disturb the principles of medical science, and appear to endow with practical existence the ideas of the natural philosophers of bygone ages. In tracing the history of the doctrine of the nature of puerperal fever, there was, up to a certain point, no great difficulty; but now, instead of being able to regard it as a special form of disease, we must allow that it is only one of a large class. We can understand the idea involved in the explanation of its symptoms resulting from a "diphtheritic process" excited by the presence of certain forms of bacteria. We can see the importance of physiological experiments like those of Panum, which had for their object the determination of the pathological effects of emboli of different substances upon the tissues they happened to be arrested in. The local changes which followed the introduction of a globule of mercury, corpuscles of healthy pus, or decomposing fluids, were found to differ to such a degree, that we must admit the value of Panum's conclusions, that the constitutional symptoms which occur in the last instance can only be explained on the supposition of a putrid intoxication, as he terms it, of the blood.

We begin to wish to know more of the minute organisms which seem to be the chief cause of the symptoms. We find our attention being attracted to the interesting question of their generation, their various forms, and their specific characters; and we feel disposed to examine the early researches of Ehrenberg, and the later attempts of Hallier, Cohn, Lister, Billroth, and others, to reduce them into some order of classification. Such a study is, however, the work of a lifetime. As pathologists, considering the important connection between the presence of bacteria, without special regard to their species, we desire to know why an embolus of pus or fibrin may excite slight, if any, pathological changes, unless it contains micrococci, or gives rise to them by decomposition; and then we find ourselves engaged in the difficult problem of the earliest changes produced in the process of inflammation.

We begin to perceive that we are crossing the line that separates the practical from the scientific, if such a line can be said to exist; for I venture to express the opinion that you will agree with me in thinking true practical knowledge is the result of scientific conception, and that all knowledge which is not practical in no way deserves the title of scientific. I have had at command, in the preparation of these lectures, numerous works of reference, as well as opportunity of testing the truth of the theory under discussion. The difficulty has been to judge of the merits of those works rather than to analyse their contents. To sift them thoroughly, and to do them justice, and this, too, with patience and good feeling, I need hardly assure you, was a task which might have occupied a very long period of investigation.

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

By J. CRICHTON BROWNE, M.D., F.R.S.E.,
Medical Director of the West Riding Asylum.

(Continued from page 411.)

IN reviewing these experiments, which have been briefly described, the first reflection that occurs is, that picrotoxine is an energetic poison, and that the symptoms which it produces, at least at one stage of its action, in many respects resemble those of epilepsy. It causes sudden excessive and paroxysmal discharges of nerve-centres, in which movements are co-ordinated. It induces spasms, which at first involve one group of muscles, and ultimately affect nearly all the muscles of the body, with biting of the tongue, foaming at the mouth, and loss of consciousness. It induces changes in the pulse, respiration, and temperature, similar to those which accompany epilepsy; and, when there is a cessation of the spasms, it entails some degree of paralysis or loss of muscular power analogous to epileptic hemiplegia. It leaves *post mortem* appearances in the nervous centres, which at once recall those which are seen after death in the *convulsions* of epilepsy. But, if some of the effects of picrotoxine recall the phenomena of epilepsy, there are others which recall those of tetanus. The continuous, although remittent, discharges, the drawing back of the head, and the arching of the body, are all essentially tetanic in character.

But surely these similarities in the effects of picrotoxine-poisoning to the symptoms of disease ought to enable us to ascertain upon which nerve-centres the poison of picrotoxine more particularly expends itself. It may be that it finally affects the whole nervous system, but it is obvious that it does not do so in the first instances, but invariably makes its earliest attacks upon certain definite points, and pursues its encroachments by certain definite routes. First of all,

when the poison begins to enter the blood, there is a slight degree of stupidity, lethargy, or drowsiness, corresponding with the preliminary coma observed by Dr. Roeber in frogs, connected obviously with some alteration or defect in consciousness, and therefore traceable to the cerebrum. Secondly, there is some restlessness, with unsteadiness in gait or slight impairment of power in the hind limbs, which may be ascribed to the sense of uneasiness which accompanies a state of high tension of cerebral centres, or to vertigo, or a slight nervous discharge, and to enfeeblement of the spinal cord, due to the commencing action of the poison upon it. Thirdly, there are the distinct convulsive paroxysms, which afford the true clue to the course of action which the poison pursues, and point unmistakably to one part of the hemispheres as the centre upon which it first operates. For I can perceive no justification for the theory of Roeber, that these clonic spasms are attributable to stimulation of the medulla oblongata. It is beside the question to argue that they are so because they may be produced after all the centres above the medulla oblongata have been removed. We now know that the impressions and movements which are represented in a lower centre are re-represented in a higher one, and that the co-ordinations of the pons Varolii and medulla oblongata are more highly re-co-ordinated in the cerebrum. Because the thumb and index-finger may be moved by galvanic stimulation of the median nerve, we do not argue that the movements of these parts are not ordinarily originated and controlled by volition; and so because clonic spasms may occur in rabbits by irritation of the medulla oblongata after all parts above that centre have been cut off from it, we cannot argue that such clonic spasms may not proceed from the cerebrum when it remains intact. True it is that, the lower we descend in the scale of animal life, the more have the pons and medulla to do with movement; the more do they in that direction supplant the cerebrum. But, in the case of rabbits, we have sure proof that clonic spasms, exactly like those brought on by picrotoxine, may be induced by stimulation of the cerebrum itself. Ferrier's experiments have put this beyond doubt, and have shown that convulsive seizures indistinguishable from those caused at first by picrotoxine may be caused by electric stimulation of the hemispheres; but not only so, but his experiments have afforded us a rational explanation of the march or order of advance of the motor symptoms in picrotoxine-poisoning, by connecting them with certain regions of the hemispheres. The discharge upon which these motor symptoms depend gradually increases in strength, and, as it does so in accordance with a well known law, it spreads more extensively. At first, only a few muscles, those of the head, are affected by spasm; ultimately nearly all the muscles of the body are so affected. The discharge travels laterally and longitudinally, and, in its former mode of propagation, the influence of an arterial region is, I think, plainly discernible. The spasmodic movements which are earliest noticed—twitchings of the ears and shakings of the head, dependent on the muscles of the neck—may be traced by the light of Ferrier's discoveries to a region in the lower part of the frontal lobes of the cerebrum, close to the main trunk of the middle cerebral artery, which there gives off many important branches, and affords a rich blood-supply to the corpus striatum. The spasmodic movements which are next developed in order of time—those of the eyebrows, eyelids, mouth, and fore-paws—may be localised in an area surrounding the region to which the former movements were traced, and corresponding with the distribution of the middle cerebral artery; while the movements which are still later in appearing—those of the hind legs and tail—may be referred to a more remote point close to the median fissure, and corresponding with the outermost ramifications of the same artery. It seems that a particular point may be fixed upon, in the frontal lobe, and close to the middle cerebral artery, in which the discharge originates, and from which the condition causing the discharge spreads forwards, upwards, and backwards over the hemispheres.

But, of course, violent discharges like those caused by picrotoxine have another and longitudinal mode of propagation. They would explode the centres which lie below them, even if these were themselves unsusceptible to the action of the poison; but the probability is, that these centres are themselves stimulated by the poison circulating in the blood, although more tardily than the cerebrum. At any rate, the corpora quadrigemina cerebellum, pons Varolii, and medulla oblongata are speedily drawn into the vortex of morbid perturbation. The occurrence of opisthotonos probably marks the time when the corpora quadrigemina begin to participate in the *émeute*. When nystagmus commences, the cerebellum is implicated; and, when a sudden exacerbation in the convulsive movements takes place, it may be inferred that the pons and medulla are also engaged in the terrific discharges which ensue.

The modifications of consciousness which are associated with the action of picrotoxine are instructive as to its mode of attack. After the early lethargy or drowsiness which has been already alluded to, there

is a stage of liveliness, and it is in this stage that the first or partial fits arise. In these partial fits, affecting a few muscles, and due to discharge of but a small cerebral area, consciousness is not interrupted. The animal may be seen making efforts to oppose or counterbalance the clonic spasms, and the instant they are over it is as lively as ever. But, as the fits become more general and severe, owing to a more serious discharge of a larger cerebral mass, stupor sets in, and this advances into coma or loss of consciousness, which certainly betokens that the highest nerve-centre, the cerebrum itself, has been exhausted or destroyed by the poison. That the spinal cord does not share in that instability of nerve-tissue which is set up by picrotoxine, and is manifested by excessive discharge of energy, is, I think, shown by the fact that, throughout the whole action of the poison, there is no hyperæsthesia, but a decided blunting of sensibility in those parts from which afferent impressions have to be conducted through the cord. Pinching, pricking, or irritating the feet or tail, which in strychnia-poisoning would certainly induce spasms in animals under the influence of picrotoxine, occasion no disturbance. As will be seen hereafter, where picrotoxine is given with chloral, the hyperæsthesia which the latter induces is materially diminished. It is remarkable, however, and very significant of the mode of action of picrotoxine, that, while sensory impressions do not bring on a recurrence of the spasms, voluntary movements which imply a condition of cerebral activity, inevitably do so. When an animal that is under the influence of picrotoxine, and has suffered attacks of clonic spasms, attempts, during an interval of quiescence, to walk about, another attack is immediately inaugurated; and, when an animal actually suffering from slight clonic spasms, without loss of consciousness, makes any spontaneous movements, the spasms are at once exaggerated. There are besides, perhaps, certain areas or epileptogenous zones, the sensory impressions or muscular sensations from which have the power of starting clonic spasms. In a guinea-pig that had gone through three fits, convulsions could not be reinduced by loud noises, by blowing upon the face, nor by pinching of the paws, but were at once brought on by squeezing between the finger and thumb the skin and muscles of the cheek.

If further corroboration of the view, that picrotoxine acts upon the cerebrum, were wanted, it might be found in the fact, that the convulsions which it evokes are so severe and so long-sustained. Such an immense volume of movement implies the evolution of an enormous quantity of molecular force in the nerve-centre in which it originates, which must, therefore, be a nerve-centre of a highly elaborate structure, richly endowed with grey matter or explosive material. But there is no nerve-centre except the cerebrum which adequately conforms to this condition, and it may legitimately be inferred, therefore, that it is the cerebrum that has to do with the production of the voluminous convulsions in question.

The mode in which picrotoxine acts upon the cerebrum can only be a subject of speculation. The alteration in function which it occasions is evidently, in the first instance, in the nature of excess. A state of instability of nerve-tissue is set up, an undue proportion of force is stored up and expended. This is, in all probability, due to some change in the composition of the vesicular matter. One of its ingredients may be replaced by some chemical congener, the result being a more explosive compound; or its nutrition may be abnormally hastened, owing to intense hyperæmia. Whatever the nature of the alteration in the vesicular matter, occasioning its excessive explosiveness, may be, there seems no room to doubt that picrotoxine has a special elective affinity for the vesicular neurine of the cerebrum. But, beyond this, it is not necessary to suppose that the elective affinities of that agent are stronger for the nerve-cells and fibrils of one district of the cerebrum than for those of another. The succession of the symptoms arising out of irritation of the cerebrum may be accounted for without resorting to any such assumption. The picrotoxine, when injected under the skin, is taken up gradually, and will then be carried indiscriminately throughout the body. At first, only a small quantity, in a combined or uncombined state, will reach the cerebrum, and of that small quantity a large proportion will be conveyed by the main artery of the brain, the middle cerebral. The proportion thus conveyed will be seized upon by the most proximate parts, which have strong elective affinities for the picrotoxine, and which draw their blood freely from the expansions of the middle cerebral; and only when, with the progress of absorption, the proportion of picrotoxine in the blood is increased, will other circles of cerebral matter obtain a supply of the poison. Then a certain time must always elapse between the application of any discharge-producing agent to vesicular matter, and the consequent discharge. When the surface of the hemispheres in rabbits is stimulated by electricity, twenty seconds frequently intervene between the withdrawal of the electrodes and the initiation of the resultant fit. And the length of time that elapses between stimulation of nerve-

matter and discharge is always in the inverse ratio of the functional activity of the part stimulated. If the functional activity be high, the time is short; if it be low, the time is long. Now, the most functional active parts of the cerebrum are those in which the most voluntary movements are localised, and therefore, in the rabbit, the most functionally active part must be that in which the movements of the ears and mouth are localised; but that part is in immediate proximity to the middle cerebral artery, and is indeed that which would first receive the poison; so that that part will inevitably begin to discharge itself earlier than any other centre, both because it had priority in the reception of the poison and because it is, by virtue of its superior functional activity, more quickly susceptible to its influence. Next to that part, these centres lying immediately around it, and controlling the second most highly differentiated group of movements, those of the eyelids, shoulders, and fore-paws, would succumb to the action of the poison, which would reach them a little later than the mouth and ear-centres, and would require a little longer time to bring them to high tension and discharge. Beyond these centres, another group more remote and less highly differentiated would be a stage later in being brought into play. Upon all centres the poison would act with a celerity and energy proportioned to the amount of cineritious substance which they contain; for the cineritious substance is far more vascular than the medullary, and is more naked and exposed, being shielded by no isolating sheaths, and is hence first acted on by any agent in the blood which is capable of changing the molecular state of nerve-matter.

The secondary action of picrotoxine upon the cerebrum after the stage of molecular disturbance and excitement is over, places it in a state of disability and paralysis. There are defect of consciousness or more or less coma, and loss of power over the muscles. Function is in abeyance. If the dose of the poison have been very large and uncounteracted, the nerve-tissue may be destroyed; the nerve-vesicles may have been irreparably damaged; the nerve-fibrils made impermeable; or a clot may have pressed upon or broken up the brain-substance. But, when only smaller doses have been received, the nerve-tissue is not permanently injured; it has only been exhausted by the strong discharge, and, after a period of repose, it resumes its functions. The exhaustion, however, or rather its manifestation, may be much enhanced by the encephalic congestion, which invariably results from picrotoxine poisoning.

In the action of picrotoxine upon the pupils in rabbits, there is nothing very distinctive. Until convulsions set in, the pupils retain their average dimensions; then, however, they commonly become somewhat dilated, contracting again during the period of clonic spasm. The state of the fundus of the eye during picrotoxine-poisoning was investigated in 1872, by my former colleague Dr. Aldridge, and was found to consist in hyperæmia.

One very constant effect of picrotoxine is to stimulate the peristaltic action of the alimentary canal. Under its influence, the bowels are almost always evacuated in the freest manner, and sometimes repeatedly, the motion being generally moist and pulpy. This change in the character of the motions, I am inclined to attribute to defective absorption, owing to the increased haste with which its contents are passed down the intestine, rather than to any augmentation in the intestinal secretions. For, although picrotoxine has been described as a gastro-intestinal irritant, I have never been able, when it is administered hypodermically, to find any reddening of the mucous membrane of the stomach or bowels, or to perceive any indications of an irritative action upon those parts. I have never seen it cause vomiting when given hypodermically, and I cannot help thinking that some observers, when watching its effects, have mistaken emprosthotonos for retching. The bladder is generally emptied more than once during the action of picrotoxine, and the flow of urine is sometimes apparently increased in amount. The flow of saliva is always greatly augmented, and the salivary glands are obviously subjected to stimulation, which is not ascribable to the violent action of the muscles in their vicinity, as the increased secretion often precedes the involvement of these muscles in the convulsive action. The modifications of respiration and cardiac action, induced by picrotoxine, can only be stated in general terms, as, during violent convulsions it is impossible to count pulsation or respiratory movements without the use of restraint, which would vitiate the results. It is certain, however, that the movements of the thorax and heart are at first greatly accelerated by picrotoxine, and continue to be very rapid until the spasms set in, when the respiratory movements are often irregular, and the heart's impulses are exceedingly feeble. When coma supervenes, the respirations become slower, and the cardiac contractions weaker and more unfrequent. After death, the lungs are not engorged nor even congested, but the right side of the heart is always distended with blood, and the left side is only partly contracted and contains blood also.

The action of picrotoxine upon the temperature of the body is very uniform and constant. Immediately after its administration, there is a slight rise, attributable to the agitation attending the exhibition of the drug, and subsequently there is a steady fall, amounting sometimes to as much as seven or eight degrees of Fahrenheit's scale, but usually more moderate, and not at all comparable with the fall which is caused by many other agents. In some instances, trifling fluctuations in temperature occur, a slight rise attending each fit, and a heavy fall marking each interparoxysmal period. As a rule, however, the fall is a steady one, and becomes slower in proportion as it recedes from the normal standard. No close relation exists between the dose of picrotoxine and the reduction of temperature, as that is sometimes as great after a small and non-fatal, as after a large and fatal, dose.

The observations made on the actions of picrotoxine may be summed up in the following conclusions.

1. It is an energetic poison, and acts chiefly upon the encephalic centres.
2. It causes first, sudden excessive and paroxysmal discharges of certain gradually widening areas of the cerebrum; secondly, continuous but remittent discharges of the corpora quadrigemina, cerebellum, pons Varolii and medulla oblongata; and, thirdly, exhaustion of all the centres discharged, coma, and death.
3. It diminishes the activity of the reflex centres, and general sensibility, by paralysing the posterior columns of the cord and the peripheral sensory nerve.
4. It first quickens, and finally retards, the movements of respiration, and the cardiac contractions.
5. It produces a decided lowering of the temperature of the body.
6. It increases the secretion of the salivary glands, and the peristaltic movements of the intestines.
7. It causes great venous congestion of the encephalon, and occasionally extravasations of blood upon its surface.

(To be continued.)

ON ARTERIO-CAPILLARY FIBROSIS.*

By RINGROSE ATKINS, M.A., M.D.,

Assistant Medical Superintendent of the District Lunatic Asylum, Cork.

DURING the short time I hope to occupy your attention this evening, I purpose considering the subject of Arterio-Capillary Fibrosis, as it occurred to me that a brief examination of this—if I may use the term for the time being—popular subject, illustrated with such specimens which I, from the limited sources at my command, could bring forward, might not prove uninteresting to those who, from the various engagements of active professional work, may not have leisure to inquire into the subject for themselves, withdrawn as it is from the beaten path of medical literature.

The first notice of this novel doctrine regarding the changes in the vascular system which are found to accompany chronic Bright's disease appeared in a paper by Sir William Gull and Dr. Sutton, read before the Royal Medical and Chirurgical Society, and published in the fifty-fifth volume of the *Transactions* of that Society. In this paper, the authors allege that the renal lesion in chronic Bright's disease, with contracted kidney, is only a part and parcel of a general morbid change throughout the vascular system, characterised by the deposit of a finely fibrous or granular material, to which they have given the name of hyalin fibroid, outside the muscular layer of the small arterioles and capillaries, and in some cases by a thickening of the inner coat also, accompanied generally by hypertrophy of the heart, and in many cases by a "fibrosis" of other organs of the body also. As the renal lesion is, from the effects it produces, be they primary or secondary, the most important element in the affection, I think it may be interesting, in the first place, to briefly examine the morbid histology of that organ when affected with the disease under consideration. In order to facilitate this, we may conveniently consider the morbid changes under three heads, as occurring—1. In the tubes; 2. In the intertubular tissue; 3. In the vessels. The changes occurring in the tubes are of two kinds; namely, those taking place (1) in the epithelium, and (2) in the basement-membrane. The changes in the epithelium are essentially of a degenerative nature; in the earliest stages of the disease, the cells appear to be shrivelling up, becoming granular, and losing their regularity of outline; and, as the morbid process progresses, they become transformed into masses of granules, filling up the tubes, and being cast out in the urine in the form of the well known "granular casts", leaving

the tubes bare and desquamated. These different degrees of degeneration are well seen in this drawing taken from the specimen under No. 1 microscope (Fig. 1), which also exemplifies the other changes taking place

Fig. 1.—Transverse Section of Kidney. (Granular contracted) — in Glycerine — $\times 400$.

A. Renal Tubules filled with "degenerated epithelium". B. Fibroid material surrounding Tubules. C. Renal Tubules (desquamated). D. Renal Tubules filled with granular debris.

in the organ, and which was taken from a typical case of this disease. The basement-membrane is found to be thickened and rendered coarsely fibrous, the desquamated tubes appearing as rings of various shapes and sizes in transverse section. Passing now to the intertubular tissue, we find it to be enormously increased in many parts of the organ, surrounding and separating the tubules, and rendering their outline irregular and distorted, appearing in some parts granular, like ground glass, and in others coarsely fibrous and wavy. This substance also exists in great density around the Malpighian bodies, and attains its maximum about the arterioles, to which we next come. The walls of these, which are of primary importance regarding the present subject, are found much thickened, the lumen often contracted, and their course tortuous and twisted. This specimen shows a transverse section of one of these vessels, its walls thickened and surrounded with the fibroid material above mentioned, which is also seen between the tubules in the drawing of the transverse section of the kidney.

Having thus glanced at the anatomical condition of the kidney, I will next, leaving until the sequel the pathological explanation of these phenomena, proceed to consider the changes occurring in the arterioles throughout the system generally, first detailing the observations of Sir William Gull and Dr. Sutton, and then examining, on experimental and pathological grounds, the correctness and tenability of their views. Sir William Gull and Dr. Sutton, at the commencement of the observations from which they finally evolved their theory of the so-called arterio-capillary fibrosis, considering the pia mater as the most suitable, both from its transparency and facility for microscopical examination, chose that membrane for the subject of their researches. Portions of the membrane taken from the bodies of those who had been the subjects of chronic Bright's disease, with contracted kidney, having first been tinted with carmine and mounted in glycerine and camphor-water, were then examined with powers ranging up to 750 diameters, and the following appearances were observed. In the larger vessels, where the three coats are distinct, the inner one was found in some cases to be thickened to a marked degree, and to have a fine fibrous or molecular appearance. The muscular coat was also found variously altered, the nuclei not absorbing carmine as readily as in healthy vessels. In some of the vessels, this coat was found to be relatively increased, while in others it was decreased, the nuclei being irregular in shape, and often

* Read before the South of Ireland Branch.