10

PHYSIOLOGICAL PAPERS.

BY

JOHN G. M'KENDRICK, M.D.,

PHYSIOLOGICAL LABORATORY, UNIVERSITY OF EDINBURGH; ASSISTANT TO PROFESSOR JOHN HUGHES BENNETT.

Reprinted from the Edinburgh Medical Journal for January, February, and July 1874.

EDINBURGH:
PRINTED BY OLIVER AND BOYD, TWEEDDALE COURT.

MDCCCLXXIV.

CONTENTS.

PHYSIOLOGICAL PAPERS.

No. I.—*Observations on the Mechanism of the Ear.*

THE vibration of the membrana tympani corresponding to the vibration of the air constituting various sounds, is the first element in the transmission of sound to the internal ear. This membrane is not only placed obliquely at the bottom of the external meatus, but its surface is curved inwards or outwards, according to the relative amount of atmospheric pressure in the tympanum and in the external meatus. As the margins of the membrane are firmly fixed to the tympanic ring, and as its middle portion, attached to the handle of the malleus, is either drawn inwards or pushed outwards, the structure is in a very tense condition, like that of a tightly-strung drumhead. Any one may be convinced of this fact by examining the membrane in a dissected preparation of the ear of any mammal, even after the disappearance of rigor mortis. Consequently any point on the membrane, when the structure vibrates by a wave of sound, will move only through a very short distance—a distance very much less than the wave-length of the sound producing the displacement. The wave-length of any given musical note is found by dividing the velocity of sound in air by the number of vibrations per second producing the note. Taking the velocity of sound in air, at the temperature of 60° F., as 1080 feet per second,[1] we thus obtain the wave-length in the immediate vicinity of the sounding body. But the amplitude of the waves decrease in the ratio of the squares of their distance from the origin of the waves. For example, if the amplitude of the wave producing a note close to the sounding body be 2 feet, at a distance of 2 feet it will be 1-4th of 2 feet; at a distance of 3 feet, it will be 1-9th of 2 feet; of 4 feet, 1-16th of 2 feet, and so on. The greater the distance, therefore, of the sounding body from the ear, the less will be the effect on the membrane of the drum. It is impossible to calculate beforehand the extent of the oscillations of a point on a stretched membrane which may be caused by sounding any particular musical note near it. There are special difficulties (chiefly relating to form and to

[1] Airy on Sound and Atmospheric Vibrations with the Mathematical Elements of Music. 1871. P. 140.

degrees of tension) in the way of doing so in the case of the membrana tympani.[1] The only method open is direct experiment. The extent of the excursion of an illuminated vibrating point on the inner surface of the membrane caused by a tone of a given intensity can, by proper arrangement, be measured. This has been done by several experimenters,[2] including Helmholtz himself; and although there are several differences in their measurements, they still afford information of the greatest importance. Helmholtz has given us data, derived from experiment, by which, if we know the amplitude of the excursion of points on the membrana tympani, we can calculate that of the excursion of points on the handle of the malleus, on the stapes, and on the membrane of the round window (fenestra rotunda). He has shown—(1) That the extent of movement of the membrana tympani as a whole is at least three times that of the handle of the hammer. This arises from the peculiar form of the membrane. (2) That the extent of movement of the process of the incus bearing the stapes, and of the stapes itself, is two-thirds of that of the handle of the hammer. (3) That the extent of movement of the stapes is about equal to that of the round window. We must now abandon the statement that the propagation of sound through the bones of the tympanum to the labyrinth must be effected by undulations of condensation and rarefaction of their particles only, and not by oscillations of the entire bones.[3] The objections to this view are at least the following two:—(1) The length of the chain of bones is only a small fraction of the wave-length of the notes readily detected by the human ear; and (2) if such a small compound body as the chain of ossicles were set into rapid vibrations, tones would be produced so high as to be inaudible.[4] The length of the chain of bones is about nine millimetres. Compare this with the wave-lengths of the following notes which I have calculated:—

	Name of Note in Musical Scale.	Vibrations per second.	Wave-length, in millimetres.
	c_1	33	10,000
	c	132	2,500
In treble stave,	c_4	264	1,250
	F	352	937
	B	495	666
	c_6	1056	312
	c_8	4224	80 nearly.

The mode of action of the bones of the ear, therefore, is not to convey across the tympanum sonorous vibrations, as such, but to

[1] Helmholtz, Mechanism of the Ossicles of the Ear, p. 53 *et seq.*
[2] Ibid. Pflüger's Archiv. f. Physiologie, i. Buck, Knapp and Moos's Archives, vol. i. 1870. Burnett, Knapp and Moos's Archiv., vol. ii. No. 2, p. 45.
[3] Müller's Elements of Physiology, trans. by Baly, vol. ii. p. 1255.
[4] Helmholtz, ibid. As to wave-motion, see Mr Sedley Taylor's "Sound and Music, a Non-Mathematical Treatise on the Physical Constitution of Musical Sounds and Harmony, including the chief Acoustical Discoveries of Professor Helmholtz." London: 1873.

convey to the fluid of the labyrinth the impulses communicated from the membrana tympani, and the mechanical arrangement is such as to reduce the extent of movement of the stapes to at least two-thirds of that of the handle of the malleus. As has been pointed out by Helmholtz, the chain of bones is a lever of the second order, having the resistance between the fulcrum and the power. The fulcrum is the process of the incus which abuts on the wall of the tympanum; the resistance is at the stapes attached to the other process of the incus; and the power is exerted on the handle of the malleus. The distance from the fulcrum to the point of resistance is just two-thirds of the distance from the fulcrum to the power, and consequently the extent of movement at the point of resistance (the stapes) is two-thirds of that at the handle of the malleus, where the power is applied. Thinking over these facts, and others which have come under my own observation in repeating Helmholtz, Buck, and Burnett's experiments, it has occurred to me to attempt to calculate the amount of movement which a point on the stapes, or the stapes itself, would perform, if impulses were communicated to it from the membrana tympani set in vibration by very high musical tones of a certain intensity. There are experimental difficulties in the way of observing vibrating points on the stapes while performing very minute excursions. It is difficult to obtain sufficient illumination to examine the point with high microscopic powers. Burnett succeeded in five experiments in observing excursions on the head of the stapes produced by an organ pipe giving 1160 vibrations per second, and in one experiment he failed. The amplitudes of excursion observed were thousands of a millimetre. Excursions on the membrana tympani can be seen more readily. The calculations which I have made are only approximations; but they show the extent to which the motion implied in the wave-length of a musical note in air is reduced by the mechanism of the middle ear. I have proceeded as follows: Taking the average amplitudes of the excursions at the point of the long process of the hammer, I have assumed, on the one hand, the correctness of Helmholtz's statement that the mean of the motion of the membrana tympani is three times as much; and on the other the evident fact (on the lever theory) that the movement of the stapes is two-thirds of that of the handle of the malleus. In the case of those tones which produce movements so slight that as yet we have not surmounted the experimental difficulty of observing them, I have also assumed that the membrane and handle of the hammer would vibrate to a smaller extent in direct proportion to an increase in the number of vibrations producing the tone, and I have calculated accordingly. This, of course, is so far an erroneous basis on which to found a calculation, because membranes do not vibrate in such a regular manner. Still, with notes of the same intensity but of different pitch, the excursions of a point on a vibrating membrane will be greater for a note of low than for a note of high pitch, and intermediate notes will occupy nearly certain definite points in the scale. In the meantime, therefore, until direct observation has been made of the vibrating point, I have hazarded the assumption. The following table shows the results in fractions of a millimetre:—

Note produced by	Mean displacement of membrana tympani.	Excursions at point of handle of malleus.	Excursions at the stapes.
50 vibrations p. second	$\frac{3}{28}$	$\frac{1}{28}$	$\frac{1}{42}$
132 "	$\frac{9}{100}$	$\frac{3}{100}$	$\frac{1}{30}$
264 "	$\frac{9}{200}$	$\frac{3}{200}$	$\frac{1}{100}$
352 "	$\frac{33}{1000}$	$\frac{11}{1000}$	$\frac{11}{1500}$
630 "	$\frac{1}{42}$	$\frac{1}{125}$	$\frac{1}{188}$
1,160 "	$\frac{1}{86}$	$\frac{1}{250}$	$\frac{1}{375}$
4,224 (highest note used in ordinary music)	$\frac{3}{1000}$	$\frac{1}{1000}$	$\frac{1}{1500}$
6,000 "	$\frac{9}{5000}$	$\frac{3}{5000}$	$\frac{1}{2500}$
8,000 "	$\frac{1}{666}$	$\frac{1}{2000}$	$\frac{1}{3000}$
15,000 "	$\frac{1}{1666}$	$\frac{1}{5000}$	$\frac{1}{7500}$
38,000 (highest audible sound)	$\frac{3}{10000}$	$\frac{1}{10000}$	$\frac{1}{15000}$

It thus appears that the amplitude of the excursions of the stapes when produced by even the highest notes is enormous as compared with the wave-lengths of light which affect the retina. This will be at once seen by comparing the figures given above with the following table, which shows the wave-lengths of the mean rays of the several colours of the spectrum in fractions of a millimetre:[1]—

Colour.	Wave-length in ten-millionths of a millimetre.
Red	6·20
Orange	5·83
Yellow	5·51
Green	5·12
Blue	4·75
Indigo	4·49
Violet	4·23

If, therefore, there be any analogy between the ultimate action of sound on the auditory terminal apparatus, and that of light on the retina, the arrangements in the vestibule, canals, and cochlea must be such as still further to reduce extent of movement. The fluid in the labyrinth is surrounded by resisting walls, and is practically incompressible. But, as Helmholtz indicates, a single shock communicated to such a fluid contained in a confined space is communicated through it in every direction many times in an inconceivably short space of time. Thus the comparatively extensive excursions of the stapes affect the fluid in the labyrinth, and the delicate thrills so produced

[1] Article on Light by Roscoe, in Watts's Dictionary of Chemistry, vol. iii. p. 600.

may act on the vibratile structures in the vestibule or on the rods of Corti, and so cause impulses quite as minute as those of the waves of ether impinging on the retina. A highly educated ear can detect many variations in sound, just as an educated eye can distinguish many slight shades of colour, and the one organ is probably as finely constituted as the other. There is this difference between them: waves of light do not require to be reduced in amplitude before they impinge on the retina, and, therefore, there are only refractive structures through which they must pass so as to be brought to a focus. The total amount of energy in light is not reduced, except to an infinitesimal degree. But, in the case of the ear, there is a complicated apparatus for reducing extent of movement. Only a small fraction of the total amount of energy of waves of sound reaches the delicate organs in the depths of the internal ear.

No. II.—*On the Inhibitory or Restraining Action which the Encephalon exerts on the Reflex Centres of the Spinal Cord.*

The question as to whether the grey matter of the brain, under any circumstances, inhibits or restrains reflex actions in the spinal cord, has been investigated by several Continental physiologists, who have, however, differed in their conclusions. Setschenoff[1] was, so far as I am aware, the first who asserted that the grey matter of the brain of the frog inhibited the reflex action of certain centres in the spinal cord. The same was asserted to be the case in dogs by another inquirer named Simonoff.[2] An elaborate experimental inquiry was made on the frog by Paschutin,[3] with the following result: irritation of the hemispheres of the brain diminished the tendency to reflex action produced by placing a drop of acid on the skin, while the tendency to reflex action excited by gentle titillation appeared to be increased. On decapitation, the tendency to reflex action excited by titillation was diminished.

On the other hand, Herzen,[4] after a series of experiments in Schiff's laboratory, was obliged to come to an exactly opposite conclusion—namely, that there is no such inhibitory action.

The theory of an inhibitory action of certain nerves over reflex nervous centres which act automatically may be now considered as established in several instances, such as (1) the action of certain fibres of the vagus on the ganglia of the heart, (2) the action of the chorda tympani partly as a vaso-inhibitory nerve, diminishing arterial tonus—that is, the normal amount of contraction of the

[1] Ueber die Hemmungs-mechanism für die Reflex thätigkeit des Ruckenmarks. Berlin, 1863.

[2] Reichert's Archives, v. 545.

[3] Centralblatt, 1865, p. 794.

[4] Beale's Archives, 1867.

vessels—in the sub-maxillary gland, or (3) the action of a portion of the splanchnic nerves as affecting the heart and the vaso-motor centres of the intestines.

I have repeated many of the experiments made by the observers above quoted. The difference stated by Paschutin as existing between the tendency to reflex action produced by acids irritating the skin and that caused by gentle titillation has not been observed. The method of inquiry I adopted was, in the first instance, to observe the amount of reflex action produced in an animal anæsthetized when an area on the skin was excited by an electrical stimulus of definite strength, and afterwards to note whether the same amount of reflex action was obtained by the same strength of stimulus, applied to the same place, during electrical stimulation of the surface of the cerebral hemispheres. The results of this method were far from being satisfactory. Sometimes, during stimulation of the surfaces of the hemispheres, reflex action was weaker, but as frequently no effect was observed.

Another mode of experiment was adopted, which satisfied me that when a strong nerve-current is transmitted down the spinal cord, reflex action may be restrained or inhibited. Instead of detailing many experiments, it will better suit the purpose of this article to give an illustration of the method. On decapitating a pigeon (after it has been chloroformed), the body lies for a second or two comparatively still. There is muscular tremor in all parts of the body. As the cord loses its supply of blood, the muscles become violently convulsed. With outspread and quivering wings, the convulsions are frequently so great as to cause the body to throw backward somersaults. Now, if, during these convulsions, the body be held loosely by an assistant, and a current from the secondary coil of an induction machine, sufficiently strong to be felt acutely by the tip of the tongue, be applied to the upper end of the cord so as to stimulate it, the convulsions diminish in violence, and may be even nearly arrested. On removing the stimulus, the convulsions recommence. In this experiment, the electrical stimulation of the upper end of the cord excites nerve-currents, which pass downwards through the cord, and these currents apparently restrain the action of the reflex centres. To succeed in the experiment, the electrical stimulation must neither be too strong nor too weak. If too strong, there will be a violent convulsive attack which exhausts the nervous energy of the cord at once; if too weak, no effect will be observed. This is in accordance with Professor Lister's observation, that the degree or amount of stimulation affects the result in all experiments on nerves.

Another kind of experiment I have made, which is even more satisfactory. There has been a dispute among experimental physiologists as to whether or not the columns of the spinal cord can be stimulated directly in any way, by electrical, chemical, or mechanical agents? The statement in the affirmative is supported by

Fick [1] and Engelken;[2] while it is denied by many other authorities, such as Van Deen, Schiff, Guttmann, Funke, Sigmund Mayer,[3] Huitzinga,[4] and Aladoff.[5] Aladoff asserts that the posterior columns are irritable while the anterior are not so. The matter is one which is not so easy to settle as might be imagined—indeed, the array of names known in physiology, which I have quoted, at once indicates a difficulty. It is possible I may have omitted the names of others who have investigated the matter. The difficulty is twofold: (1) on applying electrodes to the anterior columns, the anterior roots of the spinal nerves may be directly irritated and muscular contractions will consequently take place; and (2) on applying electrodes to the posterior columns, the posterior roots may be directly irritated so as to produce muscular contractions by reflex action. In neither of these instances can it be asserted that either the anterior or the posterior columns of the cord have been directly stimulated. In this controversy, I must place myself with the minority. By using very fine electrodes so as to touch only a minute portion of the cord midway between the points of entrance of the roots of the nerves, muscular movements may be induced, not always in the part supplied by the nerves near the electrodes, but in parts supplied by nerves issuing from the cord posterior to the point of stimulation.

Being satisfied that it was possible to stimulate the cord directly, experiments were then made, of which the following is an example:—A pigeon under the influence of chloroform was decapitated, and with as great rapidity as possible the posterior wall of the vertebral canal was removed so as to expose the posterior surface of the spinal cord down as far as the seat of the reflex centres for the legs. Two electrodes of fine wire were placed over the seat of the reflex centre for the wings, and this centre was irritated by an induction current from a Du Bois-Reymond's electromotor, so weak as just to cause slight flapping of the wings. Two similar electrodes were applied to the upper end of the cord. This second pair was in connexion with another similar electromotor, and by moving the secondary coil backwards or forwards, a current slightly stronger than that of the first electromotor was obtained. It was then found that on stimulating the upper end of the cord, the flapping movements of the wings were arrested, which were produced by stimulating the reflex centre (or, at all events, the sensory filaments in connexion with this centre). This proved that the nerve-current, set in action by electrical stimulation at the upper part of the cord, and then transmitted down the cord, was capable of restraining reflex nervous action produced by a stimulation of the posterior columns, or by stimulation of filaments derived from the posterior roots of the spinal nerves.

[1] Pflüger's Archives, 1869, p. 414. [2] Reichert's Archives, 1867, p. 189.
[3] Pflüger's Archives, 1868, p. 167. [4] Pflüger's Archives, iii. p. 181.
[5] Bulletin de l'Academie de St Petersbourg.

In the spinal cord, therefore, there are nerve-tubes conveying influences which restrain the action of reflex centres in that organ. The part of the encephalon from which these nerve-tubes originate I do not know. It may be situated in the grey matter of the cerebral hemispheres. In birds, faradization of the grey matter of the cerebral hemispheres is followed by no muscular movements, so far as I could discover, after numerous experiments, except (*a*) movements of the eyeballs, (*b*) movements of the iris, and (*c*) movements of the lower jaw. This fact has also been pointed out by Ferrier.[1] There are good grounds for believing that many of the motions of birds—such as the movements of the wings during the long flights of migratory birds—are of a purely reflex character. We cannot imagine that each act of flapping the wings is preceded by volition. The successive movements of the wings, exactly similar to each other, depend on an automatic mechanism. But this mechanism may be quickly restrained, in the way I have indicated, by nervous currents passing from some part of the brain to the reflex nerve-centre. These observations also assist in the explanation of how we are able, by a strong effort of will, to restrain in a great measure reflex actions excited by tickling. These movements are reflex, because they may occur (1) during the unconsciousness of sleep, and (2) after disease or injury of the upper part of the cord so extensive as to prevent the transmission of nervous influences upwards to the brain. During consciousness, and with a healthy and uninjured cord, we feel the sensation of tickling, and therefore there must be nerve-tubes conveying sensory impressions to the brain; other nerve-tubes probably terminate in cells situated in the reflex centre. But, as is well known, even while we continue to experience the sensation, we can, by a strong effort of the will, restrain the muscular action. This is an inhibitory influence on the reflex centre.

I have shown, in another paper,[2] that one of the most important functions of the cerebral lobes of birds is in relation to vision. This fact is corroborated by the remarkable experiments of Gudden,[3] who has shown that ablation of the organs of vision in birds newly hatched is followed in after-life by a considerable diminution in the size and weight of the cerebral hemispheres. If, in addition to the perception of visual impressions and the evolutions of nervous energy inducing muscular movements consequent thereon, we also place in the cerebral hemispheres of the bird an apparatus for controlling the reflex actions of the spinal cord which produce syste-

[1] The West Riding Lunatic Asylum Medical Reports, edited by Dr Crichton-Browne, vol. iii. 1873, pp. 33, 34, and 61.

[2] Observations and Experiments on the Corpora Striata and Cerebral Hemispheres of Pigeons, communicated to the Royal Society of Edinburgh by Prof. Turner, on 6th January 1873.

[3] Experimentaluntersuchungen über das peripherische und centrall Nervensystem. Archiv. für Psychiatrie und Nervenkrankheiten, Bd. ii. p. 693.

matic, regular, and simple movements of the wings and legs, we can readily understand how it is that faradization of the surface of these hemispheres is followed by no muscular contractions. The faradization may actually inhibit the reflex centres, and consequently no movements occur.

No. III.—*Comparative Observations on the Physiological Action of Chloral and Bromal Hydrates, and Iodoform.*[1]

CHLORINE, bromine, and iodine present many analogies, both in their uncombined state and in the compounds they form with other elements. For the purposes of this inquiry, I need to specify only one of these analogies, namely, that they are capable of replacing hydrogen from many organic compounds in which that element exists, forming substances which correspond in composition with the original body, but in which one or more atoms of the chlorine, bromine, and iodine have taken the place of an equal number of atoms of hydrogen.[2] Thus, when chlorine gas is passed into absolute alcohol ($C_2\,H_6\,O$), the alcohol is first converted into aldehyde by losing two atoms of hydrogen, and in this compound ($C_2\,H_4\,O$), three of the atoms of hydrogen are replaced by three atoms of chlorine, forming a substance, $C_2\,H\,Cl_3\,O$, termed trichloracetyl, or chloral. In the same manner, by the action of bromine on alcohol, an analogous compound, bromal, is formed; but there appears to be great doubt among chemists as to the existence of any corresponding substance produced by the action of iodine on alcohol.[3]

Hydrate of chloral, for many years a chemical curiosity, is now a valuable member of the *materia medica;* hydrate of bromal is less known; iodal in any form is not to be obtained. The physiological action of hydrate of chloral has been investigated by many competent observers, and is now well known. This substance has attracted so much attention from chemists, physiologists, and physicians, that its bibliography has become very voluminous. So far as I am aware, the action of hydrate of bromal has been examined by only three observers, Rabuteau[4] of Paris, Steinauer[5] of Berlin,

[1] Read before the Medico-Chirurgical Society of Edinburgh, 3d June 1874.

[2] Miller's Chemistry, vol. ii. p. 157.

[3] Watts's Dictionary of Chemistry, article "Iodal," vol. iii. p. 280.

[4] Rabuteau, Note sur trois Anesthesiques nouveaux, le Bromoforme, le Bromal, et l'Iodal. Gaz. Hebdom. de Méd. 43, p. 681.

[5] Steinauer, Ueber Darstellung des Bromal Hydrats und dessen Einwirkung auf den thierischen Organismus. Ber. der Deutsch. chem. Gesellschaft zu Berlin, 18, p. 645, et Repertor für Pharm. xix. 1, p. 55. Reported in Jahresbericht über die Leistungen und Forschritte in der Gesammten Medicin.

and Dougall[1] of Glasgow.[2] Iodal has received attention from only one, Rabuteau, who, in the paper just quoted, describes experiments made with this substance. As he does not mention how the iodal was prepared, and as many chemists have a doubt as to its very existence, it is not improbable that Rabuteau may not have experimented really with iodal, but with some other product of the action of iodine on alcohol. At the same time, it is to be noted that the symptoms he describes as following the introduction into the system of the substance he employed, are very similar to those produced by the introduction of iodoform, which is readily formed by the action of potash on the compound described by various chemists as iodal,[3] in a way analogous to the action of potash on chloral, and bromal, converting these into chloroform and bromoform and formiate of potash respectively.

Bromal hydrate has been specially studied in this investigation, and its action has been compared with that of chloral, with which all are acquainted, and with iodoform, in the absence of iodal, which substance could not be got. The experiments were made chiefly on rabbits, but a few were made on frogs.

I.—General Description of the Action of Bromal Hydrate on Rabbits.

The subcutaneous injection of three grains of bromal hydrate produces the following effects on a rabbit of three or four pounds weight. During the first three or four minutes, nothing is observed. The animal then becomes restless, and moves about quickly; rubs its nose with its fore-feet; the vessels in the ear become dilated and full of blood; the pupil contracts quickly, but at an equal rate, from its original diameter before injection of 6 mm. or 7 mm. to 1 mm.—that is, to its maximum amount of contraction; in one or two minutes more, the bloodvessels of the conjunctivæ, more especially on the inner surface of the lids, are injected, and there is great excess of lachrymal secretion; the mucous membrane of the

Berlin, 1870, I. p. 345; also, Ueber das Bromalhydrat und seine Wirkung au1 den thierischen und menschlichen organismus, Archiv. für Pathol. Anat. Bd. L. Heft 2, p. 235; also, Discussion über einen Vortrag Steinauer's im Berliner Physiologischen Verein, Berlin. Klin. Wochenschrift, xvii. p. 209. Reported in Jahresbericht, *ut sup.* Berlin, 1871, I. p. 345.

[1] Dougall on Bromal Hydrate, Glasgow Medical Journal, November, p. 34.

[2] Since writing this paper, I have observed that Dr B. W. Richardson has experimented with bromal hydrate. He briefly states the general results in his interesting "Report on the Physiological Action of Organic Chemical Compounds," published in the "Report of the 41st Meeting of the British Association for the Advancement of Science, held at Edinburgh in August 1871," pp. 150–1. Dr R. agrees on the whole with Steinauer and Dougall, but he does not profess to give a systematic analysis of the physiological effects of the substance.

[3] Aimé, Annal. ch. Phys. [2] lxiv. 217; Watts's Dictionary, art. Iodal, vol. iii. p. 280.

mouth and nostrils also becomes red, and a profuse secretion pours from the mouth. The amount of secretion is often so great as to endanger the life of the animal from suffocation, and it may be collected easily in a watch-glass. It is a whitish milky fluid to the naked eye. The microscope (× 250 or 300) shows numerous refractive globules of various sizes resembling globules in milk. There are no epithelial or salivary cells. The respirations become gradually more rapid until they are nearly double their normal amount. The cardiac pulsations are in the first instance diminished in number, afterwards they become more rapid, and they may become double the normal number. Towards the period of death, they are much reduced both in number and in force. The animal then lies flat on its abdomen and chest, with the fore and hind limbs in spread-eagle fashion. There is paralysis of both fore and hind extremities. There is no hyperæsthesia so far as can be determined by pinching, or by weak induction currents. In a few minutes more, the head sinks on the table, the respirations become slower and more laboured, the heart beats less rapidly and more feebly; muscular twitchings are seen, and after a few clonic spasms, the animal dies—frequently in a state of opisthotonos. This is a general picture of the action of a minimum lethal dose which kills in from one to two hours. With a larger dose, the symptoms are more intense. The animal becomes much excited, the pupil contracts with great rapidity to its smallest diameter, and after screaming for a few seconds as if in great pain, it dies in convulsions. With a smaller dose, the phenomena just noticed follow consecutively, but the symptoms are less acute, and after a period of stupor, the rabbit may recover.

A *post-mortem* examination made immediately after somatic death usually shows the following facts: (1.) The heart is still pulsating, though feebly; (2.) There is fluid in the pericardial sac; (3.) The heart is nearly in a state of diastole and cannot contract to its full extent; many of the cardiac vessels are full of blood; (4.) There are numerous ecchymosed spots on the surface of the heart, more especially on the back of the ventricles; (5.) The lungs are congested in patches, and there is frequently fluid in the pleura; the bronchial tubes and trachea are gorged with a white frothy fluid; (6.) The veins in the mesentery are intensely congested, and there is fluid in the peritoneum; (7.) The mucous membrane of the alimentary canal, more especially in the ileum, is more congested than normal; (8.) The venous sinuses of the *dura mater* and the vessels on the surface of the brain are filled with dark blood; the brain substance itself appears to the naked eye to be ex-sanguine; (9.) The blood has its normal colour; (10.) The urine is clear, free from albumen and sugar, and apparently normal.

II.—Special Analysis of each Group of Symptoms.

1. *Action on the Nervous System.*

The preliminary excitement evidently indicates either (1.) a specific stimulant action on the substance of the cerebral hemispheres, or (2.) an action on various organs or physiological systems, giving rise, on transmission to the cerebrum, to sensations of uneasiness or pain; or (3.) a combination of both of these physiological states. My impression is, that the latter is the more probable condition. A dose of five grains produces great distress within four or five minutes. The animal is excited and appears to suffer acute pain. This condition is coincident in time with the contraction of the pupil and the dilatation of the bloodvessels. During the first four or five minutes, the animal is quite able to run or leap; but at the end of that period there is staggering, and very soon the power of voluntary movement is lost. The cerebral hemispheres are evidently first affected. The action passes downwards to the base of the brain, and ultimately to the spinal cord. When the cord has been involved, severe convulsions ensue. During the paralytic condition, the nerves are still sensitive to very weak induction currents. Their sensibility and conducting power appear to be intact. The action is therefore on the cerebral and spinal centres, not on the peripheral terminations of the nerves.

2. *Action on the Pupil.*

The pupil becomes rapidly and strongly contracted. The contraction goes on with uniformity, and after the minimum size has been reached, the pupil may remain in this condition for three or four hours after a non-lethal dose. The contraction is coincident in point of time with the dilatation of the bloodvessels, and the diminution of the cardiac pulsations. This would appear to indicate, first, irritation, and, secondly, partial paralysis of the sympathetic nerve, which governs the radiating fibres of the iris. The circular fibres, under the influence of the third cranial nerve, being unopposed, contract the pupil. The amount of contraction is, however, much greater than what can be obtained by cutting the sympathetic nerve in the neck. From this I infer, that not only is the sympathetic nerve partially, or even wholly paralyzed, but there is probably also irritation of the cranial origin of the third nerve. The amount of contraction is greatest after a large dose, and is also most marked during the period of clonic spasms. The vessels of the iris also become engorged with blood. This fact may also assist in explaining the extreme contraction of the pupil.

3. *Action on the Bloodvessels.*

The bloodvessels, as seen in the ear of a rabbit, or in the web or mesentery of a frog, are first slightly contracted. Afterwards they become widely dilated. The first indication of recovery from a non-lethal dose is gradual contraction of the vessels. These phenomena also indicate irritation and afterwards paralysis of the sympathetic nerve. The effects are similar to those produced in the ear of the rabbit by cutting the sympathetic nerve in the neck, or in the web of a frog after division of the sciatic nerve. It was also observed on irritating the sympathetic in the neck of a rabbit under the influence of bromal hydrate with a very weak Faradic current that the bloodvessels in the ear contracted to their normal calibre. This experiment showed that the nerve still retained sensibility and conductivity, and hence I infer the bromal acts on the vaso-motoı centre in the *medulla oblongata*.

4. *Action on the Heart.*

The heart's action is at first somewhat slower than normal. This condition continues only for a very few minutes, and is succeeded by increased action with respect to both force and frequence. This state may be again succeeded by a period of diminished action. There appear to be two distinct effects on the heart, according as the dose is small or large. A very small dose, say one grain to a rabbit 4 lbs. in weight, causes slightly diminished action. If another grain be introduced about ten minutes after the first, the action is still further diminished, while almost invariably a third grain introduced ten minutes later causes slight acceleration, soon followed by diminished action. A lethal dose given in this way, in parts, at intervals of ten minutes, slowly weakens the action of the heart, and the animal dies of syncope. On the other hand, a large dose, say four grains to a rabbit of 4 lbs. weight, causes violent action of the heart, with no apparent depression; and if death speedily ensue, the heart presents the following appearances:—Auricles still pulsating and full of dark blood; ventricles motionless—the right being usually widely dilated, and the left in a state of firm contraction. The vessels of the heart are much congested, and there are frequently ecchymosed spots on the surface. There is usually fluid in the pericardium, and in one case there was an effusion of blood. On stimulating gently the sympathetic in the neck, the heart beats more vigorously; and if a small puncture be made into the right auricle so as to permit of the escape of a little blood, the action for a few minutes becomes almost normal. On stimulating the sympathetic, it was also observed that the vessels on the wall of the heart contracted. From these facts, it would appear, therefore, that bromal hydrate paralyzes the heart by interfering with the action of the sympathetic. I was unable to trace any action on the pneumogastric nerve. With the view of discovering whether bromal hydrate may act on the intrinsic ganglia of the heart, the heart of a frog was fed, according to Coat's method, with serum containing two per cent. of bromal hydrate. The effect was to increase the activity to a very slight extent. Serum containing ten per cent. of bromal hydrate stopped the contractions within two minutes.

5. *Action on the Glandular Structures.*

The excessive secretion from every mucous and serous surface is one of the most noticeable of the effects of bromal hydrate. The action of the salivary glands is much increased. The secretion may occasionally be seen welling out of the duct, and is sometimes so profuse as to threaten the life of the animal by asphyxia. Four grains subcutaneously injected into a cat produced a very copious flow of clear limpid saliva, containing the usual salivary elements. As has been well established by the researches of Ludwig, Pflüger, Heidenhain, and others, each salivary gland is supplied with at least three sets of nervous filaments. For example, the submaxillary gland receives filament from the facial directly, from the sympathetic and from the *chorda tympani.* Irritation of the *chorda tympani* produces, so far as the submaxillary gland is concerned, dilatation of vessels, increased flow of blood, and a large amount of clear, watery fluid. Irritation of the sympathetic, on the contrary, causes contraction of the vessels, diminished flow of blood, and a scanty viscid secretion. My impression is that bromal hydrate may cause increased secretion in two ways:—First, by paralyzing the sympathetic filaments; and, second, by irritating the filaments derived from the *chorda tympani.* This view is confirmed by the effects following the injection of atropine, which, as shown by Heidenhain, deprives the *chorda tympani* of its power of excessive secretion, without interfering with its vaso-inhibitory function. The injection of half a grain of atropine during the profuse salivation following the use of bromal hydrate in the rabbit dries the mouth and arrests the secretion within four or five minutes. It is also supported by the fact that the excessive secretion takes place soon after bromal hydrate has been given. If the dose be not soon lethal, the secretion becomes less and less in quantity, until, at the time when the animal is lying powerless and paralyzed, the mouth has only its normal amount of moisture. The inference, therefore, is that when the motor centres are paralyzed, the centre for the facial is in the same condition, and consequently the *chorda tympani* does not act, either as a vaso-inhibitory nerve, or as directly influencing the secretion. I was unable to determine the *rationale* of the action of bromal hydrate on the serous and mucous membranes. Secretion is everywhere increased. The air-passages are frequently filled with a frothy, whitish fluid, and there is always fluid in all the cavities of the body.[1]

[1] Dr Richardson states in the Report, above quoted, that bromal hydrate (p. 151) "so suddenly and effectually reduces the animal temperature, that the accumulation of fluid in the bronchial canals, from condensation, is a source of positive danger," etc. My impression is, with all deference to this distinguished observer, that this lowering of the temperature, which, to the extent of four or five degrees, undoubtedly happens, is not, at all events, the chief cause of the accumulation of fluid in the bronchial passages, because (1) the fall of temperature, acting on an atmosphere even saturated with

III.—Comparison between the Action of Bromal Hydrate and Chloral Hydrate.

1. Bromal hydrate is a more active substance physiologically than chloral hydrate. A rabbit weighing 4 lbs. requires about twenty grains of chloral to cause death, whereas four or five grains of bromal would be quite sufficient to kill.

2. Chloral hydrate produces in small doses, or soon after a large dose, marked hyperæsthesia followed by anæsthesia. Bromal hydrate never produces hyperæsthesia, and anæsthesia only when the animal is in such a state of coma that there is no hope of its recovery.

3. Chloral hydrate does not usually produce great contraction of the pupil. Bromal hydrate always does.

4. Chloral hydrate acts chiefly on the cerebral hemispheres, and never, so far as I know, has been known to cause convulsions. Bromal hydrate acts less vigorously on the hemispheres, and more on the ganglia at the base of the brain and on the spinal cord, the animal frequently dying in a state of opisthotonos.

5. After death from chloral hydrate, fluid is rarely found in the shut sacs of the body. In the case of bromal hydrate, fluid is almost invariably found.

6. Chloral hydrate does not usually stimulate the salivary glands to the same extent as bromal hydrate does, but in this instance there are exceptional cases in which chloral hydrate causes excessive secretion of saliva in animals.

IV.—The Action of Iodoform.

There is a difficulty in the way of obtaining knowledge of the action of iodoform on account of its want of solubility in any menstruum suitable for subcutaneous injection. It is scarcely soluble in water, acids, or aqueous alkalies, but it is readily soluble in alcohol, ether, and oils, both fixed and volatile. I employed a solution consisting of one grain of iodoform in five grains of alcohol, and fifteen grains of water. The effects were very similar to those produced by chloral, with these exceptions: (1.) There was no period of hyperæsthesia. (2.) There appeared to be a feeling of irritation of the nostrils, as the animals rubbed the nose frequently with the fore-paws. (3.) Ten grains subcutaneously injected into rabbits of 3½ lbs. weight, produced profound sleep for a period of four hours. Twelve grains killed rabbits of the same weight in two and a quarter hours. The lethal dose thus appears to be smaller than in the case

aqueous vapour at the temperature of the body, would not account for the amount of fluid found in the lungs; and (2) this accumulation of fluid, in the case of bromal hydrate, takes place even when means are taken, by immersion in a warm bath, to keep up the temperature of the body. From the fact that bromal hydrate causes increased secretion by all mucous surfaces and by all secreting glands, it is almost beyond doubt that the accumulation of white frothy fluid found in the lungs is to be regarded as a secretion or exudation.

of chloral. (4.) There were no convulsions. (5.) The pupils were only slightly contracted. (6.) There was no fluid in the cavities of the body.

Nieszkowski[1] has recommended the use of iodoform in powder as a local agent in the treatment of ulcers of all kinds having fœtid discharges, onychias, fistula in ano, etc. He believes it to act beneficially as a local anæsthetic, and also as a cicatrizing agent. [Dr Matthews Duncan stated in the discussion that, after a trial of this substance, he had found it of no use whatever.]

V.—Conclusion.

Whether or not the action of bromal hydrate is to be referred to bromoform produced by its decomposition, as is the opinion of Dougall, or to the formation in the blood of hydrobromic acid, or the liberation of bromine, as is supposed by Steinauer, are questions still open for investigation. I have not advanced farther in this inquiry. In the meantime, while confirming the results arrived at by the most laborious researches of Steinauer and Dougall, I have (1) indicated more specifically the physiological action, and (2) I have shown another example of physiological antagonism.[2]

No. IV.—*Note on a method of determining the difference in time between the Impulse of the Heart and the Pulse in various Arteries.*

It would be a matter of considerable interest physiologically, to measure the interval of time between the impulse of the heart and the pulse in various arteries. The problem has, no doubt, attracted the attention of many who have practically worked at the subject of the circulation of the blood. At the meeting of the Medico-Chirurgical Society of Edinburgh, held on 3d June 1874, I showed to the members an apparatus which obtains accurate results. At that date, after consulting such works on the pulse as were at hand, I could find no similar apparatus described, nor indeed any apparatus for the purpose; but I stated that the method was so simple that I would be surprised if no one had already thought of it. In an elaborate work on the pulse by Landois,[3] which I

[1] Neiszkowski, Essai sur l'Emploi Thérapeutique de l'Iodoform considéré comme Cicatrisant et Anesthesique. Quarto. 42 pp. Paris. Reported in Jahresbericht, I. p. 345, 1870.

[2] The substances used in this inquiry were supplied by Messrs Duncan, Flockhart, & Co., Edinburgh.

[1] Die Lehre vom Arterienpuls nach eigenen Versuchen und Beobachtungen dargestelt von Dr Leonard Landois, a. o. Professor der Universität, Griefswald. Mit 193 eingedructen Holschnitten. Berlin, Hirschwald, 1872. P. 360. The literature of the subject is given very fully at the end of the book.

have just received, I find that this able physiologist has investigated the matter by an apparatus of essentially the same kind, though differing in certain details. The method consists (1) of mechanical arrangements like the button and lever of a sphygmograph, by means of which the pulse breaks and forms an electric current. The current works (2) an electro-magnet having a rod for the support of a pencil or pen attached to the keeper. The end of this rod is brought into contact with a plate of glass caused to move rapidly, but at a uniform rate, horizontally in front of it, as in Du-Bois-Reymond's spring-myographion, or the end of the rod may be caused to mark on a cylinder moving with great velocity. The rate of movement of the plate of glass or of the cylinder may be accurately timed by the vibration curves of a tuning-fork of known pitch. Two of these electro-magnetic arrangements are fixed firmly to an upright support, one of them being in connexion with the apparatus on the heart, while the other is in electric communication with the apparatus on the pulse.

If both markers be now brought up so as to touch the cylinder or the glass plate in the same vertical plane, and if both electro-magnets acted simultaneously, it is evident that one of the vertical marks obtained on the recording surface by electro-magnet A, would be exactly over the mark made by electro-magnet B. If, on the other hand, one of the electro-magnets acted an instant of time (the $\frac{1}{1000}$th of a second even) later than the other, the two marks would not be in the same vertical line; but as the glass plate or cylinder must have moved a certain distance between the time of action of electro-magnet A and that of B, the one mark would be a little to the side of the other. The horizontal distance between the two marks expresses therefore the time between the action of the two electro-magnets. With one apparatus on the heart and another on the pulse, the electro-magnet in connexion with the latter acts an instant later than the one in connexion with the former. Thus, minute intervals of time may be accurately measured, as has been done by Landois, and his measurements are recorded in the work above quoted, p. 290 to 303.

PRINTED BY OLIVER AND BOYD, EDINBURGH.