

and constitutional symptoms; that is, between local pathological changes and general constitutional disturbance.

This evidently becomes necessary for the purposes of treatment. Allowing that the local action of septic agents is the production of those changes of tissue which we term inflammation, the question arises whether there are other causes for the same effects as well as septic material.

This question is answered by some in the following manner. "It is possible that inflammation may be excited by various causes other than the presence of bacteria; and we would distinguish the former from the latter by the term simple traumatic pyæmia and specific traumatic pyæmia, pyæmia being used in the general signification of sepsis. From simple traumatic pyæmia may follow metritis, endometritis, parametritis, perimetritis simplex, or diffuse peritonitis. In surgical cases, this disease assumes the form of erysipelatous rubor around the wound; that is to say, conditions depending on local causes. Phlebitis and thrombosis may also be consequences of simple traumatic pyæmia. The only difference between these and the specific form of pyæmia is the presence of bacteria." These are the views of Billroth, Heiberg, and others.

Now, it does not unfrequently occur that cases present themselves in which we find only those alterations of tissue which are attributed to simple traumatic causes, and yet the history and other circumstances of these cases are the same as those in specific traumatic inflammation. What must always be a difficulty appears to me to be the diagnosis between the one and the other form of inflammation. It is difficult, I think, to obtain a very clear idea of what simple traumatic inflammation is, as distinguished from the other. Does it not seem that we are defining it by negative characters; in fact, that, instead of being simple, it is a very complex expression, for it may be anything; that is, any substance or force except bacteria? If we are to call one simple in its nature, the most definite ought to have the first claim to the title. We are aware that, pathologically considered, there is no difference, as far as we can tell at present, between cellulitis or phlebitis of the thigh, as it occasionally occurs in men, or as we meet with it in the puerperal condition in women; so that, in any particular case, we are obliged to depend upon the history for information as to the origin of the disease, and upon the general symptoms for evidence of septic infection.

This is the clinical aspect which the subject presents, and, regarded in a practical point of view, it appears doubtful whether the division proposed is consistent or useful. We may have cases of metritis which have originated in abortion; but, by active treatment, the decomposition of organic matter within the uterine cavity has been prevented from infecting the system, and no symptoms are present which enable a diagnosis to be made between simple traumatic metritis and specific metritis. It may be remarked, that the difference which is assumed and appears to exist between simple and specific inflammation was present to Cullen's mind when he observed: "Whether there be any belonging to the order of phlegmasia is doubtful." (*Op. cit.*, p. 80.) In speaking of erysipelas, he remarks: "It is doubtful if this disease be properly, in nosology, separated from phlegmasia." (*Op. cit.*, p. 377.) Or, again, "It is probable that an erysipelas is sometimes attended with, or is a symptom of, a putrid fever." (*Op. cit.*, p. 379.) Looking at the question from a common sense point of view, we may reasonably ask whether there is not a danger of making confusion in our views of the symptoms, pathology, and treatment of the disease we are considering by allowing the use of an indefinite or ill-defined word like "traumatic" into the terms of definitions. It sometimes happens than we can discern the flaw in an argument or proposition without much trouble; at other times, we are withheld from consent by a feeling that, though the logical process by which the conclusion is arrived at be correct, there is a certain want of character in it which makes us hesitate. If we take the trouble to examine carefully any proposition of this kind,—and we know how frequently they present themselves to the physiologist and physician,—we shall find that there is some slight incorrectness in the premises of the argument. It is quite open to discussion whether metritis in all its forms, which are said to be traumatic, may not have been occasioned by the influence of an organic poison developed under certain conditions, or of external forces, such as cold, injury, and others. It is not difficult to perceive the direction which such reflections must give and are giving to pathological research. To return, however, to puerperal fever—a disease which, we are induced to believe, is to be explained in all respects by the influence of septic poison—it would appear that, in most cases, we are to search for the focus of decomposition in the cavity of the uterus or the surface of the mucous membranes which are connected with it. Whether we can prove that there is organic substance undergoing decomposition or not, we are to be satisfied by the symptoms which are

present that such is the case. We are also required to admit that, under several conditions, all of which involve the presence of septic substance, symptoms similar to puerperal fever may be developed; and that, whatever differences are observed in the acute or chronic character of such symptoms, we are to refer them to the rate of admission of the poison into the system. We assume that we may explain the peculiarly acute form of puerperal fever with which we are acquainted by the fact of the existence of venous sinuses in the walls of the gravid uterus, and of large lymphatic vessels by which the septic material easily enters the circulating fluids; and, when asked to define what we mean by a septic agent, by sepsis, or by any other term involving the same idea, we may make the basis of our definition the existence of active living organisms resulting from the decomposition of organic matter, having special microscopical characters, producing special effects on the system of man and beast, and the transmission of which is regulated by ascertained principles.

(To be continued.)

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

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THE admirable report of the Committee of the British Medical Association, appointed to investigate the antagonism of medicines, which we owe to Dr. Hughes Bennett's powers of lucid exposition, suggested to me, when reading it, various instances beyond those which received the attention of the Committee, in which a direct physiological antagonism between the actions of remedies in all probability exists. Of the conjectures which thus occurred to me, I have as yet been able to put one only to the test of actual experiment; but the results which this single investigation has afforded me are so interesting and important as to appear to me to merit early publication.

It was when perusing the description given of the effects of chloral hydrate in reducing the force and frequency of the tetanic convulsions which follow a fatal dose of strychnia, that I began to speculate that, in all likelihood, the same agent might exercise a similar influence over the somewhat analogous symptoms which follow the administration of a fatal dose of picrotoxine. An inquiry, which I commenced some years ago, into the actions of that substance had satisfied me that, in some respects, its effects upon the living organism resemble those of strychnia. Tonic and clonic spasms of great severity and violence, culminating speedily in death, are induced by large doses of it, and opisthotonos and gasping and respiration are frequently present. The very particular in which the toxic effects of picrotoxine differs from those of strychnia, in that they are exercised to a greater extent over the cerebral and to a less extent over the spinal centres, seemed to hold out an additional hope that chloral hydrate would effectually counteract them; for chloral hydrate powerfully diminishes the activity of the brain, and so might be expected to mitigate the influence of any agent which irritates that organ and stimulates it to excessive and irregular discharges of energy.

In proceeding to put to trial the theory thus formed as to the antagonism of picrotoxine and chloral hydrate, it was thought desirable, in the first instance, to arrive at definite notions as to the physiological actions of the former. And these could scarcely be derived from books; for, although *cocculus Indicus*, of which picrotoxine is the proximate principle, has been recognised as a medicine since the days of the Arabian physicians, by whom it was designated *Maderadsch*, its modes of operation and uses may still be said to be undetermined. Christison says of it, that it was probably first known in Europe as a means of taking fish, which it first throws into violent irregular motion and then stupefies; and that it is an active poison, adequate to occasion death, producing chiefly giddiness, staggering, tetanic convulsions and coma. He adds, that nothing is known of its medicinal properties or actions in small doses, more than that it is beneficial as an external application in scabies, ring-worm, and porrigo. Taylor intimates that it gives rise to nausea, vomiting, and griping pains, followed by stupor and intoxication; and he describes one of the few recorded cases in which it has proved fatal, and in which these symptoms were present, and extended over a period of nineteen days. Dr. Glover describes it as a narcotico-acrid poison that acts on the spinal cord, raises the animal temperature, and causes great congestion at the base of the brain. Dr. Roeber of Berlin, who experimented with picrotoxine,

and whose researches, published originally in the *Archiv v. Reichert und Du Bois Reymond*, 1869, are quoted in the *Journal of Anatomy and Physiology*, found that, in frogs, a comatose condition is first produced by it, and then a series of tetanic spasms, which, by and bye, become clonic. He further demonstrated that during the stage of clonic spasms, the inspirations are greatly exaggerated, so as abnormally to inflate the lungs; and that the heart's action is rendered slow, and the diastole prolonged. He alleges that the occurrence of spasms could not be prevented by the removal of the cerebrum or optic lobes, but that they never appeared after separation of the medulla oblongata from the medulla spinalis. He infers, therefore, that the spasms are dependent on stimulation of the medulla oblongata, and that the slowness and even stoppage of the heart's action, as well as the inflated condition of the lungs of the frog, are caused by this stimulant action affecting the vagus centre. To verify the observations of Roeber, and to obtain practical acquaintance with the action of picrotoxine, a few preliminary experiments were performed. In these, as in all subsequent experiments, the picrotoxine employed was obtained from one of the most trustworthy of sources, the house of Messrs. T. and H. Smith of Edinburgh, and was dissolved in ether, and administered by hypodermic injection.

Experiment I.—Rabbit weighing 2 lbs. 10 oz. One-fortieth of a grain of picrotoxine was injected under the skin of the shoulder. In four minutes, the animal was dull and lethargic. In ten minutes, it was exceedingly listless and stupid, and had lost its natural timidity, making no efforts to move when approached, touched, or pushed. It was not drowsy nor comatose, however, and its head did not droop nor nod; but it sat huddled together, its fur ruffled, and with a general aspect highly suggestive of a feeling of sickness and oppression. In twelve minutes, it voided a large quantity of urine, and its bowels acted copiously. In fifteen minutes, it was more lively, but somewhat unsteady in gait, and exhibiting stiffness and clumsiness in its movements, particularly in those of the hind limbs. In seventeen minutes, its bowels were again freely evacuated, the feces being of a rather soft and pulpy consistence. In twenty minutes, its breathing was very hurried and irregular, and there was slight shaking of the head. In four-and-twenty minutes, there were twitchings of the ears, which were held rigidly erect, and occasionally moved about in a singular jerking manner. In five-and-twenty minutes, the movements of the ears continued, and there were also munching movements of the lips, with dribbling of saliva from the mouth, which was drawn to the right. In thirty minutes, all movements had ceased, but there were considerable prostration and drowsiness; the animal lay upon its belly, with its legs stretched out as if helpless. In forty minutes, there was more liveliness. In sixty minutes, there was restlessness and uneasiness. In ninety minutes, recovery might be said to be complete.

Experiment II.—Rabbit weighing 2 lbs. 12 oz. One-twenty-fourth of a grain of picrotoxine was injected under the skin of the back. In five minutes, there were stupidity and lethargy. In seven minutes, there were a large evacuation from the bowels, and hurried and embarrassed respiration. In fifteen minutes, there was restlessness; the animal was moving about stiffly, manifesting no apprehensions of the persons around, but trembling a little from time to time, especially in the hind legs. In twenty-two minutes, there were twitchings of the ears, which had a distinctly paroxysmal character. The ears were raised, and rapidly jerked about for eight or ten seconds, and then remained at rest for twenty or thirty seconds. In twenty-three minutes, there were shakings of the head and clonic spasms of the eyelids and eyebrows, causing forcible winkings. In twenty-four minutes, the ear-twitching still continuing with increased severity, the head was drawn slowly and rigidly backwards, until the erect ears rested upon the back; the fore-paws were spread out, and the body was then, with convulsive starts, drawn backwards and upwards, until the fore-paws were raised in the air, and the animal sat in the position of a squirrel when eating, all its muscles, however, being agitated by clonic spasms. In a few seconds more, the animal tumbled backwards, and, the clonic spasms suddenly ceasing, it scrambled on to its feet. In twenty-six minutes, there was another convulsive seizure, like the former one, and also ending in a tumble backwards; and, in twenty-seven minutes, there was another, in which the head was drawn round to the right side, until the nose was pressed against the shoulder; the animal then turned round rapidly three times from left to right, after which all the muscles were affected by clonic spasms; these were at first coarse in character, causing sudden startings, and then fine, causing tremblings and twitchings. There was dribbling of saliva from the mouth, with incessant movements of the lips, whiskers, and cheeks; the eyeballs were drawn upwards and backwards, and were occasionally affected by nystagmus. The pupils became dilated at the close of

each fit. In twenty-eight and in twenty-eight and a half minutes, there were further seizures, and, at the close of the last, the animal fell on its left side, and was unable to regain its feet. The convulsions then became continuous. The head was thrown back, the ears were jerked about, the limbs were all extended, and worked rapidly, as in running, and there were incessant munching movements of the lips and cheeks. Peculiar murmuring noises or little short cries were emitted, and a large quantity of viscid saliva streamed from the mouth. Universal clonic spasms of this kind continued uninterruptedly for ten minutes; but their severity gradually abated. In thirty-eight minutes after the injection, there was a brief period of freedom from convulsions, and thereafter snatches of rest became more frequent and prolonged. In fifty minutes, the rabbit was lying quietly on its side in a drowsy state, broken in upon by occasional sudden irregular muscular twitchings, but giving no evidence of sensibility, or even of reflex excitability. Pinching of the tail or paws did not evoke movement of any kind. In two hours after the injection, the rabbit was still on its side, and subject to slight twitchings. Then, however, it got on to its feet, and endeavoured, in a helpless stumbling way, to move about; but, for three hours more, it was sickly and feeble, and not until five hours after the injection was it quite itself again.

Experiment III.—Rabbit weighing 3 lbs. One-quarter of a grain of picrotoxine was injected under the skin of the shoulder. In two minutes, it was sickly and frightened-looking, and its respirations were much quickened. In five minutes, it was able to move about, but was very unsteady, and dragged its hind legs after it. In seven minutes, there were quiverings of the ears, shaking of the head, and sudden startings. In nine minutes, munching movements of the mouth began; every effort at voluntary movement at once increased the twitchings of the ears and lips. In ten minutes, there were violent twitchings of the eyebrows, cheeks, and mouth, and the head was drawn first downwards, the ears at the same time becoming erect, and then backwards. At the same time, the bowels acted, and saliva began to trickle from the mouth. In eleven minutes, there was a distinct and violent convulsive seizure, characterised by sharp twitchings of the ears, drawing of the head first to the right side and then backwards, munching movements of the lips, lapping movements of the tongue, and clonic spasms of the paws, causing the animal to jump and prance upon the floor. The fit lasted twenty-five seconds, and then ended abruptly, and was followed by four other similar fits, each, however, more severe than that which preceded it. These four fits, with the intervals between them, were spread over three minutes. It was quite obvious that any attempt at voluntary movement on the part of the rabbit during the intervals between the fits at once brought on tonic and clonic spasms. At the end of the fifth fit, the rabbit, after manifesting some restlessness, suddenly sprang forward in the wildest and most precipitate manner, and ran about the room with great unsteadiness and recklessness, dashing itself against obstacles, and struggling violently. In ten seconds, however, it fell upon its side, and was strongly convulsed. The head was drawn backwards, the back formed a curve, with its concavity upwards, and the tail was raised and drawn towards the head. The ears, which felt hot, were twitched, and so were the eyebrows, eyelids, and eyeballs, the latter being drawn upwards and backwards, and oscillating a good deal. The pupils were widely dilated; the nostrils were distended; the lips were retracted, so as to expose the teeth, which were ground together; and the tongue was forcibly protruded every now and then. Large quantities of saliva, mixed with blood from the tongue, which had been bitten, flowed from the mouth. The limbs were extended, and were in incessant movement, as in vigorous running, and the toes also, with each clonic spasm, were extended and abducted. From this time, there were no distinct interparoxysmal periods; but convulsions of the kind just described continued without interruption and with extraordinary violence. In nineteen minutes, however, it was observed that the movements of the limbs were feebler, though those of the head and face were as severe as ever. The head was drawn back to the extreme possible point, and was shaking incessantly. The crunching of the teeth was loud and frequent, and the contortions of the nose and lips were unmitigated. The animal was quite unconscious; but peculiar short cries and murmuring expiratory noises were emitted from time to time, and saliva still drained away in large quantities from the mouth. The pupils were dilated to the fullest extent, and a considerable amount of a milky whitish secretion trickled from the eyelids. There was no sensibility nor reflex irritability. In twenty-two minutes, the spasms were much weaker; and, in twenty-three minutes, death took place.

Experiment IV.—Rabbit, weighing 3 lbs. 12 oz. One-fortieth of a grain of picrotoxine was injected under the skin of the back at

5.55 P.M. Normal temperature taken for 12 consecutive minutes, 103.2 deg. Fahr.

Temperature		Temperature	
6	P.M. ... 103.2 deg. Fahr.	6.45	... 100.1 deg. Fahr.
6.5	... 103.2 "	6.50	... 99.8 "
6.10	... 102.9 "	6.55	... 99.4 "
6.15	... 102.4 "	7.0	... 100.0 "
6.20	... 102.0 "	7.5	... 100.2 "
6.25	... 101.5 "	7.10	... 100.1 "
6.30	... 100.9 "	7.15	... 100.8 "
6.35	... 100.4 "	7.20	... 102.1 "
6.40	... 100.2 "		

Experiment v.—Rabbit, weighing 2 lbs. 8 ozs. One-thirtieth of a grain of picrotoxine was injected under the skin of the shoulder, at 6.54 P.M.; the normal temperature having been, by observations extending over 15 minutes, ascertained to be 102.0 deg. Fahr.

Temperature		Temperature	
6.55	P.M. ... 103.0 deg. Fahr.	8.5	P.M. ... 96.9 deg. Fahr.
7.5	... 103.2 "	8.15	... 97.6 "
7.15	... 100.9 "	8.25	... 97.9 "
7.25	... 99.9 "	8.35	... 98.4 "
7.35	... 98.4 "	8.45	... 99.2 "
7.45	... 97.8 "	8.55	... 101.3 "
7.55	... 97.4 "		

Experiment vi.—Rabbit, weighing 2 lbs. 10 lbs. One-third of a grain of picrotoxine was injected under the skin of the shoulder at 3.44 P.M.; the normal temperature having been ascertained to be 99.8 deg. Fahr.

Temperature		Temperature	
3.45	P.M. ... 99.9 deg. Fahr.	4.5	P.M. ... 96.6 deg. Fahr.
3.50	... 98.2 "	4.10	... 96.1 "
3.55	... 96.8 "	4.15	... 95.2 "
4.0	... 96.6 "		Death took place at 4.16 P.M.

Experiment vii.—A terrier dog, weighing 10 lbs., had three-eighths of a grain of picrotoxine injected under the skin of the back. In eleven minutes, there were general tremor and shivering; and in twelve minutes, convulsions, ushered in by rotation of the head to the right, and twitchings of the cheeks, mouth, and fore-paws, and rapidly becoming general. The fit lasted nearly two minutes, and ended abruptly, when the head fell forwards as if the muscles of the neck had become powerless, and the breathing became stertorous. After a minute's interval, convulsions again came on with marked opisthotonos, in which the head was drawn back and the tail became erect and rigid. After four more fits, all terribly severe, and lasting each about two minutes, the convulsions became continuous, and then very soon feeble in character, while deep coma set in. The animal died just ninety-one minutes after the injection. On opening the head, the dura mater and its sinuses were found to be enormously engorged with dark blood. In the cavity of the arachnoid, was a large soft layer of dark clot covering the anterior half of the left hemisphere. All the vessels of the brain were much engorged with dark blood, as were also those of the spinal cord. The grey matter was much injected. The right side of the head was full of dark and clotted blood, and the left side was uncontracted, and contained a small quantity of dark fluid blood. The lungs were unusually pale and anæmic; and the liver was in the same condition. The bladder was empty, although no urine had been passed during the experiment. During the action of the picrotoxine, the respirations and cardiac pulsations of this dog were from time to time carefully counted, and its temperature was taken in the rectum.

TABLE I.—Showing Number of Respirations and Cardiac Pulsations and Temperature in a Dog after a Fatal Dose of Picrotoxine.

No. of minutes after injection	Condition	Respirations	Cardiac Pulsations	Temperature
2	Somewhat agitated	—	138	100.
8	Quiet and natural	17	66	99.7
11	General tremor	30	126	99.4
15	Much convulsed	38	164	98.1
18	Severely convulsed	—	132	98.6
20	" "	—	69	98.8
22	" "	36	63	99.3
28	" "	18	—	99.4
33	" "	18	25	99.4
43	Coma	33	—	99.4

Experiment viii.—Guinea-pig, weighing 1 lb. 6 oz. One-fortieth of a grain of picrotoxine was injected under the skin of the back. In six

minutes, it was dull and stupid, and its respirations were much hurried. In nine minutes, there were general shuddering and quivering of the upper and anterior part of the left ear. In thirteen minutes, sharp paroxysms of general shivering continued to recur every few seconds. In nineteen minutes, it voided a large quantity of urine, and its bowels acted. In twenty-four minutes, the head was drawn to the right, there were munching movements of the right side of the mouth and right cheek, and the left paw was raised off the ground, and performed a number of rapid beating movements in the air. The fit lasted twelve seconds. In twenty-seven minutes, there was another and more severe fit, in which the head was drawn to the left, and there were violent twitchings of the face and fore-paws. Throughout the fit, consciousness was not apparently lost, and after it the animal was quite lively and well.

Experiment ix.—Guinea-pig, weighing 1 lb. 3 oz. One-thirtieth of a grain of picrotoxine was injected under the skin of the back. In eight minutes, it was drowsy, and there was quivering of the ears. In fifteen minutes, there were shakings of the head. In sixteen minutes, the head and mouth were slightly drawn to the left. In thirty-five minutes, the bowels acted, and the animal was very unsteady in its movements, stumbling as it endeavoured to walk about. In thirty-nine minutes, there was a fit. The head shook, the mouth twitched, the body was thrown first on to the left and then on to the right side, after which the animal regained its feet. By a series of jerky movements, the body was then raised, the fore-paws drawn backwards until they were off the ground, and the animal tumbled over when the fit ceased, upon which there were violent sneezing, and severe foaming at the mouth. In forty-four minutes, there was another fit, followed by repeated yawning and drowsiness. After this, there were several violent fits, accompanied by unconsciousness, incessant low cries, and copious flow of saliva, distinct nystagmus, and crunching and grinding of the teeth. Then came continuous clonic spasms, gradually becoming feebler, coma, and death sixty-two minutes after the injection.

(To be continued.)

SOME NEW RESEARCHES ON THE CAUSE AND ORIGIN OF FEVER FROM THE ACTION OF THE SEPTINOUS POISONS.*

By B. W. RICHARDSON, M.D., F.R.S.

THIS was a continuation of the author's paper read before the Society ten years ago, viz., in 1865. The author commenced his present lecture by giving a *résumé* of that which he had read in 1865. In that communication he had shown, from a series of experiments made with the serous fluids derived from a patient suffering from pyæmic fever, and under the care of Mr. Spencer Wells, that such fluid when inoculated into healthy animals, produced a distinct and fatal disease which could be transmitted to other animals through several series or generations. To the poisonous matter thus produced he had given the name of *septine*, and he had laid before the society specimens of salts obtained from the septinous matter, viz., a hydrochlorate and a sulphate, both of which possessed poisonous properties similar to those belonging to the mother liquor. He had inferred, therefore, that the poisonous substance was of an alkaloidal character. He had also, in the same paper of 1865, stated the following conclusions as the result of his experimental researches.

1. All the organic disease-producing poisons are modified, *i. e.*, poisonous secretions.
2. The secretions are rendered poisonous by two processes: (a) by contact with organic poison pre-existing; (b) by direct decomposition.
3. The poison of each secretion possesses several qualities: it can only be absorbed by particular channels, and it can only provoke farther disease by coming into contact with a secretion allied to that from which it was itself derived.
4. The reproduction of the poisons depends on the continuance of the process of physical changes in a continuous secretion. The force of secretion is the force of reproduction.
5. The poisons kill by various means: (a) by the secretion causing obstruction of necessary function; (b) by exhaustion from excessive secretion; (c) by extreme irritation of nerve and reflex injury; (d) by the absorption of the poisoned secretion into the blood and disorganisation.

From this point Dr. Richardson went on to describe that since the announcement of the facts had been put forward originally respecting septine, similar results had been obtained by Coze and Felz, Davaine,

* Abstract of a paper read at the Society of the Medical Officers of Health.