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ANÆSTHETICS USED IN EXPERIMENTS ON ANIMALS

NINETY-SIX and a half per cent. of all experiments on animals in this country are inoculations, or of the nature of inoculations. For these inoculation-experiments, anæsthetics are not used. But no cutting of any kind, more severe than the lancing of a superficial vein, is allowed to be done, except on an animal under some anæsthetic of sufficient power to prevent it feeling pain.

There are three ways of preventing pain: (1) local anæsthesia, by the use of cocain or eucain; (2) anæsthesia by the use of such drugs as morphia or chloral; (3) anæsthesia by the use of chloroform, ether, or nitrous oxide. (1) Local anæsthesia is very seldom used in experiments on animals. Sir James Russell suggested to the Royal Commission that it might be used, under certificate A, before an inoculation: "More for the sake of the feelings of some experimenters than for the needs of the animals. There are several experimenters who shrink from even the use of the hypodermic needle, and these are the very men who are apt to transgress by using an anæsthetic." That is to say, there have been cases where a licensee, making inoculations under certificate A, which dispenses with the use of anæsthetics, has anæsthetised the animal to avoid the momentary pain of the introduction of the needle: for which purpose he ought to have held, not

certificate A, but certificate B. But local anæsthesia is not applicable to, and has never been employed in, experiments involving any sort of operation.

(2) Morphia and chloral and urethane and similar drugs, to produce anæsthesia, must be given, and are given, in large doses. "The question of complete anæsthesia," says Dr. Starling, Professor of Physiology at University College, "will in each case be a question of the dose, whether you are dealing with chloroform or whether you are dealing with morphia. Morphia is a complete anæsthetic if it is given in large enough doses." Not a month passes in this country without some person killing himself or herself with morphia or chloral. They die profoundly anæsthetised; they cannot be roused, or, if they outlast the morphia and recover, they remember nothing or next to nothing. "My experience in this matter," says Prof. Starling, "would show that, after opium poisoning, if the patients have been saved, they are not conscious of the very strong shocks they have been given in order to try and hurt them while in that state of poisoning." For the use of morphia and of chloral in experiments on animals, we have the following evidence given to the Commission :—

Mr. Thane (Government Inspector).—*Q.* May I ask whether morphia is sometimes used on dogs as an anæsthetic, without chloroform or ether? *A.* Morphia is very rarely used as an anæsthetic alone, that is quite certain. *Q.* You think that morphia could be administered so as to secure complete anæsthesia? *A.* Morphia can be administered so as to secure complete anæsthesia; there is no question about it, but you probably would have to give a fatal dose. *Q.* You think that chloral and urethane would be effective? *A.* I am quite sure

that urethane would be. I have seen experiments with it. And I have no reason to doubt that chloral would be effective; but I have not seen actual experiments under chloral.

Dr. Schäfer (Professor of Physiology at Edinburgh).—*Q.* Would you say that morphia only dulls pain, and does not remove it? *A.* Certainly not. A sufficient dose of morphia absolutely removes all signs of pain.

Sir T. Lauder Brunton.—*Q.* We have been told here repeatedly that morphia is not an anæsthetic; that depends, of course, upon the quantity. We have been told also that chloral is not an anæsthetic; that also depends upon the quantity. These animals receive poisonous doses in order to completely narcotise them? *A.* Yes; and as to the statements that chloral and opium or morphia are not narcotics, and do not remove pain, there is no other word for it, it is simply a lie; you may as well say that chloroform does not remove pain. If you give any animal a sufficiently large dose of chloral or opium, you so completely abolish sensibility that there is nothing you can do that will awaken its sensibility. The animal is as senseless as a piece of board.

Mr. Henry Morris.—*Q.* Do you think that an animal, a dog or a cat, which receives a poisonous dose of morphia or opium, is in a condition to feel pain up to the time that death occurs? *A.* No, I do not think so. They suffer no pain. *Q.* We have been told here by several witnesses that opium is not an anæsthetic, and therefore, even when a poisonous dose is given, the animal is probably suffering tortures until death occurs. *A.* That is not so.

Dr. Dixon (Professor of Materia Medica at King's

College). We do not use (or very rarely) morphin alone as an anæsthetic, not because it is not one, but because it leaves the motor cells active, and the animal is reflex. But it is quite commonly used for man now in Germany, when it is given with some drug which also paralyses the motor cells as well as the sensory; and so in Germany, and to a limited extent in England, it is given with hyoscin (the so-called morphia scopolamine narcosis) for operations where chloroform is deemed unsuitable.

Dr. Dudley Buxton.—*Q.* In your opinion is morphia a complete anæsthetic? *A.* Quite. *Q.* For severe operations? *A.* Certainly. *Q.* No pain would be present? *A.* Not if you had a sufficient dose of it.

As to the doses of morphia, chloral, and urethane, which are used in experiments on animals, we have Prof. Starling's evidence. "Urethane is used in man, as a simple narcotic, to produce sleep. A man weighing 50 kilos receives from one to five grammes; to an animal, we give $1\frac{1}{2}$ grammes per kilo, that is, *about fifty times as much.* We give that intravenously. We first give what would induce anæsthesia in the ordinary way, namely, morphia and chloroform; then, if for some reason or other we do not want to go on with chloroform, we should inject into the veins this very large dose of urethane. Or (if the high blood-pressure with urethane were a disadvantage) we might use chloral hydrate. In man, we give from 5 to 20 grains of chloral hydrate, that is, about 0·02 gramme per kilo. In the animal, we give $\frac{1}{2}$ gramme per kilo, that is *fifty times as much*, and then we get complete anæsthesia. Then, again (if the vaso-motor action of chloral were a disadvantage), we have morphia. Morphia is generally used as an adjunct to chloroform and ether. If the

animal has had a previous dose of morphia, it will then go on with a small dose of A.C.E. mixture, instead of having to have a large dose constantly administered to it. In some cases morphia can be used as an anæsthetic; this is a use which has been much criticised. When we give morphia as an adjunct to chloroform or ether, we give from one-sixth to a quarter of a grain (about the usual dose for a man). When we give it as an anæsthetic, we give *from one and a half up to fifteen grains*, according to the size of the animal: that is to say, *a dose that is practically fatal.* Sometimes, in one or two cases, dogs do recover from the average amount, if they are kept perfectly warm; but in nearly all cases they die of the dose. It is a fatal dose."

(3) With regard to the use of chloroform or of ether, or of a mixture containing chloroform and ether, the evidence before the Royal Commission proves that animals can be and are profoundly anæsthetised by this method, and can be kept absolutely unconscious to pain for many hours if necessary. This fact is proved, not only by evidence in physiology, but by evidence in the daily practice of veterinary surgery. (See Mr. Hobday's evidence, vol. iv., Q. 16284–16523.) We have, with much else to the same effect, the following evidence:—

Sir James Russell. "I do not think that the licensees would dare to do in a hospital what they do in laboratories in the way of giving anæsthesia. I have frequently seen animals they have killed before beginning the operation, owing to pushing the anæsthesia too far. The result of my personal observation of experiments on dogs has been that they were very fully under. *Q.* You have said that they were as completely anæsthetised as a human being would be, and as carefully? *A.* Generally more so, those I have seen.

Q. Do you think it is perfectly possible to keep, for example, a dog under complete anæsthesia during the whole of that time (an hour and a half, or longer)? *A.* I do not see any difficulty in it. . . . What I have seen, as I have said already, is that experimenters nearly always push the anæsthesia more boldly than they would in human patients. . . . And, further, if it is an operation before a class, say, in the Edinburgh University, where the professor has 200 or 300 critics in front of him, I think he would be a very bold man, even if he had the heart to do such a thing, who would venture to show an experiment where the anæsthesia was not complete."

Prof. Schäfer. "In all experiments which come under license, complete anæsthesia is secured during the whole period of the experiment, however many hours it lasts. I do not mean to say that an animal will never make a movement when it is under anæsthetics; of course, an animal will as a man will. But the object of the experimenter is to keep the animal under anæsthesia; his objects are likely to be entirely frustrated if the animal moves; and although the condition of anæsthesia may be more or less complete, the amount of anæsthesia used in physiological laboratories is in almost every case vastly deeper than that which is used in the operating theatre. It does not matter very much to us whether the animal dies of anæsthesia or not. The suggestion that we knowingly, or even unknowingly, allow the animal to come out of the anæsthesia is, on the face of it, an absurd suggestion, because it would absolutely defeat the object of our experiment. . . . I have witnessed a great many operations, in Germany and other countries; and the statements which fly about regarding the callousness of foreign physiologists

to the sufferings of animals are wild, and quite unconfirmed by anything which I have seen. And I have seen at congresses of physiologists large numbers of operations performed, always under full anæsthesia. *Q.* But assuming that in this country an anæsthetic has always been applied, the suggestion rather is, that it has not been applied fully and carefully, and so as to ensure complete insensibility to pain? *A.* That suggestion has no grain of foundation."

Prof. Starling. "With common care, it is easy to keep animals for hours under the influence either of chloroform or ether, or of a mixture of these two drugs, in a state of complete insensibility. . . . The administration of anæsthetics is a routine practice, just as it would be in the operating theatre. Nobody ever thinks of doing any cutting operation without thorough anæsthesia. . . . I think it would be a good thing if some of the Commissioners who doubt as to the completeness of anæsthesia would come and see an actual experiment."

Dr. Cushny (Professor of Pharmacology at University College).—"*Q.* Is there no difficulty in putting a dog and keeping it for a long time during a severe operation under perfect anæsthesia? *A.* There is no difficulty whatever. I have had a dog for six hours under anæsthesia. *Q.* And under perfect anæsthesia? *A.* Under perfect anæsthesia."

Sir Lauder Brunton.—"*Q.* You have been connected with people who have been experimenting on living animals for many years? *A.* Yes. *Q.* Have you ever known of any case of inhumanity or want of consideration for causeless pain; I am speaking of England, of course? *A.* No; in England certainly not, and I

do not remember any case abroad, because, as I said before, most of my experiments were done in Prof. Ludwig's laboratory in Leipsic, and he was always most careful of the feelings of the animals that were experimented upon. *Q.* You have had experience of chloroform given to a vast number of dogs? *A.* Yes. *Q.* And you have entirely convinced yourself that they have been under anæsthesia? *A.* Yes, entirely. *Q.* And complete anæsthesia? *A.* Complete anæsthesia; as complete as any patient could possibly be under on the operating table."

With chloroform, ether, or the A.C.E. mixture (alcohol, chloroform, and ether) the anæsthetic is given on a mask, or on a fold of lint, or, in some cases, through a tracheotomy tube. This last method is used in surgical practice for many operations on the head and neck. For the more usual method of giving the anæsthetic, we have the evidence of Prof. Starling and of Dr. Dudley Buxton.

Prof. Starling. "The usual thing we do is to give the animal, half an hour before the experiment, a hypodermic injection of morphia, of about a quarter of a grain—from a quarter to a third. The effect of that is that the dog becomes sleepy and stupid, and then sometimes it will lie down quietly, and if it is very sleepy you can put a mask over its nose containing the chloroform, alcohol, and ether mixture, which it takes quite quietly. If, at the time one wants to begin the operation, the animal is not fully under the influence of morphia—if it still seems restless—it is put in a box, and there it has some wool saturated with the A.C.E. mixture put in the box. The air gradually gets saturated, the dog gets more and more sleepy, and finally subsides at the bottom of the box."

Dr. Dudley Buxton: "In physiological experiments on dogs, of which you have seen a great many, they are all strapped down, first of all, are they not, before the chloroform is administered? *A.* No, certainly not. *Q.* Is there not some difficulty in administering it? The dogs struggle against it? *A.* They are in a box; you can put them into a box. *Q.* The dog struggles, I presume, to get out of the box? *A.* No, it generally lies down and goes to sleep. *Q.* Not at first. In the early stages does it not struggle or bite the box? *A.* As a rule, my experience is that the dog turns round once or twice and goes to sleep. *Q.* And then is it strapped down? *A.* Yes, when it is unconscious, and tied on a board. *Q.* That, you say, is to prevent reflex action? *A.* No, I did not say anything of the sort."

Curare

Curare is not an anæsthetic under the Act; it is illegal to use it as an anæsthetic. In this country it is seldom used at all, and is never used alone in any experiment involving any sort or kind of surgical operation. In every such case a recognised anæsthetic must be given, and is given.

It is the general opinion of physiologists that curare, though in small doses it only abolishes motion, in large doses also abolishes sensation. The evidences in favour of this opinion are: (1) the well-known case of arrow poisoning recorded by Mr. White, Q. 15920; (2) Schiff's experiments on the local exclusion of the poison from one limb of a curarised frog by ligature of the main artery of that limb; (3) the relationship of curare to other drugs. It is thus described by Prof. Dixon in his evidence before the Royal Commission:—

"It is not an isolated drug, having this peculiar action all by itself. There are lots of other drugs having the same type of action. It is, perhaps, the one which has the most characteristic action on the motor nerve endings, but there would be no difficulty in picking out a whole host of others that do the same. All this group of drugs paralyses the nerve cells, the brain, and every one of them paralyses the motor nerve endings, and they may all cause convulsions by acting on the spinal cord. These three facts apply to all of them. Some members of the group have one action well defined, and others another. Thus, nicotine first paralyses the nerve cells and later the motor nerve endings, whilst hemlock (conium) paralyses the nerve cells and nerve endings almost together. Curare first paralyses the motor nerve endings and later the nerve cells, whilst hemlock (conium)—the poison that killed Socrates—paralyses the nerve cells and nerve endings, roughly, about the same time. I picked those three examples from a group to show the various stages, how one produces its action at one time, and another at another time. I mention this to show that even curare, given alone, is a complete anæsthetic, if enough is given, although we in England, conducting experiments, assume that curare has no action on the nerve cells, and always give enough of some other anæsthetic to completely paralyse the brain. Of course Claude Bernard really started this idea that curare acts on the motor nerve endings, and not on the sensory nerve endings or cells. But Claude Bernard's experiments only apply to the spinal cord; he did not prove anything else at all; all that he showed was that the sensory cells in the spinal cord are not paralysed by curare. That was all his experiments meant. None of these other drugs paralyse the sensory cells in the spinal cord in moderate

doses. Chloroform, except in the largest doses, does not paralyse the sensory cells in the spinal cord. . . We believe that small doses of curare would paralyse the motor nerve endings before the brain cells were paralysed, but that large doses of curare will paralyse the whole of the brain like chloroform."

With regard to the general characters of curare, we have the evidence of Prof. Starling and Prof. Cushny. Prof. Starling is asked : " What is curare, is it a herb ? " He answers : " It is an arrow poison, the South American arrow poison. It is used for poisoning arrows by the Indians, and is brought by them into commerce in gourds. It is now becoming extremely difficult to get curare, and it is getting more and more impure, more and more poisonous in its effects, so that it is being used as little as possible." Prof. Cushny says the same. He is asked whether curare is much used by experimenters in this country, and he answers : " I do not think it is much used anywhere ; to tell the truth, it is very difficult to get, and the reason why I refuse to give any definite statement as to curare is that it is so indefinite. We have not the same curare that we could have got thirty or forty years ago. As a matter of fact, at the present time, much of the curare that we get fails to paralyse muscles or anything. I tried to get it in a number of places a few years ago, and I could not get any curare that would paralyse the muscles at all. What is called curare is very often quite inactive."

As to the infrequency of the use of curare, we have the evidence of several witnesses before the Royal Commission. Sir James Russell, Assistant Inspector in Scotland, says : " I have not seen it used for years. I did see it once used in a blood-pressure experiment about fifteen years ago. In that case the anæsthetic

used was a very heavy dose of urethane, administered before the experiment began, and the animals were heavily narcotised. I happened to see that experiment from beginning to end."

Dr. Gotch, Professor of Physiology at Oxford, says: "I have had very little experience of curare." Later he is asked: "Did I rightly understand you to say that in the course of your twenty years' experience you have not had occasion to use curare on your own responsibility?" and he answers: "I have not used curare. I do not use it for the blood-pressure experiments that I show. I have not used it for the research experiments that I have done upon the nervous system."

Sir Lauder Brunton says: "I have very rarely used it. I do not think I have used it at all since the passing of the Act, because I always had the feeling that curare alone might not completely destroy sensibility. I may, perhaps, mention that I was very anxious to find that out, and when I was in Leipsic in 1869, I proposed to Prof. Ludwig to give me curare, and then, perhaps, apply a hot iron or something to the back of my hand, and keep up artificial respiration till I came to life again; and then I would tell him whether it would hurt or not; but he said that the risk was too great, that the means of keeping up artificial respiration were not sufficiently good, and he thought it was not worth while to do it—and he did not do it."

Prof. Schäfer says: "I have not used curare at all for years. I have not been engaged in any experiments which require the use of curare."

It is plain, from the evidence before the Royal Commission, that curare is seldom used at all, and is never used without an anæsthetic in any experiment cal-

culated to give pain. Indeed, apart from all question of humanity, it is impossible to imagine an experimenter deliberately using curare instead of an anæsthetic. As Sir Richard Douglas Powell said to the Royal Commission, "Curare is very expensive, and very difficult to obtain—very difficult indeed—and I cannot conceive of any man using curare for any other purpose than to prevent reflex muscular movements which would interfere with his experiments under an anæsthetic. To substitute it for an anæsthetic would be a piece of clumsy extravagance which I cannot imagine any sensible man making use of."

It is to be noted that curare is only used in conjunction with an anæsthetic in those cases in which the animal is killed under the anæsthetic without recovering consciousness; thus, Prof. Starling is asked (*Q.* 4056), "Is curare ever given under certificate B in cases of animals that are to recover from the anæsthesia?" *A.* Never. *Q.* 4057. "Therefore every animal that has curare is, so to speak, bound to die under the anæsthetic?" *A.* Yes.

Prof. Starling explained to the Commission the circumstances which would require the use of curare. "A case in which one must use curare is where one is exciting, say, a nerve going to the arm.[1] We know that this nerve going to the arm contains fibres which will cause contraction of muscles, and which will also cause contraction of blood-vessels. If we want to get a contraction of blood-vessels, we cannot record these, or see whether they contract, if the muscles are contracting at the same time; so we should give curare, which would paralyse the nerves ending in the muscles, but would not paralyse

[1] It hardly needs to be pointed out that the stimulation of the efferent fibres of a nerve does not cause pain.

the nerves ending in the blood-vessels, so that, after curare, if we stimulate this nerve *here* (*describing the same*) the blood-vessels would contract alone. It is under that sort of condition that one has to give curare."

Further questions were put to Prof. Starling as to the use of curare, as follows :—

Q. 3620. It not being clear that it is an anæsthetic (you say it may possibly be one, and your own opinion, I rather understand, is that it is one), it must be assumed that it is not? *A.* Yes.

Q. 3621. And, of course, an anæsthetic must be given in such a case? *A.* Yes.

Q. 3622. And anyone who did not give an anæsthetic, but used curare, would clearly be doing wrong? *A.* Yes; he would be contravening the Act, for one thing.

Q. 3623. And might possibly be inflicting great pain on the animal? *A.* He might be, and, therefore, it would not be approved of in our laboratories at all while there is a shadow of a doubt that it is an anæsthetic.

Q. 3624. Have you yourself ever used curare in a painful experiment without adequate anæsthetisation? *A.* No; and I have never seen it used in this country without simultaneous and adequate anæsthetisation.

Q. 3625. Neither as a student nor as a professor? *A.* No.

Q. 3626. It paralyses the voice too, does it not? *A.* Yes; it would paralyse all the motor nerves, and, therefore, it would paralyse the voice as well as other movements.

Finally, many witnesses before the Royal Commission were asked as to the possibility of pain occurring from the passing off of the anæsthesia in an animal that had also received an injection of curare. Prof. Starling is asked: "Are there any means, other than the cries or struggles of the animal, by which you can tell whether the anæsthetic is passing off?" And he answers: "Yes, you can tell it by the blood pressure. Struggles have also what we call their visceral side. This activity of the muscles of the body is associated with activity of the centres which govern the blood-vessels, and when one is working without curare one notices that the pressure goes up, and then, if one does not attend to it, after that comes a little movement, and you give more anæsthetic."

Q. 4055. "So that the presence of curare does not prevent your knowing whether the anæsthesia is complete?" *A.* No, it would make it more difficult; but you have that clue. What one does, of course, is to ensure the complete anæsthesia, and continue that anæsthesia during the curare—continue the same amount.

Dr. Langley, Professor of Physiology at Cambridge, is questioned on this same point, and answers (*Q.* 15169): "I have had experience of the use of curare for particular experiments, and having obtained a knowledge of the way to administer anæsthetics, I am confident that there is no difficulty in keeping up the anæsthesia while curare is given. The operator must start with complete anæsthesia, and he must know from past experience the amount of the anæsthetic which it is necessary to give in order to maintain it. For instance, with chloroform, the chloroform is given at the intervals and in such doses as his previous experience has shown will maintain com-

plete anæsthesia. Pain would cause a rise of blood pressure, but I should myself always rely on the previous experience of the anæsthesia, how it is produced, and the depth of it, and see that it is maintained in just the same way as if the curare were not given."

Dr. Waller, Director of the Physiological Laboratory of the University of London, gives a similar answer: "I know, if you give the animal 2 per cent. of chloroform vapour, it is of necessity under the influence of the chloroform vapour. I know that I am on the safe side as regards pain to the animal."

Prof. Schäfer, *Q.* 10087, and Dr. Thane, *Q.* 1705, give evidence to the same effect.