after etherization, and in Table III this fall occurs in 9 out of 13 cases. In half of the cases which show a rise, that rise is only fractional. As might be expected from the total nitrogen results, in every case except ix and xiii the maximum urea excretion was reached on days 5 and 4, and was in excess of that on day 1. The percentage columns in Table IV, to which special attention is drawn, show that there is a general tendency for the percentage excretion of urea nitrogen on day 2 to rise above, and on day 4 to sink far below, its percentage on day 1. Such a fall, in the face of the average doubled output of total nitrogen on day 4 and the low amount and low percentage excretions of uric acid nitrogen, is most significant, and points to a profound change in the composition of the urine, in virtue of which nitrogen tends more and more to be eliminated by other bodies than urea. In the individual cases, such a fall in percentage on day 4 is shown in 8 cases out of 13.

EXCRETION OF URIC ACID.

One of the most interesting results in the whole investigation has been that in connexion with uric acid. In every single case the anaesthesia has been followed by a marked rise in the percentage excretion of uric acid, and in every case but one (xii) the maximum is reached on the day after the operation. Naturally, this result is very well marked in the composite case, which also shows clearly that the average daily excretion on days 2, 3, and 4 is almost always in excess of that on day 1. The regularity of this increase in percentage excretion of uric acid contrasts so strongly with the irregularity observed in the individual cases in respect of the excretion of urea and xanthins as to suggest the existence of some constant physiological factor in the case. Halliburton includes amongst conditions leading to an increase of uric acid (a) diminution of oxidation processes, (b) processes leading to metabolism of nucleins. The former condition certainly obtains in ether administration by the closed method; the latter is the necessary consequence of most surgical operations and of the starvation diet accompanying them. Besides which in two cases (not included in my series) prepared for operation, but not operated on, a distinct percentage rise of uric acid nitrogen took place on day 2 and day 3 respectively. This suggests that the nervous state of the patient may have something to do with the phenomenon.

EXCRETION OF XANTHIN BODIES.

From the method in which these bodies were calculated it will be seen that in total amount and percentage they must vary inversely as the urea, and that in consequence their accuracy is at best relative, and stands or falls by the correctness of the urea estimations. It therefore merely remains to attempt to account for their presence and proportionate amount.

Mr. Tyrrell⁵ quotes a patient's statement with approval, that "taking ether for an hour and a-half is very hard work," and there certainly is an analogy between the effects of prolonged etherization and exhausting bodily work.

Drs. Dunlop, Paton, Stockman, and McAdam state that in all persons severe muscular exercise is followed by increased output of total nitrogen and of urea, but that if the person is out of condition the output of uric acid and extractives is also increased.

Whilst probably none of the cases in the present series were in any athletic conditions, it is noteworthy that of the

whole series those five cases whose total xanthin percentages for the four days exceed the average as determined by the composite table include both the tuberculous cases and the necrosis and sarcoma cases (Cases i, vi, ix, and xi), and only one case who was presumably in fair condition, namely, Case x. The other cases were in general health or as (in Case v, bilharzia) had been for a long time under hospital treatment, which is clinically known to put a patient in the very best position for standing an operation or anaesthetic.

I have only in conclusion to tender my sincerest thanks to Dr. W. S. Lazarus-Barlow for permitting me to make all the estimations in the Westminster Hospital Clinical Laboratory, and for much help and advice; and to the staff of the hospital—most especially to Mr. Spencer—for permission to make use of the cases under their care.

I also desire to state that I have previously worked at urea excretion in collaboration with Dr. Eldon Pratt, now of Henfield, Sussex. My departure on active service brought our joint experiments to an abrupt conclusion. I have therefore left the question of publication entirely in his hands.

REMARKS.

1. Percentage of total nitrogen contributed by urea. "Eighty-six per cent. is not below the average determined by Gumlich and Bohland."⁷

2. Average daily excretion of uric acid as here determined may be compared with Smith-Jerome's determinations. In my cases the diet is certainly not highly nitrogenous, and the uric acid average compares fairly with that given by him both for "ordinary" and "nuclein" diets.⁸

3. If it be granted that my results coincide fairly with those of the above-mentioned authorities as to urea and uric acid, my reduced figures with regard to xanthin bodies may be allowed as fairly accurate. They are, I think, larger than is usually admitted.

REFERENCES.

- ¹ "Action des Inhalations Chloroformiques sur l'Élimination de l'Azote par les Urines," *Bull. Soc. Chirg., Paris*, 1884. ² BRITISH MEDICAL JOURNAL 1900, vol. ii, p. 833. ³ *Uric Acid in Health and Disease*, p. 587. ⁴ BRITISH MEDICAL JOURNAL, January 24th, p. 194. ⁵ *Transactions of the Society of Anaesthetists*, vol. i. ⁶ *Journal of Physiology*, vol. xxii, p. 90. ⁷ Paton and Eason, *Journal of Physiology*, vol. xxvi, p. 109. ⁸ *Journal of Physiology*, vol. xxv, p. 99.

THE PROCESS OF CHEMICAL SYNTHESIS IN LIVING THINGS.*

By ARTHUR CROFT HILL, M.A., M.D.,
Late George Henry Lewes Student in Physiology.

SOME years ago—it was in 1896 that I began experimental work on this subject—I was struck by the fact that nothing was known of the manner in which the synthetic process occurred in living organisms, although, concerned as it must be in such elementary functions as tissue nutrition and the growth and multiplication of the tissue units, it is ultimately the most fundamental phenomenon of life. Building up and breaking down of tissue considered together constitute what is known as metabolism, and are the constant characteristics of all forms of life, down to the simplest organism known. They must, too, be considered together, for as it is the object of this paper to set forth, they are but phases of one and the same process, and it is because the process of breaking down has not been fully understood in the past that the process of building up has not been seriously studied at all, but, on the contrary, has been relegated to a realm outside the exact sciences, and ascribed to a mysterious "vital" force of an only less mysterious protoplasm.

Foster, in his introduction to his *Textbook of Physiology* (ed. v, 1891), divides physiology into two great divisions, one having to do with the renewal of substance and the replenishment of energy, the other having to do with the setting free of energy. With regard to the general problem of how metabolism of living substance takes place, he says, "the answers which we can at present give can hardly be called answers at all."

From theoretical considerations alone, I was able to construct a hypothesis for the anabolic process in which intracellular ferments played a leading part, but it required for its justification the experimental proof that ferment action, at that time known only in connexion with chemical change in

* Abridged from a Thesis for the M.D. degree in the University of Cambridge.