REMARKS

ON THE

TOXIC ACTION OF IMPURE CHLOROFORM.

An account of Experiments on Animals made in the Pharmacological Laboratory of the University of Berlin.

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PROFESSOR PICTET's new method of refining chloroform offers great facilities for deciding certain questions hitherto treated with remarkable indifference by medical men: What is the difference between the action of pure and impure chloroform? Do the impurities of chloroform increase its dangers? Have they any particular toxic action? Opinions on this subject are divided and even uncertain. Though it is by no means generally acknowledged by surgeons that the impurities are dangerous, still after an accident as a rule great concern is shown to have it proved that the drug was pure. Sédillot asserted, and Lucas-Championnière has shown by clinical evidence, that the dangers of chloroform may be due to impurity. Nevertheless, nobody has undertaken to investigate the physiological action of the impurities described and communicated to the scientific world by Mr. Dott.

Pictet's process mainly consists in subjecting chloroform to intense cold, by which it is caused to crystallise. The mother liquor being drawn off and the crystals being allowed to liquefy, it is obvious that the liquid obtained must be chemically pure chloroform. All the impurities of the original material must now be contained in the mother liquor. From this, on repeating the operation, a considerable quantity of crystallised chloroform may again be separated; but in order to be on the safe side the proceeding is not strained to the utmost, and the ultimate residue still contains so much chloroform that it is hardly to be distinguished from the ordinary drug. The numerical proportion of this residue to the original quantity is 3-5:100.

Thus, the chloroform as ordinarily used is divided by Professor Pictet's process into two portions, one of which is undoubtedly pure, whereas the other as assuredly contains all the foreign substances contained originally in the whole. By comparing the physiological action of these two portions we shall be enabled to answer the questions put above.

TABLE I.

	Residue.		Chlorof. Medicinale (Pictet).	
	Minutes of Duration.	Frequency in $\frac{1}{4}$ -min.	Minutes of Duration.	Frequency in $\frac{1}{4}$ -min.
	10*	6	10*	11
	10	9	10	10
	10*	10	10*	9
	10*	11	10*	9
	12*	5	10*	8
	13*	6	10*	8
	13	7	13*	6
	15†	3	15†	10
	15†	5	—	—
Total ...	108	62	88	71
Average ...	12.0	6.6	11.0	8.8

Note.—An asterisk marks the figures corresponding to experiments with the undistilled mother liquor, a cross those taken after inhalation of the drug from cup under dry cover.

A preliminary series of experiments on the heart of the frog was conducted in the following manner: The frogs were placed in dishes with low glass covers, containing about half an inch of water, with an addition of 1 per cent. of chloroform or of the impure residue. After a more or less prolonged exposure to the action of the drugs, the animals were taken out, the heart laid bare, and its action studied. The tracings taken from these experiments are marked in the figures by an

asterisk. In order to increase the difference between the chloroform and the residue later on, the latter was concentrated by distilling. The method was also varied by simply placing a small cup with chloroform or residue with the frog under the glass cover, without any water. The figures referring to these experiments are marked with a cross. A small number of curarised frogs was examined for comparison.

The frequency of the heart-beats was found to be more diminished by the action of the impure residue than by that of the pure chloroform. While in five curarised frogs the mean frequency in 15 seconds was 11 to 12, under pure chloroform it was only 8 to 10, and under the influence of the impurities 6 to 8. These figures are taken from experiments of medium duration only, as will be seen from Table I.

After too short or too long an exposure to the influence of the drugs, the result was less constant, frequency in some cases decreasing nearly to the lowest standard immediately, and in others rising above the normal even after prolonged intoxication. Still the total average of all the observations made, shown in Table II, is also slightly in favour of the pure chloroform.

TABLE II.

	Residue.		Chlorof. Medicinale (Pictet).	
	Minutes of Duration.	Frequency in $\frac{1}{4}$ -min.	Minutes of Duration.	Frequency in $\frac{1}{4}$ -min.
	7*	9	5*	6
	7*	12	5*	6
	8*	9	20†	1
	8*	9	20	
	20†	9	20†	5
	20†	13	20†	5
	22†	6	21†	9
	23†	5	22*	11
	23†	5	22†	10
	25†	3	22†	9
	30†	8	30†	5
	30†	7	—	—
Total ...	223	95	207	83
Carried forward— previous total ...	103	62	88	71
Grand total ...	331	157	295	154
Average ...	15.7	7.5	15.5	8.1

Extreme slowing was only noted under the influence of the impure residue. The difference of action showed equally in the character of each contraction of the heart. Under chloroform the movement appeared simply slowed but otherwise normal, whereas, under the residue, diastolic expansion took place in two phases, the ventricle at first relaxing its tension and then being suddenly expanded by the contraction of the auricle. The heart remained abnormally long in diastole. In many cases the contraction was of the peristaltic type common to heart depressants, in others the lower portion of the ventricle appeared to be paralysed.

In order to be able to analyse and compare these observations at leisure, tracings of the movement of the heart were taken by means of an apparatus constructed by Dr. Cowl and Professor Gad. A few words will suffice to explain the method, and enable the reader to interpret the tracings for himself. The apparatus consists of two equal parts, intended to trace the movement of two separate parts of the heart simultaneously. Each of them is simply a pivoted lever with one branch resting by means of a wire prop immediately on the surface of the heart, while the other longer one acts as a pen in contact with the drum of the kymograph. The relative position of the levers is adjustable by means of a double sliding action, and they are moved to and from the drum by means of screws. The pressure of the props on the heart can be regulated by movable weights, one end of the lever going down; the other, of course, goes up. Contraction of the heart, therefore, is marked by a rise, expansion by a descent, in the tracing. Details will easily be understood by reference to the typical tracing and its explanation as given by the first observers and quoted here. (Fig. 1.)

Fig. 1.—Typical cardiographic tracing of the frog by Cowl and Gad. *Physiol. Centralb.*, 1888. From a to b the tension of the ventricle increases till at b the valves are forced open. From b to c the blood is leaving the ventricle, from c to d the empty ventricle remains in systole. The rise of the tracing from d to e corresponds to the descent of the prop into the surface of the relaxing ventricle previous to its expansion. From e to f the ventricle is refilling; from f to a the ventricle remains in diastole.

One lever was applied to the base, the other to the apex of the heart without particular result, as either the tracings of both were identical, or one showed hardly any movement at all. One of the tracings obtained from a curarised frog corresponds very nearly to that given by Cowl and Gad, with the only difference that the expansion is not so marked, and, therefore, the rounded angle of the tracing between diastolic relaxation and the commencement of tension is more developed (Fig. 2).

Fig. 2.—Cardiographic curve of curarised frog. $F=11$.

In the chloroform tracings two distinct types appear; the first is pretty nearly normal, and has the shape of a wave, rising in a convex line to a sharp angle. This tracing results from experiments of medium duration (Fig. 3).

Fig. 3.—Cardiographic curve of frog under chloroform after ten minutes. $F=8$.

After prolonged intoxication the wave is depressed and rounded; frequently the tension movements cause peculiar and even irregular tracings (Figs. 4 and 5).

Fig. 4.—Cardiographic curve of the frog after twenty-two minutes under chloroform. $F=8$.

Fig. 5.—The same after fifteen minutes. $F=10$.

The same distinction holds good with regard to tracings under the residue. In a slight degree of poisoning the shape of the wave is even nearer to the normal one than that of the

Fig. 6.—Cardiographic curve of the frog after ten minutes' action of the residue. $F=7.8$.

pure chloroform, only that it shows nearly straight lines and sharp angles. The rising part is slightly concave, the systole

is very short, and the relaxation marked by a sudden break in the tracing which forms a peak, as it is immediately followed by a rapid descent corresponding to the expansion of the ventricle. Commencement of tension is likewise marked by a straight line (Fig. 6).

If intoxication is carried very far, only a low concave wave line appears on the tracing (Fig. 7). Irregularities also occur, sometimes of a periodic type (Fig. 8).

Fig. 7.—Cardiographic curve of the frog after twenty-five minutes' action of the residue. $F=3$.

Fig. 8.—Cardiographic curve of the frog after thirty minutes' action of residue. $F=8$.

The main difference between the tracings obtained under chloroform and under the residue consists in the concave outline and narrowness of peak in the latter. If they represented blood pressure, the work done by the heart to produce the residue tracing might be said to be less than half that required for the chloroform tracing. A cardiographic tracing, however, only indirectly represents the work done by the heart, so probably the actual difference is not nearly so great.

The possibility of establishing the difference of physiological action being thus demonstrated, the experiments were continued on rabbits.

The drugs were administered by inhalation through a tracheal cannula, in order to prevent irritation of the upper respiratory tract. An ordinary test tube containing the drug, and some cotton wool to assist evaporation, was placed before the cannula, air being free to enter on all sides. During inhalation the blood pressure was marked by a Hürthle's manometer connected with the carotid artery, and the respiration by a Marey's drum communicating with the cannula at the point where it was fixed in the trachea. The experiment was generally continued until respiration ceased. The animal was then restored by means of artificial respiration, and allowed to come round till pressure, reflexes, respiration, and general appearance had returned to their normal state. Then the other drug was tried, so as to compare the difference of action on the same animal. This double experiment was in some instances repeated twice, though, as a rule, the animal could not be considered a fair subject for observation after being twice resuscitated. In some experiments the inhalation was interrupted after having lasted sufficiently long for the purposes of demonstration. At the close of the last intended experiment the animal was not allowed to die, but first made to recover, so as to prove that no permanent paralysis of heart or respiration had occurred.

A third series of experiments was made later on, the only difference being that, instead of Hürthle's manometer, a mercury manometer, and instead of the kymograph a paper roll was adopted, in order to obtain a continuous tracing of respiration and blood pressure during the whole experiment. In the fourth experiment an attempt was made to substitute for the test tube a spherical long-necked bottle, but, its action proving uncertain, as will be seen from the remarks in the table (Table III), the original plan was taken up again. After this experience greater care was taken to insure saturation of the breathing air with chloroform. The cannula was forced as far as possible down in the opening of the test tube, the tube itself being held nearly horizontally, the cotton pulled close to the cannula and well saturated by occasional shaking. In the last experiments a roll of blotting paper was put into the tube instead of the wool, in order to obtain a larger surface for evaporation. This method, rough as it may seem, after some experience allows the experimenter to calculate very accurately the

TABLE III.—Showing Results of Thirteen Experiments on Resistance of Respiration and Changes of Blood Pressure.

No. of Experiment.	Weight of Animal in Grammes.	Series of Intoxications.	Drug Employed.	I=Interruption of Exp. S=Stoppage of Resp.	Duration in Minutes.	Arterial Pressure at Commencement of Experiment.		Arterial Pressure at the End of Experiment.		Remarks.
						Diast.	Syst.	Diast.	Syst.	
1	1,600	a	Residue	I	13	—	—	—	—	Abcissa pen has been moved, but it is evident that pressure at the end of b remains higher than in a and c, though the tracing was rising in c. <i>Vide</i> Experiment No. 10.
		b	Chl. Med.	S	20	—	—	—	—	
		c	Residue	S	9	—	—	—	—	
2	1,500	a	Chl. Med.	I	10	80	95	—	—	Figures of blood pressure by measurement on tracing at later date only comparatively exact.
		b	Residue	S	7	55	70	13	27	
		c	Chl. Med.	S	12	70	75	20	32	
3	1,700	a	Chl. Med.	S	27	—	—	—	—	a, momentary interruptions several times. Abcissa line disturbed. Pressure, mean higher, and differences greater in a than in b.
		b	Residue	S	14	—	—	—	—	
		c	Chl. Med.	I	20	—	—	—	—	
		d	Residue	S	7	—	—	—	—	
4	1,950	a	Residue	I	32	—	—	—	—	Dregs of residue in bottle instead of test tube. Big rabbit. No anaesthesia. Other sample of residue for c, does not act for twenty minutes, after shaking up. Death in three minutes.
		b	Chl. Med.	I	26	—	—	—	—	
		c	Residue	S	23	—	—	—	—	
5	1,350	a	Residue	S	9	77	89	24	35	
		b	Chl. Med.	I	15	—	—	—	—	
		c	Residue	S	10	80	89	8	11	
6	1,400	a	Chl. Med.	I	17	75	90	—	—	
		b	Residue	S	9	70	75	30	58	
		c	Chl. Med.	S	12	70	75	36	55	
7	1,100	a	Residue	S	3	110	125	30	42	
		b	Chl. Med.	S	16	125	135	40	55	
		c	Residue	S	3	80	85	42	45	
8	1,250	a	Residue	S	15	85	95	75	27	Resuscitated with difficulty after a. Three-quarters of an hour intervening between a and b.
		b	Chl. Med.	S	10	100	120	25	33	
9	1,050	a	Chl. Med.	S	5	70	100	36	55	
		b	Residue	S	4	100	120	15	20	
10	1,350	a	Residue	S	3	115	120	18	24	Just before stoppage of respiration, temporary rising of blood pressure. Compare Experiment 185, 2 of the Hyd. Comm., <i>Lancet</i> , 1890, i, p. 1391. At its greatest height Diast. = 22, Syst. = 32.
		b	Chl. Med.	S	10	110	125	18	25	
11	—	a	Chl. Med.	S	26	85	115	24	32	
		b	Residue	S	4	100	110	20	25	
12	950	a	Residue	S	2	80	98	27	30	The same rising in the blood pressure as in Experiment 10, a. The blood pressure apparently higher accordingly.
		b	Chl. Med.	S	3.5	80	90	23	27	
13	1,650	a	Chl. Med.	S	14	90	115	38	50	
		b	Residue	S	7	95	120	38	40	
		c	Chl. Med.	S	7	100	120	37	47	

intensity of administration. Thus the experiments as a whole came to represent a series of rising intensity, and the result was found to be the same, whether the drugs were administered sparingly or more freely.

Regarded as experiments on the action of chloroform in general, the results obtained by these experiments corroborate previous observation. The blood pressure appears to be gradually and uniformly lowered from the beginning, but not effectually till the respiration is affected. For some time after respiration has ceased the heart continues beating. The pulse rate is on the whole below the normal, but may rise above it for a period.

The special result of the investigation, that is, the difference found between the physiological action of pure chloroform as opposed to that of the impure residue, is as follows:—

1. No difference was found in the shape of the pulse waves nor in the frequency of respiration, the former being equally affected by both drugs, the latter varying freely.

2. The pulse rate, compared in nineteen cases, is higher at the close of the experiments with residue than of those with pure chloroform.

3. The blood pressure in by far the greater number of the experiments at the moment the respiration stops is higher after inhalation of pure chloroform than after inhalation of the impure residue.

4. The residue causes stoppage of respiration much more quickly than pure chloroform. The periods are as in Table III.

In some cases (Experiments 7 and 15) the expected result did not take place, probably because the dregs of samples of the impurities were being administered. This calls attention to a fact which bears upon all the experiments. The boiling point of pure chloroform is 60° C., that of the residue attains 150° C. The samples in question did not boil under 87°. The vapour tension of the residue is consequently less than that of chloroform; in other words, the residue is far less volatile. The quantity of chloroform inhaled at every breath therefore must have been much larger than the quantity of residue. If both drugs, therefore, killed at the same time, there would still be a difference in favour of the pure chloroform. No method could be devised to avoid this inequality, because the residue is in itself so variable a mixture. Moreover, even without correcting this inaccuracy, the noxious action of the impurities is clearly proved.

In drawing conclusions from these results with regard to the practical use of chloroform, the following facts ought to be borne in mind: The raw material from which Pictet's chloroform is prepared is originally chloroform of superior though not special quality, and pure according to the *Pharmacopœia Germanica*. The impurities accordingly are present even in chloroform ordinarily considered unobjectionable, though, of course, in an extremely diluted state. It seems as if sub-

B.

Fig. 9.—Tracings of Experiment 19, A and B. A.—Residue, 14 minutes; pressure at commencement 108, at end, 18. B.—Chloroform, Med. 2½ minutes; pressure at commencement 103, at end, 18. a, Respiration; b, blood pressure; c, seconds of time.

stances that are noxious only to a degree when concentrated, could not be of much account when diluted in a proportion greater than 1,000:1. This is quite a mistake. Dilution with so powerful an agent as chloroform does not weaken, but, in fact, assists toxic effects by lessening the resisting powers of the organism.

From the above, the doctrine that impure chloroform is dangerous would seem to be experimentally proved. To the rules for administration of chloroform so often given, one omitted by all except Sédillot and his school ought, therefore to be added: That the quality of chloroform be carefully examined, and only the very best procurable employed.

Fig. 10.—Tracings of Experiment 9.

TABLE IV.—*Showing Results of Seven further Experiments with Mercurial Manometer.*

No. of Experiment.	Weight of Animal in Grammes.	Series of Intoxications.	Drug Employed.	Duration in Minutes.	I= Interruption of Exp. S= Stoppage of Respi.	Mean Pressure at Commencement of Exp.	Mean Pressure at End of Experiment.	Remarks.
14	1,450	a	Residue	11	S	—	—	Manometer leaky.
15	2,230	a	Residue	25	I	110	—	Dregs of sample employed. Rabbit large, white, much frightened; resisted violently. Movements and reflex action during experiment. The liquid in the test tube does not smell. New sample for c.
		b	Chl. Med.	4	S	—	14	
		c	Residue	12	I	—	—	
		d	Chl. Med.	16	S	—	—	
16	1,000 1,600	a	Residue	6	S	62	12	Died immediately after connection with manometer. Could not be resuscitated.
17	1,600	a	Residue	3	S	82	10	
		b	Chl. Med.	4	S	90	10	
		c	Residue	2½	S	90	8	
		d	Chl. Med.	3	S	86	8	
18	1,350	a	Residue	2	S	80	17	Blotting paper in test tube. In a accidentally, in b on purpose, a few drops were thrown into the cannula. Pressure fell immediately, but recovered in b.
		b	Chl. Med.	4	S	80	8	
19	1,420	a	Residue	1½	S	108	18	Blotting paper. In c clotting prevents noting the pressure.
		b	Chl. Med.	2½	S	108	18	
		c	Residue	1½	S	—	—	

THE COMPARATIVE SAFETY OF CHLOROFORM IN OBSTETRIC PRACTICE.

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IN the BRITISH MEDICAL JOURNAL of January 16th of this year, Dr. Lombe Atthill remarks: "Chloroform is admittedly nearly safe in midwifery practice; why it should be so when complete anaesthesia is so often produced during obstetric operations I am unable to say. Possibly because, in these cases, involuntary expulsive efforts seldom entirely cease, and, as at the expiration of these, comparatively deep inspiration follows, it may tend to prevent asphyxia, but then the deeper the inspiration the more chloroform will be inhaled."

It appears to me that, presuming chloroform kills mainly by paralysing the respiratory centre, then its greater safety in obstetric work is explicable physiologically. The act of parturition brings into play all the associated movements of extraordinary expiration. This occurs not once only, but as the labour proceeds, the expiratory efforts are intensified in vigour and frequency. In this connection it is most instructive to note the remarks of Professor Foster.¹ The main points are: "A tracing of the respiratory movements is taken from an animal. If the trachea be suddenly closed at the summit of inspiration there is a temporary inhibition of inspiration, and sometimes an attempt at expiration. If the trachea be suddenly closed at the end of expiration the result is an increase of the subsequent inspiration. And assuming on the strength of analogy the existence in the vagi of two sets of fibres, we may say that expansion (of the lungs) stimulates the endings of the fibres which inhibit inspiration, and concurrently tend to augment expiration, while collapse stimulates the fibres which inhibit expiration and augment inspiration."

In the greatly increased expiratory effects of parturition, especially with a temporarily closed glottis, we have a condition which sets the activity of the inspiratory portion of the respiratory centre at a higher index. The waning of increased expiration stimulates the waxing of increased inspiration. Hence, I take it, the centre is less likely to be overwhelmed by an inordinate, or even an ordinary, amount

of chloroform vapour passing through it. It is pleasant to note that Dr. Atthill's observation of the regular sequence of deep inspiration is supported by physiological experiment, but his last sentence that "some would suppose the danger of an overdose being then taken" appears to me scarcely in point. It is a question, not so much of the blood absorbing more chloroform because of the deeper inspiration, but rather of the recognition of the facts that the patient is sufficiently under the influence of the anaesthetic, and that the breathing is going on well. So that, according to all the rules for the administration of anaesthetics, one would diminish the amount of chloroform, allowing only just so much to be inhaled as is necessary to maintain complete anaesthesia with safety.

I am still one of those who, clinging to traditions older than the Hyderabad Commission, deem it necessary to watch the pulse as carefully as the respiration, believing that sudden changes may arise from paralysis of the cardiac centres equally with the respiratory. I can allude to two instances in which the pulse ceased before the respiratory movements. But I fail to agree with Dr. Fancourt Barnes² that the "weaker the heart the more readily does it succumb to the paralyzing action of chloroform, and that when the heart is strong—stronger than usual, as in the hypertrophied heart of pregnancy—it can more easily withstand the action of chloroform." I am inclined to believe that chloroform acts on the respiratory and cardiac nerve centres, and not on the motor apparatus. Further, will anyone advance the proposition that the nervous system is also stronger and more stable during pregnancy? Rather, it is more responsive to unusual stimuli, hence the greater effect of extraordinary expiratory movements during parturition.

SOCIETY FOR RELIEF OF WIDOWS AND ORPHANS OF MEDICAL MEN.—A quarterly court of the directors of the society was held on January 13th. The chair was taken by Mr Henry Lee, V.P., in the unavoidable absence of the president, Sir James Paget. Two new members were elected, and the deaths of four reported. Grants to the amount of £1,436 were made, to be distributed among the 64 widows and 18 orphans receiving assistance from the society. A fresh application for a grant was read from a widow and assistance was given. The death of a widow in receipt of grants since 1879 was reported. The expenses of the quarter were £78.

¹ *Textbook of Physiology*, Fifth Edition, vol. ii, pp. 593-595.

² BRITISH MEDICAL JOURNAL, January 23rd, 1892.