

destroyed, infomuch that actual contact would not produce the disease, where the administration of vinegar had been ample to the patient, his apartment, and every thing about him. I shall, in a few weeks, submit to you some Observations on the efficacy of Elaterium and Digitalis in certain diseases. In the interim, I am, &c.

9th March, 1802.

HUGH MOISES, M. D.

To the Editors of the Medical and Physical Journal.

GENTLEMEN,

MR. Cooke's practice of washing patients affected with contagious fever, as well as persons exposed to the risk of contagion, with vinegar, cannot be too generally adopted. I have no doubt it will give him much pleasure to be informed that a similar mode of treatment was followed, with the most marked success, in the plague which occasioned so much havoc in Russia, in the year 1771. In various parts of his Treatise, De Mertens advises ablution with vinegar; and in his account of the means by which he kept the great Foundling Hospital at Moscow free from the pestilence, he particularly mentions that he directed the "children who were brought (from infected families) to the quarantine-house, to be stripped to the skin; after which their clothes were burnt, *their bodies washed all over with vinegar and water*, and new clothes put upon them."

March 13, 1802.

ANTILOIMICUS.

Observations on the Modus Operandi of Opium.

[Continued from Vol. VII. p. 137.]

AS I have not repeated the experiments with which I concluded my last paper, I shall only observe, at present, that should they be confirmed by future experiments, we shall be authorized to conclude, that opium, introduced into the system, through the medium of the absorbents, operates *directly* as a sedative.*

I am

* I find by the following note which occurs in p. 33, of Dr. Wilson's Essay on Opium, and which I must have overlooked at the time, that Dr. Alexander

I am now to proceed in endeavouring to prove that opium does *not* act as a stimulant.

The 9th Experiment* is liable to the same objections as the 1st, 2d, 3d, and 4th.

EXP. 10.† “Through a very small opening, I injected into the cavity of the abdomen of a rabbit about half an ounce of the same aqueous solution, preventing as much as possible the admission of air. Twenty minutes after the animal was opened, and the surface of the intestines appeared much more red than usual, and apparently inflamed.”

So far is this experiment from proving that opium is a stimulant, when *all* the effects which follow its exhibition in this way are considered, that it would have been extremely difficult to have adduced any thing more unfavourable to that opinion.

It has been proved by experiments made on an extensive scale, on different animals, and by some of the first Physiologists of the age, that by injecting a solution of opium into the cavity of the abdomen, the sensibility, irritability, and mobility are *diminished* in a very remarkable degree; effects which cannot be owing to a *stimulant* property in the medicine, as they are not preceded by any symptom of increased action or excitement. The *primary* effect it produces, is a *diminution* in the *frequency and force* of the pulsations of the heart and arteries; the animals soon become *torpid and languid*, and continue in this state as long as life remains.

The following experiment is taken from Dr. Whytt's Essay on Opium,‡ “The same young gentleman, Mr. Ramsay, at my desire, made the following experiment. On the 9th of April, 1755, after making an opening into the cavity of the abdomen of the dog on whom the last experiment was made, he injected by the wound a drachm of opium dissolved in two ounces and a half of water; but before he could stitch up the wound, about an ounce of the solution escaped. The dog lost the *power* of his hinder limbs almost *instantaneously*. Two minutes after the injection was made he began to be convulsed; and

Alexander does not assert that opium applied externally is never absorbed, which might be inferred from a remark which occurs in my last paper. Med. and Phyl. Journal, Numb. xxxvi, p. 125. “Dr. Alexander was led from his experiments on this head, to conclude upon the whole, that although we cannot positively assert that opium is not absorbed, yet we have no proof of its being so, at least to such a degree as to kill.” I am sorry I did not find out the mistake in time to correct it.

* Inquiry, p. 54.

† Inquiry, p. 54, 55.

‡ Ess. & Obs. Phyl. & Lit. Vol. II. p. 327—329.

and in two minutes more, after having raised himself upon his fore-legs, he *fell down* senseless. At this time Mr. R. laid bare the thorax, by dissecting off the teguments, *which did not seem to give the dog any pain*; and could plainly feel the motion of his heart through the pleura; it beat 76 times in a minute, but became gradually slower.*

"Immediately after counting the pulse, Mr. R. cut the ribs on each side of the sternum, which he laid back in the usual way. The heart, which was thus brought in view, appeared quite turgid, and continued in motion about five minutes; during which time it performed only between 60 and 65 *weak* vibrations; for they were not complete contractions. While the heart was thus moving, warm saliva was first applied to it, then cold water, and last of all oil of vitriol; which shrivelled the parts it touched almost in the same manner as a hot iron would have done; but none of them accelerated the heart's vibrations, *which became gradually slower, till they ceased altogether*. The fibres of some of the intercostal muscles on the right side of the sternum, continued to be agitated with a weak tremulous motion near half an hour after the injection was made into the *abdomen*; but the intercostal muscles attached to the ribs, on the sides of the thorax, were not observed to move, nor did the diaphragm make any motion when its fibres were pricked or cut.

"*Nothing remarkable was seen in the abdomen*; only, although it was opened ten minutes after making the injection, the *intestines had no motion*; whereas, in another young dog, which had got no opium, Mr. Ramsay observed the peristaltic motion continue half an hour after laying open the thorax.

"The dog lost little or no blood in making the wound into his abdomen, nor were any of his bowels hurt by it."

The experiments I shall next introduce are from Dr. Monro's Essay on Opium.† They are, if possible, still more decisive in proving the *directly* sedative properties of opium.

"To determine this question satisfactorily, it was necessary to discover some other way in which the animal could much more quickly be affected to a violent degree. This I found might be done by pouring thirty drops of the solution of opium, through a small hole, into the cavity of the abdomen.‡

(SEVEN

* The dog's heart, in a natural state, and before the injection of the solution of opium, beat 150 in the minute.

† Ess. & Obs. Ph. & Lit. Vol. III. p. 317, 318.

‡ "Like to what Drs. Langrish and Whytt had observed of lauro cerasus and opium on dogs."

(SEVEN TRIALS.)

“ For in *two* minutes thereafter *the heart did not beat above half its usual number of times in a minute, and after four or five minutes, not above a third part of the usual number*; and, on examining the foot with the microscope, I found that the blood in its vessels HAD ENTIRELY CEASED FROM MOTION. And now the whole muscles were repeatedly convulsed, and the limbs extended, so as to render the animal *unable to move out of the place where it lay*.*

After a quarter of an hour it scarcely discovered any outward sign of life, though the heart was found to contract *feebly about ten times in a minute five or six hours thereafter*.”

Dr. Wilson has been at considerable pains to ascertain in what manner opium acts in producing the abovementioned phenomena, and has happily succeeded.†

I shall only make such extracts from his Work, as are necessary to confirm and elucidate the experiments I have just cited.

“ I therefore repeated Dr. Monro’s experiment more than once, but found the result as he has stated it. *The beating of the heart became less frequent, ALMOST IMMEDIATELY, on injecting the solution into the cavity of the abdomen*.” P. 58.

“ These circumstances led me to consider, whether or not there is any other way in which a solution of opium, injected into the cavity of the abdomen, can be supposed to influence the motion of the heart, besides through the medium of the nervous system, or that of the absorbents.

“ A conjecture occurred to me, which is confirmed by several of the following experiments, namely, that opium applied to the coats of the blood vessels, by destroying their muscular power, (*opium, it was found, destroys the power of action in all muscles to which it is immediately applied*) must affect the circulation in these vessels; and, consequently, thrown into the cavity of the abdomen, influence the motion of the heart by impeding or entirely interrupting that of the blood, in nearly one third of the whole animal; by which the supply to the heart is diminished, and a greater than usual obstacle opposed to its perfect evacuation.

“ The first circumstance, then, to be ascertained, is, whether opium applied immediately, or nearly so, to the blood vessels of a living animal, impedes or wholly interrupts the circulation

* Frogs were the subjects of these experiments.

† Essay on Opium, p. 57 — 69.

lation in those vessels, independent of any general affection of the system?

“ It is to be observed, that in the following experiment, the opium is not applied immediately to the coats of the blood-vessels, but injected into a cavity, between which and these vessels a dense membrane of cellular substance is interposed. The skin of a frog, except in a few places, (chiefly the joints) does not adhere to the parts which lie beneath it.

“ Having adapted the web of a frog’s foot to a microscope, I injected eight or ten drops of a solution (nearly as strong as the stronger solution) under the skin of the leg.

“ In a few seconds the circulation became languid, and no motion could be perceived in some of the larger blood-vessels. It gradually became more obscure in the rest, till, in the space of about two or three minutes after the injection of the opium, it ceased altogether. Nor did this interruption of the circulation proceed from any general affection of the system, since the motion of the blood still continued in the other foot.

“ Left it might be suspected, that in applying the foot to the instrument the vessels were compressed, it is proper to observe, that the circulation in the foot, after it was applied to the microscope, continued as vigorous as natural, till the solution was injected. On another occasion, indeed, I have observed the circulation in the foot of a frog, applied in the same way to the same microscope, vigorous for several hours.

“ This experiment was made three times, in the same manner, and with the same result.

“ After determining that opium is capable of interrupting the circulation in the part to which it is immediately applied, independent of any general affection of the system; all that is necessary, in order to ascertain whether it is in this way that it suddenly affects the motion of the heart, when thrown into the cavity of the abdomen, is to interrupt the circulation, and observe the effects of this drug, applied in the same way, when it can only act on distant parts, through the medium of the nervous system.” P. 59—63.

A particular account of the experiments immediately succeeds (p. 64—68.) The following is the conclusion they suggest.

“ The inference from these experiments is, that the diminished frequency of the heart’s motion, observed almost immediately on throwing a solution of opium into the cavity of the abdomen, does not proceed from any action of the opium on this organ, through the medium of the nervous system, but from its impeding or entirely interrupting the circulation in nearly one-third of the whole animal.” P. 68, 69.

Effects nearly similar were observed to result from injecting opium into the abdominal cavity of guinea-pigs, by the Abbé Fontana.

His words are, "Those into the bellies of which the aqueous solution of opium was injected, died in less than two hours: *They lost the greater part of their motion in less than half an hour, and were violently convulsed.*"*

On summing up the evidence derived from the above experiments, it appears that opium injected into the cavity of the abdomen of different animals *deprives them of voluntary motion almost instantaneously; that it impedes or interrupts the circulation of the blood, in the vessels of the abdominal viscera; the pulsations of the heart almost immediately become feeble and slow, and the circulation of the blood ceases in the extremities; the peristaltic motion of the intestines is retarded and destroyed: The sensibility and irritability are impaired to such a degree, that the dog, in Mr. Ramsay's experiments, did not seem to feel any pain when that gentleman laid bare the thorax, by dissecting off the teguments, though the heart was beating 76 times in a minute at the time; nor did the diaphragm make any motion when its fibres were pricked or cut.*

Dr. Crumpe's view in making the experiment seems evidently to have been, to observe the *local appearances* resulting from the application of a solution of opium to a tender irritable surface; and this accounts for his omitting to notice any other circumstance. But after having *proved to a demonstration*, that the *primary and general* operation of opium injected into the cavity of the abdomen is DIRECTLY AND POWERFULLY SEDATIVE (both the voluntary and involuntary motions yielding to its influence) it necessarily follows, that the *increased redness and apparent inflammation* † could not have been the consequence of the opium having acted as a stimulant, unless we suppose that it acts as a stimulant and a sedative *at the same time*, which would be absurd; and, indeed, Dr. Crumpe has shewn that idea to be unfounded. ‡

As

* Treatise on Poisons, Vol. ii. p. 363. (Skinner's translation.)

† These appearances seem not to have occurred in Mr. Ramsay's experiment. Dr. Whytt says, nothing remarkable was seen in the abdomen; only, although it was opened ten minutes (20 minutes had elapsed in Dr. Crumpe's experiment) after making the injection, the intestines had no motion.

‡ "It is in the first place to be remarked, that opium cannot be separated into any two principles, endowed solely with the opposite qualities of a stimulant and sedative, as will be seen by recurring to the chapter in which

As they cannot be explained therefore by supposing the *modus operandi* of opium to be stimulant, it may be worth while to enquire, whether they do not admit of a satisfactory explanation, by supposing it to act as a sedative.

We have seen, that opium destroys the muscular power of the coats of the blood vessels, though it is not applied immediately to their coats, but injected into a cavity, between which and these vessels, a dense membrane of cellular substance is interposed.*

It therefore follows, from the unequivocal manner in which this medicine acts, that this effect will be produced in a greater degree, when the solution is applied *immediately*, or nearly so, to their coats, as it is to those of the peritoneum when injected into the cavity of the abdomen; consequently, the vessels having lost their *tone* as well as their *action*, they will appear enlarged, and more red than usual: Vessels which were before invisible to the naked eye, will now be readily distinguished, and the parts may thus assume an inflamed appearance, similar to what takes place when an aqueous solution of opium is applied to the tunica sclerotica of a sound eye, or to the cutis, recently deprived of the cuticula.

The above explanation was suggested by the experiments which have been adduced to prove, that opium injected into the cavity of the abdomen does *not* act as a stimulant: It has one advantage, (a negative one to be sure) *it is not at variance with established facts*; but however unsatisfactory it may be deemed, that will not tend to invalidate either the experiments or the arguments which have been employed.

which its analysis is contained. The principal argument on which those who attribute to this medicine both stimulant and sedative qualities rely, is deduced from its being found first to increase, and afterwards diminish the frequency of the pulse: But, as will be hereafter shown, this effect can be explained in a much more satisfactory manner, so that there is no necessity of resorting in this case to a supposition, rendered highly improbable from considering, that we know of no simple in the whole *Materia Medica* possessed of powers in their nature opposite, and operating, when it is exhibited, separately and distinctly. But even granting that opium is endowed with these contrary qualities, it will be difficult to explain on such data the consequences of its exhibition; for as the effects of such principles are supposed to be diametrically opposite, it naturally follows that one must counteract the other; and hence, if both exist in equal proportions, the medicine would turn out perfectly inert; if one preponderates, it will act solely in consequence of the excess of that principle; and to it alone, whether stimulant or sedative, will all its effects be ascribable." Inquiry, p. 167, 168.

* Wilson's Essay on Opium, p. 60—63.

EXP. II.* "I raised the sternum and laid bare the contents of the thorax of a dog which had been just hanged; the heart was still contracting, but in a very irregular manner. I opened the pericardium and waited till all contraction ceased, and then let fall on it a few drops of the aqueous solution, milk warm. The contractions were instantly renewed and continued for about a minute, and the surface of the heart became unusually red. Upon the contractions ceasing, they were again renewed, but for a short time, by a similar application: A third attempt was ineffectual; but on injecting a small quantity into the superior venous sinus, the whole heart was again thrown into action, which continued for a short time, and was the last effort it could be roused to. I made a similar experiment with plain warm water. Its first application produced a slight renewal of the heart's contractions, the second and third were ineffectual."

Here some other cause must have been applied, that alleged being inadequate to the effects produced.

"I opened the pericardium (says Dr. Crumpe) and waited till all contraction ceased, and then *let fall* on it *a few drops* of the aqueous solution, milk warm. The contractions were *instantly* renewed, &c."

Now it is a well-known fact, that the shock occasioned by allowing any liquid to *fall* upon a part possessing sensibility is a powerful *stimulus*; besides, is it probable that a *few drops* of a solution of opium, containing *five-eighths of a grain to ten drops of water*, † could produce *any sensible effect*, applied to the external surface of the heart of a dog, in the situation here described, (whatever may be the *modus operandi*) *if applied without the addition of mechanical force?*

"Upon the contractions ceasing, they were again renewed, but for a short time, by a similar application: A third attempt was ineffectual; *but on injecting a small quantity into the superior venous sinus, the whole heart was again thrown into action*, which continued for a short time, and was the last effort it could be roused to."

I shall be able to adduce the most positive and unequivocal proofs, that an aqueous solution of opium applied to the internal surface of the hearts of frogs, (*no mechanical force being superadded*) INSTANTLY puts a stop to their contractions.

Dr.

* Inquiry, p. 55, 56.

† "This solution, and that used in all the succeeding experiments, was made by dissolving opium in warm water, in the proportion of one drachm of the former to two ounces of the latter." Inquiry, p. 24.

Dr. Crumpe adds, "I made a similar experiment with plain warm water. Its first application produced a slight renewal of the heart's contractions; the second and third were ineffectual."

And the inference he draws from this experiment is, that "Dropped on the hearts of animals, it accelerates their motions or rouses them into action if they have previously ceased to vibrate." P. 169.

And yet the only inference that can be drawn from the 30th experiment, (p. 129, 130) and which Dr. Crumpe evidently intends his readers to draw from it, is, that opium *diminishes the irritability and power of motion* in the hearts of frogs, when applied to them immediately after their separation from the body. But I shall give the experiment and his arguments, verbatim.

Fontana concludes from experiments related in his Supplement, that, "The hearts of animals taken from the body, and consequently deprived of blood, when immersed in watery solutions of opium, are *not* deprived of *irritability and the power of motion*, sooner than hearts immersed in pure water."*

"This fact (says Dr. Crumpe) I am under the necessity of denying, although the learned Haller is of the opinion, as well as the Abbé Fontana. Whytt asserts, from the result of seven experiments which he particularly details, that the *irritability and motive faculty* of the heart is, *as well as that of other muscles*, DESTROYED by opium.† In determining this point, it is to be observed, that if the hearts of a number of frogs, the animals on which such experiments are usually made, be separated from the body, though no application whatever be made to any of them, some will die, or lose their irritability, many minutes before others. It is therefore only from many experiments, and from taking a general view of the whole, that we can determine the point in question; and after having tried the experiment upon a great number of hearts, I do not hesitate to declare, that the *irritability* of that organ is *destroyed* by opium, *long before it would naturally disappear*. I think I have in general observed, that the larger the animal, the longer does its heart, when separated from the body, continue to vibrate; and in comparing the effects of plain water and opium,

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* It has been fully ascertained by experiments made both before and since, that this conclusion of Fontana's is erroneous; but this very circumstance (as must by this time appear, and will be shewn more fully afterwards) throws another insurmountable difficulty into the way of Doctor Crumpe's Theory.

† "Essays Ph. & Lit. V. ii. Art. xx."

we should, as nearly as possible, match the hearts employed in size. The liquors should also be of the same temperatures, as a variation in this point will occasion a manifest difference.

“With these precautions in view were the experiments above-mentioned conducted. The following are the particular results of the last instituted on the subject.”

Exp. 30. “Having taken three frogs, one of a very large, another of the middle, and the third of rather a small size, I separated the hearts from their bodies, and immersed them in pure water. The first lived *forty-five* minutes; the second and third *forty* minutes. Immersing the hearts of three frogs, of nearly equal sizes, in a watery solution of opium; the first lived but *twenty* minutes, the second *eleven*, the third scarcely *ten*.” Inquiry, p. 127, 130.

After what has been advanced, it must appear sufficiently evident, that on the present occasion there is a want of consistency in Dr. Crumpe's arguments; and the following experiments shew, in a clear and decisive manner, how far his 11th experiment is capable either of elucidating the subject of the *modus operandi* of opium, or of supporting the theory for which Dr. C. contends.

“It remains to examine (says Dr. Monro) how far animals are affected by the absorption of opium, and its mixture with their circulated blood.

“But previous to this inquiry, I thought it might be of use to know what effect opium has when applied to the heart and vascular system.

(FOUR TRIALS.)

I therefore laid bare the heart, and then injected into a large vein, which runs along the under middle part of the abdomen on the outer side of the peritoneum, a few drops of the solution,* viz. twelve drops into that vein of two frogs, and six into that of two others; and observed, that *as soon as the solution had entered the ventricle of the heart, that organ was rendered incapable of expelling its contents; and, in much less than one minute thereafter, became so entirely paralytic as not to make the least contraction on the strongest irritation, whether applied to its outer or inner part; whilst, at the same time, the extremities were agitated incessantly with convulsions, which continued for about three-quarters of an hour, gradually becoming more and more feeble; nor was the animal able to perform any voluntary motion during this whole period.*

“REMARKS.

* Consisting of a drachm of opium to an ounce of water.

"REMARKS.

" 1. When we compare that part of the foregoing experiment which relates to the heart, with some experiments made by Dr. Whytt, when the opium was applied to its outer part, we see how greatly the delicacy of feeling of the inner side of the heart exceeds that of its outer side.

" 2. We learn that the heart is so far from being exempted from the influence of opium, as the learned Dr. Haller supposes, that, perhaps, *no muscle of the body can by any means be proved to be so much under its dominion as the heart, when the opium is brought into contact with its inner side; in which way it will be applied if absorbed.*"*

The following experiments are equally applicable to the present purpose.

" After securing the aorta by ligature in twelve frogs of different sizes, a few drops of the strong solution of opium was injected into the heart of each. *It immediately ceased moving.* This, however, was not followed by the slightest convulsion in any part of the body.

" The frogs all died in exactly the same manner as these animals do when the heart is cut out; that is, when the circulation is interrupted, and when they lose as much blood as in this experiment.

" I could not perceive that the injection of the solution had any effect, *but that of putting a stop to the motion of the heart.*

" A similar experiment was made in the following manner: After dividing the aorta in ten frogs, most of them full grown, a few drops of a solution of opium, (not quite so strong as that used in the last experiment) were thrown into the heart of each. ITS CONTRACTIONS INSTANTLY CEASED, but no convulsions supervened."

I shall pass over the remarks which immediately succeed the above experiments.

" This, however, suggested another mode of making the experiment, which seems perfectly conclusive. †

" I slit the heart in six frogs. Notwithstanding its contents were thus instantly evacuated, *it continued to contract with vigour.* A little of the same solution used in the last experiment was then dropped into it.

" No

* Essays, Ph. & Lit. Vol. iii. p. 330—332.

† These experiments were made with a view to ascertain how far opium, applied to the heart, is capable of affecting any distant part through the medium of the nervous system.

“ No part of the solution, applied in this way, can be sent through the arteries to the brain; but as all the nerves are left entire and uncompressed, if the convulsions which follow the injection of opium into the heart depend on any action of that drug on the nervous system, they ought to be observed in this experiment.

“ On dropping the solution into the heart, it immediately ceased moving, but no convulsions supervened.” †

To attempt any comments upon the above important and decisive experiments, would only weaken their force; I shall, therefore, only add, that it is *fully ascertained by thirty-two experiments, that opium, applied to the hearts of animals, IMMEDIATELY PUTS A STOP TO THEIR MOTIONS; and it is also ascertained, on the authority of four experiments, that they become so entirely paralytic in less than one minute thereafter, as not to make the least contraction on the strongest irritation, whether applied to their inner or outer part.*

“ It has been shewn (says Dr. Wilson) that opium, applied to the external surface of the heart, very little, if at all, affects the muscular power of this organ; applied in considerable quantity to its internal surface, it immediately destroys it.” †

Dr. Whytt's experiments upon the hearts of frogs, separated from the body, and immersed in a solution of opium, shew very clearly that opium directly diminishes their mobility, sensibility, and irritability; but the fact is so generally known and acknowledged, that I shall pass on to his conclusion, p. 335.

“ It appears, beyond doubt, from the preceding experiments, that the heart is not exempted from the power of opium, as the learned Dr. Haller has affirmed, § but has its motion destroyed by it, as well as the other muscles, only not so soon.”

EXP. 12. || “ Having separated, by inflation, the skin and muscles of the lower extremities of a frog, I poured between them a quantity of the watery solution; both limbs were deprived of the power of motion in about nine minutes; the animal died in fifty-five minutes.”

The plain and necessary inference suggested by this experiment, is diametrically opposite to the conclusion Dr. Crumpe endeavours to establish.

It is evidently his design to prove, that opium is a *stimulant*; and, as a proof of the *validity* of the doctrine, we find, that on pouring

† An Essay on Opium by A. P. Wilson, M. D. p. 48—50, and 53, 54.
 † Essay, p. 85.
 § Act. Gotting, Vol. ii, p. 147 and 154.
 || Inquiry p. 56.

pouring a solution of opium between the skin and muscles of the lower extremities of a frog, *both limbs were deprived of the power of motion in about nine minutes.*

These, to be sure, are *strong proofs of a STIMULANT OPERATION*; and when several *other consequences* of injecting opium between the skin and muscles of frogs (which occurred to Dr. Monro) come to be added, without doubt they must appear in the aggregate perfectly convincing.

In the following experiments the effects of the opium were not confined to the limbs, but acted generally.

“*EXP. 6.* I next endeavoured to ascertain the effect of the opium on the muscles when immediately applied to, or in contact with them, and how far the nerves of the skin would suffer by applying the opium to its inner side.

“For this purpose, I cut a hole in the skin at the top of the thigh, and poured the opium into the cellular membrane, between the skin and muscles.

(THREE TRIALS.)

“I first poured forty drops of the solution under the skin of the left thigh and leg, having before hand broke, with a probe, a partition between these made by the cellular substance of the knee.

“I did not attend to the effects till half an hour thereafter, when I found that whole member paralytic, its toes and skin having *lost their sensibility*, and the muscles their motion. *The animal seemed much stupified*, and could scarcely move its body from the place by the help of the other hind extremity; *and the blood had ceased from motion in the small vessels of both feet; though on examining the heart, I found it still gave twenty-two regular, but feeble, strokes in the minute.* After ten minutes more, all the members of the body were extended and convulsed, and the animal was quite unable to move its body out of the place where it was laid, and soon after died.”

(TWO TRIALS.)

“I then tried the same experiment with twenty drops only of the solution, and observed, that *in about a quarter of an hour that extremity was much weakened and less sensible*, and in five minutes more was not only *motionless and insensible*, but *the animal seemed to be much stupified and lay still*, unless when it was hurt, and after nearly the same time as those above, had its members extended and convulsed, and soon expired.

(TWO TRIALS.)

After that I tried the same experiment with *ten drops only*. After twenty minutes, *that leg seemed to be weaker*, and in ten minutes more, *its muscles had lost their power*, and *the toes had*

little sensibility; and now the animal seemed to be a good deal stupefied, and the heart of one of them examined gave only 25 strokes in a minute. An hour and a half after the beginning of the experiment, the toes seemed to have quite lost their sensibility, and the muscles their motion; but the other parts were not convulsed, and the animal jumped by the help of the other hind extremity. And two days thereafter, this leg had recovered both its sense and motion, and the animal seemed quite well, and continued so for fourteen days at least.

(TWO TRIALS.)

“In the last place, I poured ten drops under the skin of the thigh only in one frog, and the like quantity under the skin of the leg only in another, without finding that either of these members lost their sense or motion, or that the rest of the body was observably affected.”*

In the following experiment the *modus operandi* is very clearly illustrated. In this instance the effects of the opium are confined to the limb.

“Having adapted the web of a frog’s foot to a microscope, I injected eight or ten drops of a solution, (nearly as strong as the stronger solution) under the skin of the leg.

“IN A FEW SECONDS the circulation became languid, and no motion could be perceived in some of the larger blood vessels. It GRADUALLY became more obscure in the rest, till, in the space of about two or three minutes after the injection of the opium, IT CEASED ALTOGETHER. Nor did this interruption of the circulation proceed from any general affection of the system, since the motion of the blood still continued in the other foot.

“This experiment was made three times in the same manner, and with the same result.”†

It must appear extraordinary after perusing the 12th, and especially when we come to consider the 30th, 32d, 36th, and 42d of Dr. Crumpe’s experiments, that he should have expressed himself in such *unqualified terms*, as he every where does, when speaking of the *modus operandi* of opium.

P. 168, he says, “The facts and arguments I am about to relate have induced me to conclude, that ALL its effects are the result of a *stimulant property alone*.” And yet, Dr. Crumpe is so far from denying the existence of sedatives, that he allows the consequences resulting from fourteen of his own experiments, to denote a *directly sedative operation*; as will be
shewn

* *Essays Ph. & Lit.* v. 3, p. 309—312.

† *Wilson’s Essay on Opium*, p. 61—63.

shewn when we come to consider the 32d and the succeeding experiments. The reason will also then appear, which induced him to draw a conclusion that is *contradicted even by his own experiments*, and still more pointedly *by a large body of indubitable evidence*, collected from various, and from the most respectable, sources of intelligence.

Exp. 15.* “The pure resin of Exp. 13, when rubbed between the fingers, had more of the peculiar smell of opium than the gum; when chewed, it had no peculiar bitterness or pungency. The gum of Exp. 14, had more the smell of extract of liquorice than opium; to the taste it was extremely bitter and pungent.”

I have introduced this Experiment for the purpose of remarking, that though the activity of opium resides chiefly, if not entirely, in the resinous part, as is proved by the 17th and 18th of Dr. Crumpe’s Experiments; yet that it possesses no peculiar bitterness or *pungency*; and that the gum, when separated from the resin, though it is inert, or nearly so, compared with the resin, yet to the taste it is *extremely bitter and pungent*.

Exp. 17.† “Of the pure resin, procured by the means mentioned in Exp. 13, I took two grains dissolved in a very small quantity of spirit of wine, at one in the afternoon, my pulse beating 70 in a minute:

In	5	10	15	20	25	30	35	40	45	50	55	60	75	90	Min.
P. beat	78	78	80	78	78	76	70	72	60	65	63	65	63	66	

“In fifteen minutes, there was an evident increase in the fulness as well as frequency of my pulse; in 60, perceived a pleasing languor and drowsiness; in 90, this was so much increased, that I lay on the bed and slept for an hour; on getting up found myself languid, very thirsty, and affected with a slight vertigo and lightness of my head; on taking a glass of Port wine all these symptoms were relieved, and I ate my dinner with as good an appetite as usual.”

The only mark of a stimulant operation, either in this, or in any of Dr. Crumpe’s experiments, (or indeed in any experiment I have met with on the subject) which has an *unequivocal* claim to be considered as such, is a slight and transitory increase in the frequency, strength, and fulness of the pulse. Now, did this effect *constantly* follow the internal use of opium, which is well known to be by no means the case, of what force or consequence could it be of, in whatever point of view it might be considered, when contrasted with the many *clear and*

* Inq. p. 62.

† Idem. p. 65.

decisive marks of a SEDATIVE operation, which INVARIABLY follow, whenever opium is taken in a sufficient dose to affect the system at large?

Besides, it will be demonstrated (if it has not been done already) that in every *other* practicable mode of introducing it into the system of different animals, (except by injecting it into the skull, or into the spine) whether it be injected into the cavity of the abdomen; into the blood vessels; between the skin and muscles; into the rectum; applied immediately to the internal surface of the heart; or externally to the skin, it DIRECTLY DIMINISHES the frequency and force of the heart's contractions, and produces immobility, and total insensibility to stimuli of every kind; and these effects (*diametrically opposite to those produced by stimulants*) commence in some of these experiments in a few seconds, and in ALL of them speedily, after the introduction of the opium, and increase gradually or rapidly, and are temporary or permanent, according to the quantity of opium which has been introduced, or the ability of the animal to sustain its power.* And the introduction of the practice of applying opium externally by means of friction, has furnished us with a very strong argument against the stimulant theory, for in this mode of applying it, it is conveyed by the lymphatics to the thoracic duct, and being there mixed with the chyle and lymph, passes with them into the subclavian vein, and from thence to the heart, the brain, and every part of the body.

Thus, as soon as it quits the absorbent system of vessels, (where I apprehend it undergoes no material change, except dilution) it is almost immediately applied to the centre of the sanguiferous and nervous system; consequently, its genuine effects, whether stimulant or sedative, must infallibly appear; and there can be no difficulty in deciding whether it *increases* the mobility, and *excites* the motion of the nervous power; or *diminishes* the sensibility and irritability of the system, and *thereby the motions and powers of motion in it*.

A brief recapitulation of the result of two Experiments I lately made,† will place the matter in so conspicuous a light, as to prevent even the possibility of a mistake.

The

* Opium injected into the substance of the brain, or through the spine, in frogs, neither retards nor accelerates the action of the heart; the reason of which is obvious; in this way of applying it, it can only act upon the heart through the medium of the nervous system. See Wilson's Essay on Opium, p. 74—85.

† Medical and Physical Journal, Vol. VII, p. 136, 137; and Vol. VI, p. 478—486.

The first was made at 6 P. M.—Before the commencement of the friction, the pulse was 108, firm and regular. In ten minutes, when nearly half of the tinct. of opium was rubbed in, it was reduced to 88, and was soft. In twenty minutes it was reduced to 84, was still soft, and Mr. Hall (the subject of the experiment) was affected with drowsiness, complained of being cold, and his eyes had a dull heavy aspect (a common occurrence when opium is introduced by friction). In thirty minutes, he complained of being cold and drowsy; pulse 84, and soft. In forty minutes 84, but weaker; still cold and drowsy. In fifty minutes, pulse 72, feeble and small; countenance pale; coldness continues, and is accompanied with disagreeable sensations. In sixty minutes, p. 76, weak, and not quite regular; complains of great debility. In seventy minutes, p. 90, regular, and rather stronger. In ninety minutes, p. 92. In one hundred and twenty minutes, p. 96; still complains of being cold, and the disagreeable sensations did not go off till after supper, when his appetite was *better than usual*.

The second Experiment was made before he had breakfasted or used any exercise; the tinct. of opium was increased from two to three drachms, and the mixture was made warm before it was applied; the pulse was 95. In fifteen minutes, p. 86, soft, and easily compressed. In thirty minutes, p. 83, weak and soft; he complains of being very weak, cold, and shivery; countenance looks sickly, skin feels cold. In forty-five minutes, p. 83, soft; complains much of being cold all over, but particularly his feet; is shivery and very weak, spirits depressed, feels drowsy, eyes look heavy. In sixty minutes, p. 90, weak and small; back painful; complains of being affected with a greater degree, and a different kind, of coldness to any he ever experienced before. I now asked if he had felt exhilarated at all, either in this or the former experiment? He answered, No; and could not help smiling at the question, as indeed he had reason. He ate his breakfast with an *uncommon appetite*, and was soon relieved from every disagreeable sensation.

The efficacy of opium applied externally, having been demonstrated in a variety of morbid affections, and its having produced, in every instance, a series of consequences directly the reverse of stimulant, renders the above experiments, in my mind, perfectly conclusive; because, having only to pass through the lymphatic vessels in its way to the heart, it is much less adulterated than when taken internally; being then exposed to the action of the gastric juice in the stomach, and afterwards mixed with the grosser parts of the food, the bile, &c. It is therefore demonstrable, that when opium does accelerate the circulation, raise the spirits, or increase the heat of the body, these

these effects must proceed, either from its immediate and topical action as a sedative upon the primæ viæ, or from some other *adventitious* circumstance, and not from its operating as a stimulant.

As this is a point of primary importance, and may have some weight in enabling us to form a just decision, I shall beg leave to suggest a few remarks, which may perhaps assist in the investigation.

Does not an aqueous solution of opium destroy the power of action, in all muscles (not excepting the heart) to which it is immediately applied? *

Does it not produce the same effect upon the blood-vessels of the lower extremities, when injected between the skin and muscles? †

Does it not put a stop to the peristaltic motion of the intestines, almost immediately on being injected into their cavity? ‡ And does it not operate in the same manner, but in a less degree, when injected per anum? §

Is there any essential difference in the structure of the stomach and intestines? ¶

Has not the stomach a vermicular or peristaltic motion as well as the intestines?

Can the functions of the one be affected independently of those of the other?

If these questions be answered in the affirmative, no farther proofs can be required, to convince us, that a solution of opium applied to the internal surface of the stomach, must diminish the sensibility and irritability, and thereby the motions and powers of motion, not only in that organ, but in the system at large; or in other words, that it must act in this, as in every other instance, directly as a sedative.

This theory will be found consistent with the experiments as well as with the observations of different writers; or may rather be considered as the natural result of both.

“The

* Whytt's Ess. loc. cit. p. 323—325. Monro's Ess. loc. cit. p. 309—314, 330, 331. Wilson's Ess. p. 48—50, 53, 54, 60, 85.

† Monro's Ess. p. 309, 310. Wilson's Ess. p. 59—63.

‡ —, “Applied to the external surface of the intestines, I could not be certain that it at all diminished the peristaltic motion; on injecting it into their cavity, they almost instantly became paralytic.” And in a note, Dr. W. says, “From this effect of opium on the internal surface of the intestines, we are at no loss to account for the coltiveness which attends the use of this drug.” Wilson's Ess. p. 85, 86.

§ Monro's Essay, p. 314, 315.

¶ Except that the intestines are not furnished with a set of vessels which secrete a liquor similar to the gastric juice, and this difference is of no importance on the present occasion,

“The virtues of opium, (says Dr. Alston) internally taken, depend chiefly on its action or influence on the stomach. I have often observed a violent tenesmus removed in a moment by a few drops of liquid laudanum, vomiting stopped, pain eased, yea and sleep procured the same way, and almost as soon.”†

Every medical practitioner can bear testimony to the truth of these observations.

“In presence of, and assisted by Mr. Robert Fullarton, a curious gentleman, and very dexterous in microscopical observations, (in August, 1733,) I conveyed through a small glass tube a few drops of a solution of opium in water into a frog’s stomach, and putting the animal into a glass cylinder, adapted it so to a good microscope, that we had a distinct view of a part of the membrane betwixt the toes of its hinder foot, where the circulation of the blood may easily be seen. My design was, since I found opium killed frogs, to observe if there was any visible change made by it in the blood itself, or in its motion; neither of us could indeed see any alteration of the blood, as to its consistence, colour of the serum, magnitude, figure or colour of the red globules; but we very distinctly saw a surprising diminution of the blood’s velocity, for it did not move half so swiftly as it uses to do in these creatures. We alternately looked at it again and again, and in less than half an hour saw the velocity of the blood gradually increase, the uneasy frog recover its wonted vigour, and the blood its common celerity; upon which we took out the paddock, put it in a basin of clean water, and allowed it half an hour to refresh itself; then gave it another dose of opium, fixed it to the microscope WITH ALL EXPEDITION, and viewed it as before; the blood then moved yet slower than it did the first time, and its velocity gradually decreasing, at length it stagnated, first in the smaller then in the larger vessels, and in about a quarter of an hour the animal expired. One thing was very observable all along, viz. that notwithstanding the diminished velocity of the blood, there was no sensible diminution of the frequency of the pulse; yea, when there was no circulation or progressive motion of the blood in this part, the pulse was visible by an undulatory motion; that is, the blood returned as far back at every diastole of the heart as it was protruded by the preceding systole; this continued till the frog was quite dead, or at least appeared to be so. When we had lost all hope of its recovery I opened it, and found nothing in its stomach but a clear mucus like a jelly, a little coloured with the opium, of which it was full; every thing else seemed perfectly

† Medical Essays, vol. v. part i. p. 165.

perfectly natural. *This experiment we frequently repeated, and it had always the same appearances and event.* The recovery, however, of one of the frogs, which for a considerable time seemed to be dead, is not to be omitted. My friend and I one evening killed, as above, a couple of frogs with opium; one of them, which was the strongest, I laid half in water on a tile, in the bottom of a water pot, that if it recovered it might sit either wet or dry, as it liked best; the other I left on the earth dry under a hedge. Next morning, when I returned to the garden, I found the one under the hedge dead as I left it, but the other in the water pot was alive and appeared to be in perfect health.

While we were thus employed, another thing occurred, which though foreign to the present subject, it may not be amiss to mention. One of the frogs we got for the above experiments, *had not the use of one of its hinder legs, which was of a pale reddish colour.* This made me desirous to observe by the microscope the circumstances of the circulation in this paralytic, and apparently inflamed member; and we found that *the red globules were entirely dissolved; that the blood-vessels were distended with a reddish homogeneous liquid, as if the part had been injected with a bloody water; and that neither sense nor motion remained in it.*"†

In the beautiful experiment just related, though it was frequently repeated and always with the same appearances and event, we do not find the circulation was accelerated, after the solution was thrown into the stomach of the frog; but on the contrary, that Dr. Alston and Mr. F. very distinctly saw (from the first) *a surprising diminution of the blood's velocity; they alternately looked at it again and again, and in less than half an hour (when the action of the opium was over,) saw the velocity of the blood GRADUALLY INCREASE, THE UNEASY FROG RECOVER ITS WANTED VIGOUR, AND THE BLOOD ITS COMMON CELERITY; and, (which compleats the illustration) after allowing the frog time to refresh itself, they gave it another dose of opium, fixed it to the microscope, with all expedition, (five or six minutes might probably suffice,) and viewed it as before; the blood then moved yet slower than it did the first time, and its velocity gradually decreasing, at length it stagnated, first in the smaller, then in the larger vessels, and in about a quarter of an hour, the animal expired.*"

Manchester, March 9, 1802.

M. WARD.

[To be continued.]