noticed. Inherent vital peculiarities also manifest themselves in cases in which a moderate rise of temperature is far more damaging to the vital phenomena of the normal bioplasm than a corresponding fall. If the average temperature be a little above or below that which is adapted for the growth and development of certain creatures, the organism soon begins to suffer; and many tissues, although they may be formed, never attain the most perfect construction possible, or their highest functional activity, and probably they begin to deteriorate long before those of corresponding organisms which are developed under the particular conditions suited to their special vital phenomena. Is there not something very remarkable in the fact of the existence of powers or properties in the several kinds of bioplasm, by virtue of which, each seems to grow and flourish only within its own particular range of temperature? We cannot even lay it down as a law that a low temperature is necessarily destructive of vital action, for there are organisms which flourish at or below the freezing point of water. In short, the various forms of bioplasm have their individual peculiarities and characteristics, which they inherit, and may transmit, and which are not to be accounted for by physics, and which seem in truth to belong to their constitution. Conditions which are life to some forms of bioplasm are death to others.

Some are content to be assured that peculiarities from time to time originate, and that their fortunate possessors gain thereby great advantage, so that they are enabled to overcome their less fortunate brethren, and even to utterly exterminate them. Being the fittest to live, the few soon predominate. Bioplasm, with the newly acquired properties, transmits the peculiarities to that which descends, until bioplasm, capable of producing an organism still more fit, somehow results. The organisms derived from this then prevail, and enjoy the advantage of living and continuing the race. So the experiment is supposed to proceed.

ON THE ACTIONS OF PICROTOXINE, AND THE ANTAGONISM BETWEEN PICROTOXINE AND CHLORAL HYDRATE.

By J. CRICHTON BROWNE, M.D., F.R.S.E.,
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(Concluded from page 507.)

To give greater completeness to the inquiry into the antagonism between picrotoxine and chloral-hydrate, it was judged advisable to test its existence in another class of animals besides rabbits and guinea-pigs. A few cats were, therefore, obtained, and to two of them picrotoxine alone was administered, in order to ascertain its unmodified effects.

Experiment LXXXIX.—Cat, weighing 4 lbs. 13 oz. The cardiac pulsations were 120, and its respirations 36 per minute. Under the skin of its back, one-sixteenth of a grain of picrotoxine was injected, at 12.10 P.M. An almost immediate effect was observed. At 12.15, the respirations were 48 per minute, and much fuller and deeper; there were incessant licking of the lips and slight shakings of the head. At 12.17, saliva was dropping from the mouth, and there were dullness and stupidity. At 12.19, the flow of saliva was very large, and the eyes were being constantly opened and closed. At 12.21, the blinking of the eyes continued, and there were restless movements of the ears, while the animal was dull, and not readily roused. At 12.23, the saliva, which at first dropped from the mouth, had become so viscid that it hung in long wreaths, reaching from the lips to the table on which the animal sat, blinking both eyes vigorously. At 12.25, the bowels acted freely; the respirations were at the rate of 180 per minute. At 12.27, there were slight twitchings of the eyelids, ears, and cheeks, most pronounced on the left side. At 12.29, these twitchings continued, and were more severe, while enormous quantities of viscid saliva flowed from the mouth. At 12.31, there were occasional violent startings of the head; the animal was more easily alarmed, and any loud noise caused the ears to be drawn back and flattened. The respirations remained at 180 per minute. At 12.33, the slight twitchings of the eyelids, nose, and ears were continuous, while, every thirty or forty seconds, there were more general and severe startings. Saliva still flowed in excessive quantities, and the pupils were dilated. At 12.35, the severe startings recurred every thirty seconds, and were seen to consist in a sudden movement, forwards and downwards, of the head, with stretchings of the neck, and in raising of the shoulders. The movement altogether recalled that which is made by a cat when voraciously chewing and swallowing a rather large morsel. At the same time that the head was pushed forwards, the ears were drawn backwards and downwards. Intermediate between the more violent movements, slight

twitching, particularly in the eyelids, causing blinking, continued. The animal remained in a sitting position, and was drowsy; its pupils were widely dilated, and saliva still dribbled copiously from its mouth. At 12.40, no change had taken place; but, at 12.50, there were twitchings of the left fore-paw which was first stretched out, then raised in the air, and subjected to clonic spasms; respirations 138. At 1.5, the twitchings were less incessant and severe, and, at 1.15, they ceased altogether. At 1.20, the flow of saliva was much diminished, and the animal was more lively and able to move about, the respirations being then 60 per minute. At 2.15, the animal was in all respects recovered.

Experiment XC.—A large cat, weighing 6 lbs., had one-fourth of a grain of picrotoxine injected at 2.20 P.M. An instantaneous effect was noticed; the animal was restless, and in two minutes saliva began to drop from the mouth. At 2.24, there was loud mewing, and the head began to shake. At 2.25, there was emprostotonos; the head was drawn down, until the forehead was pushed against the table, and the back arched upwards, while there were violent general startings. At 2.26, after several attacks of emprostotonos, the animal tumbled on its side, when its head was suddenly drawn backwards, and its pupils were dilated to their widest possible extent. The fore limbs were stretched out, and the toes and claws were expanded, but the hind limbs were drawn up and remained in a flexed position. There was violent working of the mouth which was surrounded with foam, as well as twitching of the nose, eyelids, and ears. There were also severe spasms of the fore limbs. Several times the animal endeavoured to get on to its feet, but was unable to do so. At 3.32, the head was drawn down between the legs, and the back was arched upwards, the fore limbs were semiflexed, and the toes and claws folded in; the ears, eyelids and brows were in constant movement, the tongue was being constantly protruded and drawn back into the mouth, and it, as well as the lips and mucous membrane of the mouth, had a livid colour. The pupils were contracted to mere slits, and the animal was apparently unconscious. At 3.36, the clonic spasms were interrupted for a little, when the pupils at once dilated, but, at 3.38, they recurred, and then the pupils became once more contracted. From this time, however, the clonic spasms were much less severe. At 3.42, there were constant slight twitchings of the upper lip, eyelids, ears, head, and paws, with low moaning sounds. At 3.47, there were momentary intervals between the discharges, and in these intervals the pupils dilated slightly, always contracting again with each fresh discharge. At 2.50, the animal died, when the pupils at once dilated widely.

The action of picrotoxine upon the cat, as exhibited in these experiments, did not seem to be very dissimilar to its action upon rabbits and guinea-pigs. Increase of the salivary secretion and of the peristalsis of the bowels, hurried respiration, tonic and clonic spasms, with coma, were all included in its effects. One of its effects, however, that upon the pupil, was more distinctly manifested than in the other animals named. It first enlarged and then diminished the size of the visual aperture, and it should be noted that the dilatation was synchronous with opisthotonos, the contraction with clonic spasms. I have remarked that in cats, in which the movements of the iris are very easily observed, toxic agents invariably induce contraction of the pupil contemporaneously with clonic spasms and dilatation of the pupils with tonic spasms. The phenomena of absinthie, strychnia, and opium-poisoning in cats, will afford verification of this statement. Sometimes, during clonic spasm, the pupils may be seen contracting with each discharge, and dilating during each interval; so that, if the discharges succeed each other very rapidly, the irides have an oscillatory motion. I think I should be justified in saying, that the dilator muscle of the iris ought to be grouped with the extensor muscles, which are generally predominant in action in acute tonic spasms, and its sphincter with the flexor muscles, which predominate during clonic spasms.

The similarity which was demonstrated to exist between the effects of picrotoxine as seen in the cat and those observed in the rabbit and guinea-pig, gave good grounds for anticipating that chloral-hydrate would control those effects as conspicuously in the former as it did in the latter animals. No misgivings of the result were, therefore, entertained when the following experiment was undertaken.

Experiment XCI.—Cat, weighing 5½ lbs. At 2.54 P.M., one-fourth of a grain of picrotoxine and twenty grains of chloral-hydrate were simultaneously injected. At 3.7, the animal was restless and uttering low cries. At 3.13, it was drowsy, and mewing occasionally. At 3.15, there was a severe fit, in which the fore legs were spread out and the head was shaken, the ears being folded backwards, while there were also violent general startings. At 3.20, the cat died suddenly without any further convulsions.

The termination of this experiment was unexpected and somewhat

perplexing. It suggested a doubt whether chloral-hydrate was at all antagonistic to picrotoxine in the cat, for, when they were given together, the cat died just as soon as when the same dose of picrotoxine was given alone. On reflexion, however, the theory was adopted that chloral-hydrate exerts its effects upon the cat more slowly than it does upon the rabbit, while picrotoxine acts upon the cat more rapidly than upon the rabbit, and that accordingly the fatal action of picrotoxine might have expended itself before the saving action of chloral-hydrate came into play. If that were so, it was probable that the same was the case with reference to strychnia, and so the next experiment was instituted to settle that important point.

Experiment XCII.—A large cat, weighing 5 lbs. 6 oz., had one-fiftieth of a grain of strychnia and twenty grains of chloral-hydrate injected simultaneously. In three minutes, its ears were strongly drawn backwards, and it was startled by the slightest noise or movement. In four minutes, there was sudden opisthotonos, the head was drawn back, the pupils dilated, the limbs extended. Tonic spasms lasted for five minutes, when death occurred, just nine minutes subsequently to the injection.

Here was evidence that chloral-hydrate is practically as inefficacious in counteracting strychnia as it is in counteracting picrotoxine in the cat. And here also was confirmation of the view that its inefficacy in counteracting picrotoxine ought to be attributed to the comparative tardiness with which it asserts its influence over the nervous centres in that animal. To obtain conclusive proof or disproof of that hypothesis, chloral-hydrate was next administered by itself to a cat, and its effects were narrowly watched.

Experiment XCIII.—A cat, weighing 6 lbs., had twenty-five grains of chloral-hydrate administered by hypodermic injection. No change was noticed in it for twenty minutes after the injection, when it became restless, and at the same time rather unsteady in its movements, staggering a little when it walked about. In thirty minutes, after violent retching and vomiting, it was decidedly restless and unsteady, swaying about when walking, chiefly, as far as could be judged, owing to impairment of power in the hind quarters. The cardiac impulses were 120 per minute, and feeble in character, and the respirations were 52 per minute. The pupils were of an average size. In fifty minutes, it was still awake and very restless, lying down for a few seconds, and then staggering about the room purposelessly. When attempting to walk, it would cross its fore-feet, reel from side to side, stop and endeavour to steady itself, then stagger onwards, tumble over on its side, and regain its feet after much floundering. Its hind legs were very deficient in power, and frequently gave way under it. Its breathing was laboured, and its heart's action very feeble and irregular. It was somewhat drowsy, and whenever it sat down, manifested a tendency to drop off to sleep. In one hour, it had brief snatches of sleep, broken by frequent movements and low cries. Its heart's action was imperceptible, and its respirations were 69 per minute and irregular. In an hour and ten minutes, it was again awake, and staggering about more unsteadily than ever, and dragging its hind-legs after it. The hind-legs, however, as well as the tail, retained undiminished sensibility. In an hour and a half, it was lying on its side deeply asleep, sometimes, however, starting, and subject to attacks of general shivering. The heart's action was a mere flutter, and the respirations were 42 per minute, and frequently interrupted. In two hours, it was lying on its side sleeping quietly. When its tail was pinched, it would emit thirty or forty low monotonous cries in succession. In three hours, it was still more deeply asleep. It lay with its tongue protruding from its mouth, and did not move or cry out when its ears or whiskers were touched, or when its tail was pinched. There were occasional shiverings; its muscles were flaccid; its respirations 40 per minute. In this state it continued for thirty-six hours after the injection, when it died. During the whole of these thirty-six hours its bowels did not act, nor was its bladder evacuated.

Experiment XCIV.—A cat, weighing 7 lbs., had forty grains of chloral-hydrate administered by hypodermic injection. It was restless for one hour, during which time it vomited and had several attacks of retching, and at the end of which it fell into a deep sleep. Its respirations became gradually slower; it uttered from time to time low growls resembling those of a tiger. In three hours, however, it was deeply asleep, and could not be roused. For fifty-six hours it remained in this deep sleep, and at the end of that time it died, having been several times fed by a tube passed down the oesophagus. Throughout the whole of that protracted sleep, or trance, it passed no urine, nor was there any evacuation from its bowels. On examination of the body, it was found that all the vessels of the skin and all the subcutaneous vessels were engorged with blood; but that the intracranial sinuses were empty, while the brain itself was very anæmic. There was, however, a patch of hyperæmia over the cervical portion of the spinal cord. The

left side of the heart contained dark fluid blood, and the right side contained, in addition to this, some membranous clots. The lungs were highly congested, and cedematous, and the bladder was distended with urine.

These experiments confirmed the opinion which had been formed that chloral is much slower in its action upon cats than upon rabbits, and they revealed some other important facts in connection with its action upon the latter animal. They showed, for instance, that in cats, as in dogs, chloral induces a stage of excitement or intoxication with impairment of muscular co-ordination prior to the stage of sopor, that it induces sleep, passing into coma, in which all the bodily functions are retarded or are arrested, and that its effects may be protracted to an extraordinary extent. One other important fact they also disclosed, and that was that the fatal dose of chloral-hydrate in cats is small when compared with that in rabbits. These and some other experiments not here recorded with reference to the fatal dose of chloral-hydrate have led me to deduce a general law, that the energy of the action of that drug is in exact proportion to the development of the cerebral hemispheres. The minimum fatal dose may, I think, be taken as a measure of the energy of action. Now, when the cerebral hemispheres are small and simple in structure and arrangement, a very large dose of chloral-hydrate in proportion to body-weight is required to cause death. But, when they are large, complex, and highly differentiated, a comparatively small dose will ensure that result. In the rabbit, the brain of which is almost smooth, the minimum fatal dose is not less than twelve grains to the pound of body-weight. In the cat, the brain of which is considerably convoluted, the minimum fatal dose is five grains to the pound of body-weight; and in the human subject, in whom the brain is supremely rich in gyri and grey matter, the minimum fatal dose is a little over one grain per pound of body-weight. In microcephalic idiots, again, I have noticed that a proportionately larger dose of chloral-hydrate is requisite to induce its physiological effects than in persons with fully developed brains. But, while the energy of chloral-hydrate appears to be in relation to cerebral development, there are other conditions, which I am not prepared to specify, which determine the rapidity or slowness with which its effects are established in different animals, and also the duration of these effects. This, however, seems to be the general rule, that, where its effects are slowly established, they are long sustained, and that, where they are rapidly established, they are more transitory.

If the supposition were correct, that the failure of chloral-hydrate to antagonise picrotoxine and strychnia in the cat in the experiments above described was due to the comparative slowness of its action, it followed that, when time was given for the establishment of its action before the administration of the picrotoxine or strychnia, the antagonism would become sufficiently apparent. To test this point, the next experiments were performed.

Experiment XCV.—Cat weighing 5 lbs. 8 oz. At 3.32, twenty grains of chloral-hydrate were injected; and ten minutes later, at 3.42, when the animal was still awake and lively, one-tenth of a grain of picrotoxine was injected. At 3.50, there were retching, vomiting, rapid and irregular breathing. At 3.56, there was emprosthotonos. The head was drawn down between the legs, while the ears and eyelids were twitched. At 3.59, there was a sharp attack of clonic spasms; and at 4 p.m. the animal died suddenly and unexpectedly.

Experiment XCVI.—Cat weighing 5 lbs. 12 oz. At 1.37 p.m., twenty grains of chloral-hydrate were injected; and an hour afterwards, at 4.17, when the animal lay upon its side in a sleep from which it could readily be roused, one-tenth of a grain of picrotoxine was injected. At 4.25, the breathing was hurried and irregular, and the heart's action intermittent. At 4.40, there was violent retching. At 4.50, the heart's action was imperceptible; and at 5.10 death took place, no spasm of any kind having occurred.

A new light was thrown upon the subject by these experiments, making it evident that, while picrotoxine and chloral are antagonistic to each other in cats in certain directions, in others again they are in fatal harmony. It became evident that chloral does oppose and nullify the action of picrotoxine upon the motor centres, but that it combines with picrotoxine to arrest the action of the heart, and so hastens death. In Experiment XCVI, the cat died without having suffered from any convulsive action; and in Experiment XCV, it died after an amount of convulsive action by no means adequate to account for death by exhaustion of the nerve-centres. On reverting again to Experiment CXIII, it was remarked that in it the cat died actually more speedily than it would have done had the picrotoxine been given to it alone, and after only one convulsive seizure; whereas the same dose of picrotoxine given alone would in the same time have induced numerous seizures. In all these experiments, death was due, not to the immediate effects of the picrotoxine, nor to the immediate effects of the

chloral, but to the combined action of both. It depended, not upon exhaustion following violent discharges of nerve-force, not upon profound coma, but upon a sudden failure in cardiac power.

The effects of chloral upon the cat are exceedingly like those of chloroform, only more protracted; and among them, therefore, is a weakening or paralysing effect upon the heart through its special vaso-motor nerves and ganglia. Then, on the other hand, among the effects of picrotoxine upon the cat, is a retarding influence on the heart and prolongation of its diastole through increased inhibitory power exerted by the vagi. If, then, the paralysing influence of chloral is exerted on the heart contemporaneously with the inhibitory influence of picrotoxine, we can readily understand why syncope and death should ensue, and why practically no antagonism exists between them, although chloral-hydrate mitigates the cerebral irritability brought on by picrotoxine, and although picrotoxine restricts the depth of the hypnotism brought on by chloral.

The danger of the conjoined action of chloral-hydrate and picrotoxine on the heart is greatest during the earlier stages of the action of the former, when some degree of excitement is present; and so trial was made of the effect of picrotoxine when given to a cat that had passed altogether through the period of chloral excitement into deep chloral sleep.

Experiment xcvi.—A cat weighing 5 lbs. 2 oz. had twenty grains of chloral-hydrate hypodermically injected at 11.45 A.M. At 1.45, it was deeply asleep, after much restlessness alternating with drowsiness; and then one-sixteenth of a grain of picrotoxine was injected at 1.50. Its sleep was disturbed; there were movements of the paws and tail, and general quiverings. At 2 P.M., however, its sleep was again calm and profound. Throughout the afternoon, it had alternate periods of sleep and wakefulness. During the latter, it got up and staggered about as if drunk, its pupils being widely dilated. During the former, it lay upon its side, its head being bent down, and its back arched in a distinctly emprosthotonic attitude. Whenever it was moved out of this position, it forthwith, without waking, resumed it. At 9 P.M., its sleep was continuous, and there were no spontaneous movements. It remained in a deep uninterrupted sleep for two days and three nights, when it began to recover itself. In a few hours more, it was quite well. Throughout its long sleep, its bowels did not act, nor did it void urine. When its tail was pinched, it did not flinch. Milk was frequently administered to it, and it was kept warm.

The description of further investigations which have been undertaken, but which are not yet complete, with the purpose of ascertaining the effects of the combined administration of picrotoxine, chloral, and atropine, picrotoxine, chloral, and digitalis, and picrotoxine, chloral, and alcohol, must be reserved for a future contribution to these pages, in which it is hoped that the effects may also be recorded of the continuous administration for long periods of small non-fatal doses of picrotoxine to animals. If, as has been repeatedly alleged, *coccus Indicus* is extensively employed by dishonest brewers to impart bitterness and inebriating qualities to the pernicious liquids which they sell as beer, it is certainly eminently desirable that we should accurately ascertain the effects upon health of such a dietetic counterfeiter; and this can only be satisfactorily done by watching the effects upon animals of minute and frequently repeated doses of the suspected adulteration. In the meantime, however, we are not without indications of the evils wrought by such deleterious additions to a popular beverage. When giving evidence before the Select Committee of the House of Commons on Habitual Drunkards in 1872, I suggested that perhaps the greater prevalence of epilepsy in England than in Scotland was to be ascribed, partly at least, to the preponderance of beer-drinking and to the adulteration of beer by *coccus Indicus* in the former country. Further observations have only tended to strengthen my belief in the theory which I then broached. Large quantities of Levant nuts are imported annually into this country, and the difficulty is to find any destination but the brewer's vat for these importations. But the action of these Levant nuts upon those who partake of them or of their active principle is to set up an unstable condition of the nervous centres, which eventuates in paroxysmal discharges analogous to, if not identical with, epileptic fits. If, then, we find that beer is adulterated with *coccus Indicus*, that *coccus Indicus* is adequate to the production of epileptic conditions, and that beer-drinking and epilepsy are generally in proportion to each other in their prevalence in the population, there are good grounds for holding that the adulteration of beer is responsible for much of the epilepsy by which this country is now so grievously afflicted.

And there are still other inquiries in relation to picrotoxine which remain to be made. Its therapeutic properties ought to receive attention. Many years ago, Sir Robert Christison pointed out that the actions of

this agent in medicinal doses were deserving of investigation; but the hint which he then gave has not yet been acted on. Now, however, we know that picrotoxine is a powerful stimulant to certain nervous centres; and we have therefore reason to hope that it will prove useful in some diseased conditions in which symptoms of diminution of function in these nervous centres are apparent.

The following general conclusions seem to be fairly established by the investigations which have been described in the foregoing paper.

1. Chloral-hydrate is physiologically antagonistic to picrotoxine in rabbits and guinea-pigs, and will, when administered in a suitable and proportionate dose, save life after a fatal dose of picrotoxine.

2. The antagonism of chloral-hydrate to picrotoxine in rabbits and guinea-pigs may be exerted so as to save life, even when it is not administered until fifteen or twenty minutes after the fatal dose of picrotoxine.

3. The antagonism of chloral-hydrate to picrotoxine is subject to two limitations: *a.* That the dose of picrotoxine may be so large as to kill before the chloral-hydrate has time to operate; *b.* That the dose of picrotoxine may be so large that nothing short of a poisonous dose of chloral-hydrate would avail to counteract it.

4. Picrotoxine is to a very limited extent antagonistic to chloral-hydrate in rabbits and guinea-pigs, by mitigating the hypnotic effects of the latter upon the brain and higher nervous centres, which it stimulates to activity.

5. The minimum fatal dose of chloral-hydrate in the rabbit is twelve grains to each pound of body-weight.

6. Practically no antagonism exists between picrotoxine and chloral-hydrate in the cat, nor between strychnia and chloral-hydrate.

7. Picrotoxine and chloral-hydrate, when administered simultaneously to the cat, cause death by stopping the action of the heart, and not by any destructive or exhausting action upon the supreme nervous centres.

8. Chloral-hydrate causes in the cat excitement and restlessness, with motor defects prior to the state of sopor, and its effects upon that animal are protracted to an extraordinary extent.

9. The energy of the action of chloral-hydrate, as measured by its minimum fatal dose, is in proportion to the development of the cerebral hemispheres.

In closing this paper, I have to express my gratitude to my colleague Dr. Lawson for much valuable assistance, in making some of the observations upon which it is founded.

ON PUERPERAL FEVER.

By EDWARD JOHN TILT, M.D.

ONE good result of discussions like that on puerperal fever, now proceeding at the Obstetrical Society of London, is, that it brings to light valuable cases, like two that were published last week in this JOURNAL by Mr. Stewart of Barnsley. He truly remarked "that they were exceedingly interesting from their tendency to throw light upon the nature and production of puerperal septicæmia, as they show that the application of decomposing lochia alone to a recent scratch or wound has been sufficient of itself to produce gangrene of the part and death of the patient in the one case, and a very severe attack of phlegmonous erysipelas in the other, although no puerperal condition existed in either of the inoculated subjects. I think we may, therefore, draw the conclusion, that the passage of decomposing lochia over any abraded surface in the vaginal passage is sufficient to produce puerperal septicæmia without the importation of any other specific poison. In this manner, we may account for the disease attacking much more frequently primiparous cases, as the vagina and perinæum are much more likely to be slightly lacerated in those than in multiparæ".

All this is no doubt true, but it has been already pointed out; and the interest of the cases lies in the fact that they show the precise channel through which a woman frequently pours into her blood the poison secreted in her womb. The lymphatics surrounding the recent scratch of one woman, and the cut thumb of the other, took up the poison, passed it on to the lymphatics of the forearm, and they into the blood. What became of the inflamed lymphatics in one case is not said, but in the other they inflamed the surrounding cellular tissue. In exactly the same way, the lymphatics in and around a rent of the circular fibres of the internal os uteri, or of the cervix, on the "fourchette", often take up the poison that comes down from the puerperal womb, and transmit the poison to the pelvic lymphatics, that pour it into the blood. The contact of the poison with these lymphatics influences them in various degrees, and sometimes acutely inflames their surrounding cellular tissue. This is called pelvic cellulitis; but, when