Calabar.

An undoubted case occurred in the years 1830-1.

Bonny.

In 1873 several deaths were recorded which might have been due to yellow fever.

In 1883 it is stated that an outbreak of yellow fever occurred, due to importation from Freetown.

In 1890-1 a very serious outbreak is recorded of what was unquestionably yellow fever. The medical officer, Dr. Parker, was certain that it was genuine yellow fever. The description of the symptoms is such as to leave no doubt as to the nature of the disease—the disease was thought by some to be malignant malaria, and was attributed to the pulling down of an old factory; others maintained that it was introduced in the straw and litter on a ship coming from South America. The natives were not affected. There were 11 cases and 9 deaths amongst the population of 15 white men.

Dr. A. J. Brown, who was in Bonny at the time, informs me that he attended two of the cases. The symptoms were headache, pain, great prostration, albuminuria, yellowness, persistent black vomiting.

Dr. Parker, who was the medical officer at the time, stated that he was convinced that the disease was yellow fever. He subsequently contracted the disease and died.

Dr. MacDonald, Bonny, has furnished me with notes of a suspicious case which occurred in 1909, six weeks after arrival in Bonny. The diagnosis at the time was "gastritis and jaundice." No malarial parasites were, however, found in the specimens of blood which were repeatedly examined.

From numerous inquiries which I have made, there can be no doubt that yellow fever occurred in Lagos in a virulent form from 1894 to 1895. Thus, I have it on reliable authority that seventeen members of a mission arrived from England in Lagos on December 13th, 1893. Of these, five had died by the end of January, 1894. In addition, a resident missionary, and the young child of another missionary, had also died. The cases presented the classical symptoms of yellow fever. According to Ott, cases were reported at Lagos in 1896.

At Sapoli in 1898-9, there were a considerable number of suspicious deaths, and in 1907 an outbreak of a severe type of fever was recorded at Widah.

Examination of the medical notes in the hospital at Lagos convinces me that genuine well-marked cases of yellow fever occurred in the years 1902-5. There were also many mild cases.

The symptoms recorded are violent headache and body pains, high temperature, slow pulse, suppression of urine, black vomit, and coma, terminating fatally. In 1905 the symptoms recorded could hardly be those of any other disease but yellow fever, yet the diagnosis made at the time included "fever and gastritis" and "fever and morbus cordis"—a diagnosis which Ott also states was made in Togoland. I am, therefore, strongly of opinion that in Lagos one of the causes of mortality in the past has undoubtedly been yellow fever. When it is recollected how little is known of the fevers amongst the 60,000 native inhabitants of Lagos, and when it is understood that by far the most abundant mosquito is the *Stegomyia*, it is not unreasonable to assume that the natives in all probability suffer from a mild type of yellow fever, and that therefore yellow fever is endemic.

Further evidence in favour of this contention is furnished by the admitted frequent presence of yellow fever in Dahomey and Togoland close by (see the paragraphs on these colonies). It must also be recollected that, just as in the case of Sierra Leone, the infected *Stegomyia* were not destroyed by fumigation, but were left to propagate the disease.

(To be continued.)

In a recent note on Cinematographic Microscopy we mentioned that Messrs. Pathé Frères, of 31 and 33, Charing Cross Road, were always willing to exhibit their films illustrative of micro-organic life to medical men on presentation of their cards. The firm now requests us to state that, owing to the number of medical visitors, it has set aside Friday afternoons for the demonstrations in question.

PUERPERAL ECLAMPSIA:

A COMPARISON WITH VENOM POISONING AND A SUGGESTION FOR TREATMENT FOLLOWING THEREFROM.*

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In a recent number of the *Journal of Obstetrics and Gynaecology of the British Empire*¹ I have gone fully into the pathological lesions found in eclampsia and their interpretation. On this occasion I wish, in the first place, to summarize some of the evidence given in that paper, and especially that part of it which seeks to show that the single, although complex, type of toxin which I take to be the cause of the disease is capable of producing a very definite polymorphism of lesion in such an organ as the liver; I should then like to add some confirmatory evidence which has come my way since that paper was published; and, finally, to give certain new therapeutic suggestions which are rendered at least plausible by the results I will lay before you.

It is very necessary that I should make it absolutely plain that I am referring to an acutely toxæmic attack occurring in the puerperal state without any evidence of pre-existing chronic nephritis. Of those convulsive and other toxæmic conditions occurring in pregnancy associated with a chronic inflammatory lesion in the kidney I can say nothing. I have had no opportunity of examining such cases, and their exact relation to eclampsia on the one hand and to uræmia on the other must at present be difficult to determine. The problems presented by uræmia itself are so vast and complicated, as may well be judged from a perusal of the experimental work on record,² that a combination of eclampsia and renal disease, with interrelation of the two, is likely to present still greater difficulties for elucidation.

You will understand, then, that I limit myself to that acute and usually convulsive toxæmia which tends more particularly to affect previously healthy young primiparae, which commences most commonly quite suddenly, but which may develop in a more gravescent form during some days or weeks (pre-eclamptic stage), which in the event of a favourable issue very rapidly and completely clears up, and which is characterized by purely degenerative, as opposed to inflammatory, lesions in the kidney.

The difference of opinion as to the nature of eclampsia is, as your know, extremely marked—the divergence ranging from the view that the disease is indistinguishable from uræmia to the idea that it is a disease as peculiar to pathology as is the ovum to pregnancy. That the condition is not a simple uræmia the most satisfactory histological evidence goes to prove. I think, too, that a correct interpretation of the lesions will show them to be peculiar neither to eclampsia nor the puerperal state, but to occur in whole or in part in certain other natural and experimental conditions.

As seen in the liver, the lesions of eclampsia consist of three definite and distinct changes. First, and without exception, there is a degenerative change widespread throughout the organ and varying in intensity in different cases. This degeneration is usually rather more marked towards the centre of the lobule, and may in that region proceed to a little irregular necrosis. Secondly, and very commonly, although by no means invariably, there is seen towards the surface of the liver a very peculiar condition of focal necrosis in the periphery of the lobule. This necrosis is strictly limited to the outer zone or to part of it, and does not gradually merge into the degeneration seen in the middle and inner zones. And, thirdly, there is frequently seen, particularly towards the surface of the organ, a certain amount of blood extravasation, especially in association with the necrosed areas.

The points of greatest importance are, first, the invariable degenerative change, and, secondly, the absolute lack of relation which this bears to the focal necrosis. In other words, the clinical severity bears no relation to the amount of necrosis seen *post mortem*.

An explanation of these peculiarities is found in the complex nature of the toxin at work. It contains both

* Read at a pathological meeting of the Liverpool Medical Institution on December 1st, 1910.

haemolytic (that is, cytolytic) and haemagglutinative elements, the universal degeneration being produced by the former and the focal necrosis by the latter, massed red cells obstructing the contributory blood vessels in those areas where the circulation is slowest. A minute examination of the blood vessels confirms this view in every detail, and indicates that the fibrinous thrombosis which is so frequently seen in the larger vessels is a merely secondary phenomenon.

Now the two processes of haemolysis and haemagglutination, while closely associated, are to some extent antagonistic, and a slight increase of haemolytic power by rapidly dissolving the red cells will absolutely prevent agglutination, and thereby necrosis. It will be seen, then, how readily the appearances may vary as the result of some slight variation in the proportion of these two to one another.

The haemorrhages are due to a third element—a cytolytic specialized for endothelial cells, and known as endotheliolysin. Its results are well seen in the liver and brain, and the changes in the vessel walls are best studied in this latter situation. There appears to be some slight relation between haemagglutination and endotheliolysis, for the haemorrhages are usually best marked in the region of the necrotic areas; but, at the same time, this relationship must be but slight, as necrotic areas can often be seen without haemorrhage, and, in the brain at least, very marked changes in the vessels leading to escape of blood occur without any evidence of haemagglutination.

Clinically, it is at once apparent that a fourth toxic principle must be present—a neurotoxin. But when one comes to examine the nervous system for evidence of this, one is drawn up rather sharply by the difficulty of distinguishing between primary lesions and those produced by vascular disturbance. I have recently, through the courtesy of Dr. Moore Alexander, had an opportunity of cutting sections of the brain of an eclamptic. Macroscopical examination showed numerous rather large haemorrhages in the substance. Microscopically, very interesting changes were made out. The cells were markedly degenerated, the Nissl granules were broken up and in places had disappeared altogether; the nuclei frequently stained defectively, and occasionally tended to be eccentric in position. Great irregularity of the epithelium lining the vessels was also seen, the cells being either swollen and granular or more commonly absolutely broken down. I would certainly have classed these nerve cell changes as primary, but Dr. William Warrington tells me that the vascular changes are sufficient to account for them. He also allows me to record an eclamptic brain examined by himself where haemorrhages were present, and the nerve cells showed the same appearances.

To sum up, then, there are four constituents of the eclamptic toxin—a haemolytic, a neurotoxic, a haemagglutinative, and an endotheliolytic. Of these only the first two can be demonstrated to be constantly present, although the third may also be there but masked. Death may ensue without marked extravasation of blood—endotheliolysis—although it cannot be doubted that a serious haemorrhage into a vital part of the brain sometimes determines a fatal result where the haemolytic or agglutinative lesions do not appear inconsistent with the continuance of life.

Coming now to experimental and natural conditions produced by toxins in part or wholly similar to the eclamptic poison, I desire to direct your attention briefly to two groups of these—first, lesions produced by the inoculation of certain immune serums; and secondly, the lesions and effect on the circulation developed in snake poisoning.

By the inoculation of serums containing *in vitro* haemolytic and haemagglutinative factors for the red cells of the recipient,⁸ there have been produced lesions in the liver and kidney which bear so marked a resemblance to those seen in eclampsia that it will be unnecessary to detail them. I will merely state that fibrinous thrombosis may there also be secondarily produced, that in neither liver nor kidney is there any round-celled deposit till a late stage, that the haemolymph elements are increased (there is some evidence that this likewise occurs in eclampsia), and that an endothelial toxin is almost, if not quite, absent.

In venom poisoning all four principles of the eclamptic toxin are found, but in very varying degree. In the cobra the results are mainly haemolytic and neurotoxic: in crotalus, mainly endotheliolytic with relatively little haemolysis and agglutination; in *Daboia russellii*, almost purely haemagglutinative. Death, however, in this last supervenes with extreme rapidity. It will be noted, therefore, that the lesions produced by any one venom are not necessarily any more representative of snake poisoning in general than are the lesions of any one case of eclampsia. This does not at all affect the general comparison; the polymorphism of lesion in eclamptic cases as a whole corresponding to that of poisoning by various snakes.

Nowak,⁶ in a study which is more cytological than histological, describes the lesions of experimental venom poisoning as consisting in the liver of fatty, granular, and vacuolar degeneration, with focal areas of necrosis towards the periphery, and a complete lack of relation of these two processes. In the kidney he notes a degenerative change, limited to the convoluted tubules.

Kilvington,⁶ in a study of the changes in the nerve cells after poisoning with the venom of *Hoplocephalus curtus*, describes a condition of the cells with chromatolysis and breaking up of the Nissl granules very similar to that detailed above. This communication has an added interest in that he found no vascular changes present, but as he remarks that the lesion closely resembles that following the administration of fatal doses of abrin (which is a haemagglutinative poison), it is not quite easy to follow him on this point.

In addition to this pathological similarity, there are numerous clinical links binding the two together. The extreme rapidity and completeness of the recovery which may occur, the preliminary raising of the blood pressure which has been described in experimental cobra poisoning, and which may last till very near the end,⁷ and the tendency to septic infection, are features common to both.

The importance of appreciating this close similarity between the two cannot be overestimated, for it gives an indication of the type of poison to be looked for. Personally, I would have conducted a recent investigation of the placenta on somewhat different lines had I known a year ago what I have submitted to you this evening.

A further importance accrues when one considers the possibility of making some practical and therapeutic use of these data. Flexner and Noguchi⁹ and others have demonstrated the very broad specificity of the venomous constituents. Anticrotalus (rattlesnake) serum prevents the haemolytic action of *all* venoms, there being only a quantitative difference, while antivenin (cobra) neutralizes the haemolysis of crotalus but imperfectly that of certain others. The question naturally arises, Is the specific nature of the haemolysin and neurotoxin limited to snakes alone or does it overlap and include to a greater or less extent such a condition as eclampsia? To settle this point it became advisable to test pregnant and non-pregnant serums with various venoms to determine whether any difference could be made out between the two as regards the resistance to haemolysis or the production of precipitins. Unfortunately I found it rather difficult to obtain a supply of venom, and only recently, through the great kindness of Dr. Calmette, have I received some dried cobra venom. Crotalus venom for precipitin tests I have not yet acquired. While awaiting venom, I carried out some experiments with antivenin, but as this proved to be without precipitating action on normal serum or haemolytic action on normal red cells it was of no service.

In the meantime, however, the most ample confirmation of my suppositions has been given by Bürgers.⁹ In a paper comparing maternal with fetal opsonins, he recalls an observation of Bauer¹⁰ that there is a cobra-haemolysin-inhibiting element in fetal blood from the umbilical cord. Bürgers accordingly tested non-pregnant, pregnant, and fetal serums for this phenomenon, and obtained "the surprising result that the mother's serum as well as the child's restrained haemolysis." I have, therefore, been forestalled in this investigation, but on the whole I do not regret it, since Bürgers's results, which are exactly what a study of the lesions had led me to believe might prove

to be the case, were obtained without the slightest thought of any etiological significance.

Since obtaining cobra venom, I have had only a short time in which to confirm this work, but so far as I have gone I am in agreement with him. I will not give my results in detail at present, as I hope they will, when completed, form part of a future communication on the diagnosis *in vitro* of pregnancy by complement-fixation and haemolytic tests. Much of this work is already finished. I should, however, like to mention that the serum from a case of eclampsia (aged 27, primipara, 6 months, considerable mental clouding, labour pains absent) has quite failed to demonstrate this inhibition. Nor was this result due to any direct action of the eclamptic serum on the red cells in the absence of venom.

There is, then, very considerable evidence that the pregnant woman is protecting herself against a poison directly comparable to a venom, and on this ground I wish to suggest that there may be some therapeutic use for antivenin in eclampsia or the pre-eclamptic state. Judging from its action in snake poisoning, the likelihood of usefulness is very much greater in the latter. I make no apology for bringing forward this idea without having practically tested it. In a disease so relatively rare as eclampsia, the experience in treatment of any one man can count for little, and such a measure as I have suggested must be tried on a large scale to be proved or disproved. I would remind you that antivenin is as harmless as any other antitoxic serum, and may, and indeed should in eclampsia, be given in large quantity by intravenous injection. There is, of course, no reason for omitting any other therapeutic measure which may be considered advisable.

There is still one further suggestion which I would make as a result of this pathological study. The convulsions of eclampsia are in no way an essential of the toxæmia. Patients occasionally die quietly in coma with lesions identical with those found in cases of convulsive seizure. Arrest of the convulsions, therefore, is not necessarily antidotal, but has the merit of saving the patient's strength. It should be accomplished, then, in a way as little harmful to the patient as possible. It follows that anaesthetics, which are powerful cell poisons, are bad. The other two standbys in this regard are veratrum viride and morphine. While both are undoubtedly useful, neither is quite free from the breath of suspicion, and it appears to me that there may be some field for intrathecal injections of magnesium sulphate. These have proved useful in tetanus, and there is no reason why they should not prove of equal service in the treatment of eclampsia.

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SCOPOLAMINE-MORPHINE ANAESTHESIA IN LABOUR.*

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In the last few years great interest has centred around the administration of scopolamine during labour. At the suggestion of the Master of the Rotunda Hospital (Dr. E. Hastings Tweedy), we decided to study the subject, and propose to give an experience in a series of selected cases—namely, one hundred primiparae. We considered that tests of such a comparatively new anaesthetic would be of more statistical value if primiparae only were selected. The average duration of labour is longer than in multiparae, and the occurrence of un-

expected abnormalities, such as *post-partum* haemorrhage and adherent placenta, less common.

It may be asked why we present a record of only 100 cases since we began our study in September, 1908. Our answer is that we only administered scopolamine when the labour ward was quiet and comparatively empty, so that strict attention could be paid to mother and child. We excluded all patients who were quiet and undemonstrative, and all those who came in well advanced in labour.

We began with a dosage of scopolamine hydrobromide $\frac{1}{100}$ grain, and morphine sulphate $\frac{1}{4}$ grain. After trying various amounts we fixed on scopolamine $\frac{1}{120}$ grain and morphine $\frac{1}{4}$ grain as a safe and efficient dose. When repeated the morphine is omitted. Merck's preparation was used throughout. It is supplied in $\frac{1}{60}$ grain tablets. As we always made up a fresh solution for each dose, it was found convenient to use half a tablet each time. This accounts for our dose of $\frac{1}{120}$ grain instead of $\frac{1}{100}$ grain as usually advised. Other makers' preparations are no doubt equally good, but many contradictory symptoms occur from using different preparations of apparently the same drug. Therefore we thought it advisable to confine ourselves to one trustworthy preparation.

When dealing with a new procedure it is natural to follow authoritative teaching, and at the start we based our method of administration on Professor Krönig's paper, read before the British Medical Association meeting in 1908. In some of our early cases we unwittingly departed from accepted doctrines, and it was from these cases that we think we obtained some of our most valuable information.

In recording our cases we have paid attention to the following conditions:

1. The power of the drug to relieve pain.
2. Its influence on the force of the pains.
3. Its effect on the child, and particularly if this were manifested to a greater degree when delivery quickly followed the administration of the scopolamine.
4. The necessity for watching the patient.
5. The occurrence of abnormalities, such as delayed labour, forceps delivery, lacerated perineum, retained placenta, and *post-partum* haemorrhage.

I.—THE POWER OF SCOPOLAMINE TO RELIEVE PAIN.

In previous papers it has been suggested that complete amnesia with unconsciousness of pain is desirable. As a rule, this is only obtained and maintained by repeating the dose every two hours for two or three doses. We are satisfied with a slighter effect, and we consider the purpose of the drug fulfilled if the patient sleeps between the pains, waking up with more or less demonstration during the height of the contraction, and again falling to sleep when the pain is over. One dose sometimes suffices to cause somnolence, and often deep sleep during as well as between pains. We endeavoured to select patients that were particularly noisy and demonstrative, in order to be able to say definitely how much effect the drug had on the sensibility of pain.

The results were as follows: Ten women exhibited complete analgesia, having no knowledge of pain even when the child was born.

In 57 cases there was a marked effect; sleep between and often during the pains, with great decrease in suffering.

In 20 cases the effect was fairly good as regards relieving the pain to a certain extent, but the patients did not sleep at all.

In 13 cases there was no effect whatever. In 4 of these the drug was lost because of rapid vomiting. Eight received too small a dose; in none of them was it repeated. One patient, after two doses by mouth and one hypodermic injection of $\frac{1}{120}$ grain, $\frac{1}{120}$ grain, and $\frac{1}{120}$ grain respectively, showed no result.

Method of Administration.

Of the 10 patients exhibiting complete amnesia, 3 received one dose by mouth, 6 received one dose hypodermically, and 1 received two doses hypodermically. After mouth administration the shortest interval to elapse before delivery was an hour and a half, the longest six hours, and the average three and a third hours. The shortest interval after hypodermic injection was an hour

* Read before the Obstetrical Section of the Royal Academy of Medicine in Ireland, October 28th, 1910.