much greater perfection in diagnosis than we at present possess; and surely careful clinical observation, aided as it is now by actual inspection of the parts in the operations so commonly performed, ought soon, by a careful comparison of the subjective with the objective, to put us in possession of such an amount of valuable material as should enable us to arrive at absolutely certain data in the matter of diagnosis.

Again, I am inclined to think that there is some risk of our losing sight of the fact that there is such a thing as medical treatment, both topical and general, and that not every case of disease of the appendages, so-called, must necessarily come under the radical treatment of the knife, the pen, in many cases, may very well be substituted for the knife: and assuredly we shall never advance the science of therapeutics if practice such as this is to be the rule. I know it is said that these cases only come to the surgeon when the physician has signally failed. No doubt this is so in many cases; but some of us are physicians and surgeons as well, and I would strongly counsel all such to take good heed to the medical aspect of their cases before they resort to surgical interference, and only to adopt the latter when all other means have been honestly and perseveringly tried, and have as signally failed. These remarks apply, of course, only to cases of disease of the appendages themselves, and do not touch those other conditions for which I have declared my opinion that the operation is perfectly justifiable.

Time will not permit my discussing, or even cursorily alluding to, the many other topics, of great value and interest, which are to come before us in this Section. I have referred to these two only because of their supreme importance, and in the belief that I ought to place on record the opinions which I hold regarding them. Many other most interesting subjects will be brought forward,—notably a paper by Dr. Lusk, of New York, on the proper moment for performing gastrotomy in abdominal pregnancy,—which cannot fail to interest both the obstetrician and the gynæcologist; also, one by Dr. Emmet, which is to bring before our notice certain moot points in gynæcology. Then we have, from Dr. Aveling and Dr. Petch, two interesting communications on the employment of electricity in extra-uterine fœtation, the former of whom is, I believe, the first in this conntry who has used this method of treatment successfully. The subject of Emmet's operation for laceration of the cervix uteri is also to be brought forward, with a record of twenty cases, by Dr. Beverley; and I may also refer, lastly, to the paper, by Dr. Fancourt Barnes, on perinæorraphy. These are sufficient to show that the meetings of our Section will certainly not be dull for want of interesting material—indeed, I may well congratulate the members of this Section on the splendid work that will come up for discussion in the papers which are to be brought forward; and gynæcologists may feel justly proud of the wonderful advances which are being made in this department of medical and surgical practice. I question very much whether there is any other department of our profession which has made such strides towards perfection in operative skill, and has achieved such signal success. But, together with this congratulation, I would like to add the expression of my earnest hope that we shall not rest content with our present skill in diagnosis, nor with the uncertainties which yet surround our therapeutics. There are still many dark corners in gynæcology upon which the light of careful, accurate, and painstaking clinical observation is required to clear up doubtful points in diagnosis; and there is a great deal more yet to be done before our therapeutics can lay claim to anything approaching an exact science. It may be an Utopian idea on my part; but I confess I do not see why we should not possess a group of remedies whose action upon the ovary, or the uterus, should be as well known and understood, and as certain in their results, as are the actions of diuretics on the kidneys, purgatives on the bowels, and cholagogues on the liver. To this end at least we ought to work; and if, at each yearly meeting of this Association, only one such remedy be announced, whose reputation is founded on careful and accurate clinical observation, then our successors will have good cause to congratulate us on the work which we have done.

CHLORODYNE DRINKING.—At the inquest on the body of a lady, aged 62, of independent means, residing with two other maiden sisters, it was stated in the course of the medical evidence, that all three of the sisters had been in the habit, for two or three years, of taking chlorodyne in large quantities, so much so, that their bodies had become emaciated, their mental condition affected, and the use of their limbs had become impaired. The body of the deceased did not weigh more than 50lbs., and death was due to continued overdosing of chlorodyne.—The jury returned a verdict of death from continued overdoses of chlorodyne.

THE BRADSHAWE LECTURE
ON
DIABETIC COMA.

Delivered before the Royal College of Physicians of London, August 18th, 1886.

BY JULIUS DRESCHFELD, M.D., F.R.C.P.,
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WHEN I received through you, Sir, the flattering request to deliver the Bradshawe Lecture for this year, I felt that only second to the high honour thus conferred on me was the difficulty of finding a subject worthy of so august and select an audience. My choice fell on a subject, which, though of small compass, is yet full of interest both to the physician and to the pathologist; it is a subject which has engaged my attention for a number of years, and in which even a slight contribution to the elucidation of the obscure pathology is not void of interest. By Diabetic Coma, we understand a peculiar train of symptoms coming on, more or less suddenly, in the course of diabetes, characterised chiefly by coma, and often ending fatally in a very short time. Now, a sudden death is not uncommon in diabetes; yet the term diabetic coma is by no means applicable to all these cases, though coma may form a principal symptom. In many there is a well-known cause, and, after death, a well-defined lesion is found. Thus, in some instances, a diabetic person may suddenly become comatose, and die after a few hours or a few days, and the necropsy reveals a cerebral hæmorrhage; others die from acute croupous pneumonia, which, in diabetes, as in Bright's disease, may come on without the usual symptoms, such as rigor or pain in the chest, may run a rapidly fatal course, without much rise of temperature or expectoration of rusty sputum, and where, unless an examination of the chest reveal the physical condition of the lung, the principal symptoms will be dyspnœa and gradually deepening coma.

Again, albuminuria is not unfrequently observed in diabetes, and, according to Stokvis, occurs even much oftener than is generally supposed, as the large amount of urine passed interferes with the detection of small quantities of albumen. Now, though the presence of albumen may be due to a variety of causes, as I shall presently have occasion to mention, yet, there are observed occasionally cases where interstitial nephritis and diabetes exist together, either independently, or, as Pavy believes, where this form of Bright's disease develops during the course of diabetes. In some of these, the nephritis may have a beneficial effect on the diabetes; in others, however, death may take place, apparently from diabetic coma, but in reality from uræmia. I have seen two cases of diabetes where, after some premonitory symptoms, such as headache and vomiting, coma with marked dyspnœa rapidly developed, and speedily led to a fatal issue. The urine contained in one case but a small amount of sugar, and in both cases only a trace of albumen. The characteristic odour of acetone, however, was not noticed, and the urine gave no reaction with perchloride of iron. The *post mortem* examination showed in both cases markedly contracted kidneys, with typical interstitial nephritis, and the heart in both cases was very much hypertrophied.

Intercurrent affections, by no means fatal in themselves, coming on in the more severe forms of diabetes, may speedily lead to death, with symptoms resembling diabetic coma; and even slight operations, though they are sometimes followed by typical diabetic coma, at other times cause death from shock, from paralysis of the heart or paralysis of the higher nerve-centres. Quite recently I had a patient under my care who suffered from diabetes, and who had also a stricture of the urethra. The breath of the patient had the characteristic odour, and the urine contained acetone, but no aceto-acetic acid. The presence of the stricture, causing a very considerable distension of the bladder, necessitated the introduction of the catheter, and this was soon followed by a rise in temperature, from the normal to 103°, and by death from collapse, within ten hours of the introduction of the instrument. The *post mortem* examination revealed stricture of the urethra, a dilated and hypertrophied bladder, and some amount of hydronephrosis; the remaining substance of the kidney showed no changes, and the heart was found free from fatty degeneration. There can be little doubt that we had here a case of the so-called "catheter fever."

If we except cases such as these, there remains yet a large number where, without any apparent cause, suddenly symptoms appear, of which a gradual deepening coma, with more or less dyspnœa, forms the most prominent feature, and which leads to death often in a few hours, or a few days. These constitute the true cases of diabetic coma; but here, again, it is essential, in order to get at the true pathology, to distinguish several forms, according to the etiology, symptoms, and pathological appearances; and it is chiefly owing to the want of clearly distinguishing the several forms, that so much discrepancy exists among the nnmerous observers who have written on this subject. In a paper which I read before the Manchester Medical Society, on October 5th, 1881, and an abstract of which appeared in the BRITISH MEDICAL JOURNAL of October 29th, 1881, I classified the cases of diabetic coma, according to the symptoms, into three groups; one form, chiefly characterised by drowsiness, soon passing into coma; a second form, resembling alcohol intoxication, a marked symptom being a staggering gait, incoherent and thick speech, an excited state of the nervous system, followed by drowsiness and coma; and a third group, including by far the largest number of cases, where dyspnœa was usually a most marked symptom, followed by coma, and where both the breath of the patient and the urine showed a characteristic odour of acetone, and the urine contained a peculiar body, giving a deep claret-colour, with perchloride of iron. I distinctly pointed out then, that these forms differed not only in their symptoms, but most probably also in their pathology. It was, therefore, a source of great satisfaction to me to find that Frerichs, in a paper published in the *Zeitschrift für Klinische Medicin*, some time after the appearance of the short abstract of my paper, and again in his great work on *Diabetes*, published in 1884, adopted an almost identical classification as regards the symptomatology, and was able, by virtue of larger material, to distinguish more clearly the pathological difference of the first group from the other two.

If we now consider the first of the three groups, which I would now call "diabetic collapse," and for the first exact description of which we are indebted to Prout, we find, as regards the symptomatology, the following:

The patient, without any premonitory symptoms, begins to suffer from drowsiness, hebitude, excessive weakness in the limbs; the extremities become cold; hands, feet, and face become livid; the pulse quick, small, threadlike, soon reaching 120 and 130; the respirations are only slightly quickened, shallow, without there being much dyspnœa; the temperature gradually falls, the skin in some cases becomes covered with perspiration, and death ensues from collapse in most cases within ten to twenty hours. During the first few hours, the patient is still able to pass urine voluntarily. With the progress of the coma the urine is retained in the bladder; but, when withdrawn, is found to contain a considerable amount of sugar (5 to 8 per cent.), but no acetone or aceto-acetic acid. In two cases which I had an opportunity of seeing, it contained a small amount of albumen. The nervous system presents few other symptoms besides the coma; the pupils re-act, though somewhat sluggish; there may be some slight headache, but active delirium and convulsions are mostly absent.

The *post mortem* examination shows no marked naked-eye changes. In about half the number of cases which I have collected from various authors, there was not found much emaciation; in some cases the body appeared stout, with a good deal of adipose tissue. The heart, in a case described by Frerichs, showed marked fatty degeneration. In the one of the two cases which I have seen, a similar change was noticed; in the other case the heart was enveloped in a great deal of fat, but its muscular structure showed but a very limited granular degeneration. The liver in this case was found affected with fatty infiltration, and it showed numerous greyish patches, which, when microscopically examined, consisted of fatty detritus.

In trying to analyse how many of the recorded cases of diabetic coma belong to this group, we meet with many difficulties, as may be imagined from the short and insufficient data. Besides the cases described by Prout and Frerichs, I find cases belonging to this group described by Donkin, Bourneville, Pavy, Taylor, and others. An analysis of such cases allows us to draw the following conclusions as regards the etiological factors.

1. Diabetic collapse occurs chiefly, though not exclusively, in older people, after the age of 40.

2. It attacks persons who have suffered from diabetic symptoms for some time, and who are, as a rule, still stout and well-nourished at the time of attack.

In short, the cases belong more to that form of diabetes recently described by Hoffman as constitutional diabetes, or diabetes of stout people, where the course of the disease is slow and protracted, and where gout or nephritis form frequent associations, and where the appearances of carbuncles and other necrotic changes are not uncommon.

The exciting cause in the majority of cases is, as was again first pointed out by Prout, some extra physical exertion, as a long walk, or a brisk walk, or some sudden shock. In a smaller number of cases, an error of diet, or, as in one of my cases, immoderate drinking immediately before the onset of attack, act as the exciting factors.

What is the cause of diabetic collapse? Frerichs believes the collapse to be due to the failure of the heart's action from fatty degeneration. Donkin and Pavy had already expressed a somewhat similar view, but have extended that explanation to apply for all, or nearly all cases, of diabetic coma. Though we have but few reliable anatomical data, yet the view of Frerichs seems to me to be supported by many facts. Thus Schmitz has shown that, amongst 109 diabetic patients, 80 showed considerable weakness of the heart; and, in several *post mortem* examinations on diabetic patients, the heart has been found to weigh only four to five ounces. Again, if death be due to sudden exhaustion brought about by a more than ordinary demand being made on the constitution weakened and altered by the diabetes, we should expect a somewhat similar mode of death in other constitutional diseases where the heart's muscle is altered, and the blood has undergone changes, but where there is no diabetes; and that this is actually the case, is easy of demonstration. I need only allude to the sudden death coming on in persons with fatty livers, where, with few premonitory symptoms, such as abdominal pain and vomiting, collapse, soon ending fatally, comes on, and where the *post mortem* examination shows, besides the fatty liver, fatty degeneration of the heart. These cases were first described by Addison, and, since then, by Saundby, myself, Sabourin, and others. Or, again, take pernicious anæmia; we find here, not unfrequently, the patient becoming more or less suddenly drowsy and comatose, and the necropsy reveals fatty degeneration of the heart and of other viscera, sometimes well marked, at other times but slightly marked.

The second form—the alcoholic form of diabetic coma—is of rarer occurrence, and is most likely pathologically identical with the third form. In its symptoms it resembles acute alcoholic intoxication, and, in one case, recorded by Kulz, the urine was found to contain large quantities of alcohol. The case was that of a middle-aged man, who had been in hospital for diabetes. He took a walk in the hospital garden, and was suddenly taken with symptoms which made even the doctor believe the patient was under the influence of drink, though it was clearly proved that the patient could have had no access to any alcoholic liquor. The patient became excited, sang and swore, the speech became thick, and he staggered like a drunken man; the pulse was accelerated, the conjunctivæ injected. This state was soon followed by deep coma and death. The urine drawn from the bladder showed, besides sugar, a considerable amount of alcohol.

For the following brief account of a similar case, I am indebted to my friend, Dr. Cullingworth. A young servant-girl called on him on May 25th, 1881, complaining of great thirst and weakness; and, on examination, the urine was found to have a specific gravity of 1035, and to contain a considerable quantity of sugar; nothing abnormal was noticed about her breath. Dr. Cullingworth prescribed some opium and nux vomica, and advised her to go to her home in Wales. The next we hear of her is an account, in one of the Manchester newspapers, of her death, which took place under very distressing circumstances. It seems that, on her way to her home, she left the train in which she was travelling, at some small station, and she seemed so excited that she was believed to be intoxicated. She called at an hotel, but was refused admission, owing to her apparently drunken condition; at last she was taken up by a policeman, who took her to a small inn, where she was seen by Mr. Reed, a local medical man, late at night, who found her in a semi-conscious state; her face very pale; her pupils dilated, acting slowly to light; her pulse rapid; her breathing quick. She was seen again by Mr. Reed next morning, when she was quite unconscious, the breathing rapid and noisy, and the extremities cold. She had passed some urine during the night, which contained sugar. The coma deepened, and she died at eight o'clock the same evening.

Frerichs describes a few cases, somewhat similar in their symptoms to alcoholic intoxication. In these cases, the expired air smelled strongly of acetone, and the urine gave the characteristic reaction with perchloride of iron; but no mention is made as to the presence of alcohol in urine. The question as to the presence of alcohol in these cases is, therefore, one which, in future observations, will have to be more fully inquired into before they can be looked upon as a pathologically distinct type.

The third form—which I would now call, for want of a better name, coma from acetonæmia, by far the most common form, of which I have observed no fewer than sixteen fatal cases, and where, in ten cases, I was able to study the *post mortem* changes—is the one which will occupy our chief attention.

Since the first exact description was given by Kussmaul, it has been the subject of such a vast number of inquiries, that I will not attempt to trace out the history of its literature. To its symptomatology, which is well known, I need also but briefly allude.

The first symptoms consist of lassitude, or some slight dyspnœa or severe gastric pain with vomiting; often there is also some slight headache, restlessness, and excitement. From this initial stage, the patient passes into a state of drowsiness, associated with marked dyspnœa, and this is soon followed by coma and death. If we analyse the symptoms more in detail, and for this purpose I have made use of more than eighty recorded cases, we find the following conditions.

1. As regards the nervous system, there is a period of excitement. During this period, we notice headache, vertigo, a state of excitement not unlike that seen in alcoholic intoxication, incoherence of language, delirium bordering on mania. Convulsions are rarely noticed, and, in the sixteen cases of my own, they occurred only once, and I find them noticed in six other cases, though jactation of the limbs is more common. These symptoms are, sooner or later, succeeded by signs of depression: hebetude, thick speech, drowsiness, and coma. The condition of the pupils is not constant; they react, though somewhat sluggish, almost to the last; they have been found sometimes dilated, at other times contracted. The special sense-organs show us noteworthy symptoms. The fundus of the eye in four cases, which I have examined for that purpose, was found healthy. Star describes in one case a peculiar tint of the retina, the vessels having a peculiar black-coloured appearance, due to fatty embolism (!) Pain in other parts of the body is often noticed, especially abdominal pain, which is often one of the first symptoms observed, and which may be so severe as to simulate peritonitis. The vaso-motor nerves are profoundly affected; the face is often flushed at first, and afterwards becomes pale; the extremities become cyanotic; the skin, at first dry, is often, later on, found covered with clammy perspiration.

2. As regards the vascular system, we notice a soft pulse of low tension, becoming quick, small, threadlike, and irregular. The heart's action is feeble. The veins in the neck are not distended.

3. As regards the respiratory apparatus, we notice marked dyspnœa; this may be one of the first symptoms, and gradually increases up to the last; it is inspiratory at first, and afterwards both inspiratory and expiratory. The dyspnœa is present in most, but by no means in all cases, and has the character described by Kussmaul: the thorax expands well in all directions; on auscultation, air is heard to enter all parts of the lungs fully, and yet there is the great breathlessness—the air-hunger of Kussmaul. The respirations vary in number; often they are not much increased in number; in some cases they may be even diminished. The patient often complains of pain in the chest, and physical examination occasionally shows the presence of limited broncho-pneumonia. The expired air has a peculiar chloroform-like smell, and that this is due to acetone can be easily demonstrated. By allowing a patient to breathe in water only for a short time, I obtained distinct acetone reaction; no aceto-acetic acid, however, could be detected. In all the sixteen cases which I observed, the odour was most marked and present from the very onset.

4. As regards the digestive system, there are noticed the dry red tongue, loss of appetite, nausea, vomiting of copious masses, with intense epigastric pain, which often constitutes one of the first symptoms. The condition of the bowels varies; at times there is at first constipation, followed by the evacuation of very copious motions; or, from the first, there may be profuse diarrhœa.

5. As regards the urinary organs, the urine is found diminished in quantity; in cases where the amount of sugar has been determined before the onset of the coma, this too has decreased, and sometimes (in one of my cases) entirely disappeared. The reaction of the urine is often very acid, but not invariably so. Ammonia is often found in-increased. The urine has the same odour as the breath, and contains acetone. It gives, with perchloride of iron, the claret-red colour which has now been conclusively proved to be due to aceto-acetic acid. In the more recently reported cases, by Minkowsky and Külz, the urine contained also oxy-butyric acid, and the β-crotonic acid of Stadelmann. In the last of my cases of diabetic coma, Dr. Liebmann, late assistant to Professor Keküle, who kindly assisted me in all the other chemical observations, carefully analysed the urine, which was withdrawn by catheter from the patient a few hours before death, and found aceto-acetic acid, but no oxy-butyric acid. In one case, the urine had a distinctly milky appearance, and microscopic examination showed the presence of large quantities of fat. The urine, in all my cases, also showed the presence of albumen—sometimes only a trace, at other times a fairly perceptible quantity. The almost constant occurrence of albumen has been noticed also by Stokvis; in a good many of the other recorded cases, however, it was not detected. In several of my cases, hyaline and small granular casts were seen on microscopic examination.

6. The temperature is usually found to rise during the first stage; with the onset of the coma, it falls, and may, just before death, descend to 95°, 94°, and, as in a case reported by Sir W. Foster, may be as low as 90°.

7. The blood, examined microscopically, shows us noteworthy changes. Where there is much anæmia, we have the usual appearances of the blood, such as a large number of microcytes and poikilocytes, whilst the leucocytes are found diminished in number. Chemical examination of the blood withdrawn during life, in four cases, showed the presence of fat in very varying proportions. In one case, already reported by Dr. Gamgee, the ethereal extract contained 12.76 per mille; in another, 2.32 per mille; in a third, 6.2 per mille; and in a fourth, 2.15 per mille. The blood, in the two cases where a large quantity of fat was found, separated, on standing, into two distinct layers, of which the upper one had a creamy appearance, and consisted of fat-granules, which, after a time, coalesced into large fat-drops.

Now, as regards the course which diabetic coma runs, it may be said to be fatal in about 90 per cent. Of the fatal cases, some run their course, without any premonitory symptoms, in a remarkably short space of time—from twelve to twenty-four hours. In about 60 per cent. of the cases, however, the disease lasts two or three days, and is ushered in by lassitude, abdominal pain, or dyspnœa. In other cases, the fatal coma is preceded for weeks or months by a condition which may be called chronic acetonæmia, where the exhaled air has the peculiar odour, and the urine contains aceto-acetic acid. When once the graver symptoms of coma appear, death, as a rule, follows. Sometimes, however, the symptoms improve for a time, and then reappear with fatal results, or gradual and steady improvement follows. This, unfortunately, happens in the smallest number of cases.

As regards the etiology, some points, I think, are clearly established.

1. Diabetic coma affects chiefly the younger persons. According to Pavy, who based his statistics on nearly 4,000 cases, 55.65 per cent. of the cases of diabetes occurred between the ages of 40 and 60; whilst, from an analysis of eighty cases of diabetic coma, I find that 70 per cent. occurred between the ages of 20 and 40, and only 24 per cent. between 40 and 60. It may occur, also, in very young persons and even children under the age of 5.

2. It may come very early in the course of diabetes; in a case communicated to me by Professor Charcot, the urine was examined two months before diabetic coma appeared, and found free from sugar; and in some of the cases which ended most rapidly fatal, the patient showed no subjective symptoms of diabetes previously to the attack of coma. In the younger persons, diabetic coma mostly appears from six to twelve months after the first symptoms of diabetes; in the older persons, coma is noticed at a later period. From these facts, we may conclude that coma occurs almost exclusively in the severer forms of diabetes.

3. As regards hereditary disposition, I have noticed some interesting facts. Quincke records a fatal case of diabetic coma in a girl, aged 16, whose brother, aged 19, and uncle, aged 29, had also died in a similar way. Frerichs observed diabetic coma in a girl, aged 12; her brother, aged 15, who also suffered from diabetes, was much affected by the death of his sister, and died from diabetic coma two days after her. In another case given by Frerichs, two sisters, one aged 18, the other 21, died from coma; the first symptoms in the elder sister appearing as she stood at the bed of her dying sister. Professor Charcot kindly communicated to me a case of death from diabetic coma in a gentleman, aged 42, whose sister died also from diabetic coma, at the age of 50, and whose father had also died from diabetes; whilst one uncle, who had phthisis, from which he recovered, died suddenly. In a case of rapidly fatal diabetic coma, which I saw with Mr. Bradley, a younger brother, who was known to have had diabetes, had died under similar circumstances. I give these facts without any comments; they seem, however, to show as if a predisposition was inherited.

As regards the exciting causes, several have been well established; of these, the principal are:

1. Excessive physical exercise. This seems to be the exciting cause in about 50 per cent. of the cases.

2. Mental shock. This contributes 10 per cent.

3. The sudden change of diet from a mixed to an exclusively nitro-

genous diet. This I have noticed in one of my earlier cases, where a rigid diet was instituted in a patient that had not been treated at all before, and where, on the second day of treatment, fatal coma set in. I know of several others; and Ebstein, Joenecke, and Von Mering relate fatal cases from exclusive meat diet. An exclusively nitrogenous diet is often, but not always, well borne, and borne with good effects, as was established by Cantani; but the change from the mixed to the nitrogenous diet should be gradual, and never abrupt.

4. Surgical operations in diabetic patients are occasionally followed by coma. It would seem as if the causal agent here was the nervous shock; it would be interesting, however, to see how far the administration of the anæsthetic is to be blamed. Thus, in about thirty operations for cataract in diabetic patients, where no anæsthetic was given, Dr. Glascott informs me he has never met with diabetic coma following the operation.

5. Lastly, intercurrent febrile affections, as croupous pneumonia and catarrhal pneumonia, an acute gastric catarrh, or a pharyngeal abscess occurring in diabetic patients, may soon be followed by the symptoms of coma.

Before discussing the pathology, we ought to glance briefly at the anatomical lesions found after death. I will not tire you with a long recital of changes which are inconstant, and have no bearing on the pathology of diabetic coma, and will only briefly allude to the more important ones, taking as a basis my own ten cases, and those recently described by English and continental observers.

The nervous system presents, as a rule, no noteworthy alterations. The changes described by Dickinson were seen in one of my cases, and have also been described by Frerichs and Ebstein. Whatever their bearing may be to the pathology of diabetes generally, they have no special relation to the causation of diabetic coma. Fat-embolism I could only see in one case where, both in the lungs and in the glomeruli of the kidney, numerous small capillary emboli were found. In all my other cases I missed this change, though I searched for it very carefully; and even in the one case, where, during life, the blood was found to contain a large amount of fat, our examination for fat emboli gave only negative results. Much more frequently did I find the necrotic changes in the epithelium of the convoluted tubes of the kidney, a pathological condition first described by Cantani and Ebstein, and more recently again by Mackenzie and Taylor, and with which I had been familiar for a long time. In six out of ten cases this degeneration was more or less marked, a proportion which is much higher than that given by Frerichs.

The glycogen reaction described by Ehrlich, and observed recently by Abeles, in the cortex of the brain in some cases of diabetic coma was looked for by me in three cases, but only in one did I detect it. It is found in cases of diabetes without coma, and even Frerichs does not vindicate for it any very close relation to diabetic coma. Of other changes, I will only note that the heart is usually found small, but rarely otherwise altered; that the pancreas is often found small and atrophied, as in four cases given by Windle; and that, in one case, Saundby found atrophy and interstitial cell-infiltration of the semilunar ganglia.

Lastly, the liver in several of my cases presented some changes. The capillaries were found very much distended, and the liver-cells atrophied; and, in one case, small greyish patches were seen, which consisted of an accumulation of fat-granules; fatty infiltration of the liver-cells was observed in several of my cases.

We are now in a position to discuss the pathology of diabetic coma; and considering the varieties of lesions found after death, and their inconstancy, it is not astonishing that so many different views exist as to the nature of the process which underlies diabetic coma. We need not stop to discuss the views which make the symptoms primarily dependent on an alteration of the nervous system, or on a thickening of the blood by an excess of sugar. The picture which a person suffering from diabetic coma presents is so clearly one of an acute intoxication of one kind or another, that our attention must be chiefly directed to those abnormal bodies which are found circulating in the blood, or which appear in the secretions. These bodies are, on the one hand, fat; on the other, acetone, aceto-acetic ether, aceto-acetic acid, and β-oxy-butyric acid.

The presence of an increased quantity of fat in the blood, and the blocking up of the small vessels in the different organs, have led Sanders and Hamilton to the well-known and ingenious view that all the symptoms observed in diabetic coma might be due to fat-embolism. The vital objections to this theory are now equally well known.

1. In the majority of cases of diabetic coma, fat-embolism is not found.

2. Fat-embolism, both in the kidney and in the lungs, is often found after death in the most varied diseases and injuries, and often without any apparent symptoms, as was shown by the observations of Moulin (*Lancet*, July 30th, 1881), and others.

3. Experiments on animals (Scribe Wiener) have shown that unless very large quantities of fat are injected, no bad results follow, as the fat is gradually eliminated by the kidneys: and some such process seems to occur also in man, for the presence of fat in the urine in diabetic patients has been noticed by Habershon, Hadden, Morrison, and others, and was also seen in one of our fatal cases of coma.

While it is thus not unlikely that, in some few cases where the amount of fat in the blood is large and the emboli extensive, the symptoms, all or in part, might be due to fat-embolism, for the large majority of cases this explanation will not hold good.

We have next to consider acetone and aceto-acetic acid and oxy-butyric acid. The breath of many patients suffering from diabetes has long been known to have a peculiar chloroform-like odour; and that this is due to acetone can easily be proved by allowing such patients to breathe into water. After a short time the water will have the same odour, and on distillation, a body passes over which gives all the reactions of acetone. Again, in the urine of such patients there is almost always found a body which gives with perchloride of iron a deep-red colour. This body, first detected by Gerhardt, and believed for a time to be aceto-acetic ether, has now been proved by Tollens and Deichmann to be aceto-acetic acid. As aceto-acetic acid is a very unstable body, and easily splits up into acetone and carbonic acid, the presence of the former in the expired air is easily understood.

It must, however, be borne in mind that in many cases of diabetes, acetone may appear in the urine without aceto-acetic acid. As many other bodies, and sometimes even normal urine, give a red colour with perchloride of iron, and as this fact seems to have escaped the attention of many of the most recent observers, I may be permitted to state briefly the characteristic tests for aceto-acetic acid: 1. The urine is treated with concentrated solution of perchloride of iron, and filtered from the phosphates, which are precipitated. The claret-red colour disappears on heating. 2. The urine, after the addition of a small quantity of dilute sulphuric acid, is shaken up with ether, and in the ether extract, which takes up the aceto-acetic acid, perchloride of iron produces again the characteristic colour which gradually fades on standing. 3. The urine, on distillation, gives characteristic reaction for acetone, as aceto-acetic acid is easily decomposed. The acetone was tested by Lieben's and Legal's test.

Lieben's test consists in the addition of a solution of iodine in iodide of potassium to the distilled urine, when a yellow precipitate of iodoform crystals appears; this test is the most delicate test, but may apply to other bodies besides acetone.

Legal's test consists in the addition to the distilled portion of a small quantity of caustic soda solution, then a few drops of a solution of sodium nitro-prusside, and then a few drops of acetic acid, when a beautiful red colour appears if acetone be present.

Now, both acetone and aceto-acetic acid are found in the majority of cases of diabetic coma. We have not missed them in any of the cases which we examined since this test was first made known, and they are present from the very onset of the symptoms.

It behoves us, therefore, to see how far these bodies have a toxic effect. The toxic effects of acetone have been investigated by Kussmaul, Buhl, Frerichs, Penzoldt, Albertoni, De Gennes, and Jaksch, and with such varying results that I thought it not unnecessary again to take up this subject. In a first series of experiments, the effect of acetone on healthy subjects was studied. My friend, Dr. Lindermann, Mr. Adami, one of my clinical clerks, and myself, took large doses, ten to twenty grammes, of acetone without any ill effects beyond a little drowsiness and headache. In one of us, a slight diminution of temperature, pulse, and respiration, was noticed, but these did not increase on administration of large doses of acetone. The exhaled air, soon after administration, contained a considerable amount of acetone; the urine, however, only contained a trace, and even this disappeared after a few hours. A good deal of the acetone must, therefore, have passed out of the lungs, and another part must have been quickly burnt off, and a very small quantity only could have entered the circulation. Dr. Lindemann tried subcutaneous injections of acetone on himself, and it was found that fifty minims could be injected without any effect being produced. The urine, however, contained acetone for twelve hours after the last injection.

In a second series of experiments, large quantities (100 grammes) of grape-sugar were taken, and then some acetone; the breath again smelled strongly of acetone, but the urine contained a trace of acetone but no sugar. Bearing in mind that acetone had been recommended for phthisis many years ago by Dr. Hastings, and recently again by Neu-

mann, we felt no hesitation in giving it to patients suffering from various diseases; and here we noticed again its ready elimination, but with certain exceptions. Given to diabetic patients, it produced no ill effect, except some drowsiness, and, in one case, most marked diaphoresis; but the urine continued to contain acetone for some days after the administration of this drug had been stopped; and, in one case, the urine contained aceto-acetic acid. The same result was seen in cases where the function of the liver was impaired, as in cases of gall-stones and of cirrhosis of the liver. It would, therefore, appear that, normally, if acetone be taken by the mouth, it is readily passed from the digestive tract into the liver, and is in part burnt up there, while another part passes into the lungs, and is eliminated; whilst, if the functions of the liver be impaired, it remains in the body a longer time, and is much more slowly eliminated. With the experimental investigation of this question, I am at present occupied; and, having only but recently obtained the necessary license, I am unfortunately, as yet, not in a position to lay the results before you.

In a third series, I traced the effects of subcutaneous injections, seeing that large doses given by the mouth had no effect. It was given to rabbits; and it was found that, if small doses, from five to ten minims, were given in sufficiently long intervals to allow it to be eliminated, not more than some slight drowsiness was noticed; the animal became quiet, and appeared drowsy and heavy, but this effect soon passed off. If, however, the small doses were administered at shorter intervals, it was found that, after five or six doses of ten minims, the animal became at first drowsy and then comatose; the respirations became slower and deeper, and spasmodic jerkings of the legs and head came on. The urine was found to contain a small trace of albumen. The animal was then killed, and the kidneys examined. No necrotic changes were seen; but, when treated after Posner's method, the albumen deposit was seen within the capsules of the glomeruli. Penzoldt and Jaksch, by modifying the experiment somewhat, so as to prevent the elimination of acetone by the lungs, obtained similar results with much smaller doses.

Aceto-acetic ether, given to healthy persons and to diabetic patients, produced no results. The urine contained acetone, but no aceto-acetic acid. Subcutaneous injections with this body in cats and dogs were tried by Quincke, who found that even small doses were followed by death from coma, with marked dyspnœa.

Aceto-acetic acid I tried in a similar way; and, like Frerichs, I found that even large doses can be borne with immunity by healthy persons, if given by the mouth. The urine only contained acetone, but no aceto-acetic acid. Smaller doses, injected into rabbits, gave rise to no symptoms. Large doses, according to Jaksch, produce albumen, which persists for a few days.

Experiments with oxy-butyric acid (which, on oxidation, gives rise to aceto-acetic acid, and which has been found, in a few cases of diabetic coma, in the urine) were tried by Albertoni, who found that it had no particular toxic effect, and did not give rise to the appearance of aceto-acetic acid in the urine. Rabbits, after the administration of six grammes, died under symptoms of depression.

Before considering the bearing of these experimental results on the pathology of diabetic coma, we will briefly notice the appearance of these bodies in other diseases than diabetes. Acetone may occur in small quantities in normal urine; in large quantities it has been found by Jaksch and others in many febrile diseases, and in some chronic disorders, especially if associated with fever. Quite recently, the same author describes a case where, in a healthy young man, after an error in diet, there followed violent vomiting, loss of consciousness, and epileptic attacks, and where the urine contained a large amount of acetone. All these symptoms rapidly subsided with the disappearance of the acetone, and this case is looked upon by Jaksch as an auto-infection by acetone.

Of much more frequent occurrence, and more closely connected with the subject under discussion, is the so-called diaceturia, where the breath has the acetone odour, and the urine gives the perchloride of iron reaction, which, in the recent cases I have observed, has been found to be due to aceto-acetic acid. This condition has been noticed by Seifert, Penzoldt, Litten, Le Nobel, Jaksch, and, in this country, by Windle. I have observed it in a healthy person, after he has taken large quantities of alcohol, in two cases of gastric ulcer, in one case of hysterical vomiting, in one case of cancer of the stomach, in a case of syphilitic cirrhosis of the liver, and in one case of exophthalmic goître; and it undoubtedly occurs frequently in the acute febrile diseases. In some of these cases, there were no distinct symptoms referable to these bodies; in others, there was marked vomiting, headache, and great general depression, and these symptoms subsided with the disappearance of the aceto-acetic acid from the urine. The case of cirrhosis of the liver died from symptoms having the closest resemblance to diabetic coma. The patient complained of a sudden epigastric pain, became very restless, there appeared marked dyspnœa, and death from coma ensued thirty-six hours after the onset. The breath had at first a marked acetone odour; the urine gave aceto-acetic reaction, but contained no trace of sugar, nor had sugar been noticed at any previous time, though the patient had been under observation for some years. (Litten observed a similar fatal termination in a child suffering from scarlet fever. Here, then, we have death from diabetic coma without diabetes.)

One peculiar feature I noticed in this case, which is worthy of mention. We found that some time before death the acetone odour disappeared, and the urine now gave no reaction with perchloride of iron, and, when tested for acetone, instead of giving a red colour with the nitro-prusside test, gave a beautiful blue colour. Now, a few days ago, a patient who had been under the care of Dr. Morgan, and who was suffering from severe diabetes, and whose urine contained aceto-acetic acid, died from diabetic coma; with the onset of the attack, the urine contained still a good deal of sugar (about 5 per cent.), and gave the characteristic reaction for aceto-acetic acid. As the coma developed, he passed some urine perfectly free from sugar; the acetone odour had disappeared, and, with it, also the perchloride of iron reaction; but, instead of this, exactly the same blue colour was obtained in testing for acetone. I have never seen this reaction before, nor has it been noticed by any other observer, so far as I know, and I cannot say to what it may be due.

To sum up, then, the experimental results, we see that none of these bodies mentioned can be said to be toxic, in the ordinary sense of the word, and that all of them can be taken by a healthy person in large quantities, without any ill effects; that acetone, if present in the blood of animals in large quantities, or if not quickly eliminated, will produce symptoms not at all unlike those of diabetic coma; and lastly, that both acetone and aceto-acetic, if injected in large quantities, will produce albuminuria.

And, as regards the clinical results, we see that, in many acute and chronic diseases, acetone and acetic acid may occur; and, whilst often only producing slight and temporary symptoms, may occasionally give rise to all the graver symptoms of the coma seen in diabetes.

If we now consider how profoundly the blood and tissues are altered in diabetes, and how often the functions of the liver and kidneys are found impeded, we can, I think, readily understand that the elimination of acetone, and the other bodies which give rise to it, is interfered with, and their toxic symptoms produced. I have already drawn attention to the presence of albumen in these cases, which I believe with Stokvis, is rarely missed. Now, whether this be due to the necrotic changes in the epithelium, or to the irritation set up by the acetone and aceto-acetic acid, there can be little doubt that, even without showing material changes, the kidneys have their function impaired.

But I believe the impairment of the normal function of the liver plays even a more important part than that of the kidneys. The observations I have given above seems to indicate this, the changes in the liver observed by Cantani. Mya and myself support it, and we further notice that it is chiefly in cases of the liver-cancer that symptoms like those of diabetic coma are seen. Whilst believing that acetone has a large share in the production of the symptoms, I hold that it is only one of a series of bodies of which aceto-acetic acid is another, β-oxy-butyric acid a third, and of which there are probably more, which, if not quickly eliminated, act powerfully on the nervous system, and thus produce diabetic coma. Whether some of these acids act by withdrawing the alkalies from the blood; in fact, whether they produce an acid intoxication, as Stadelmann and Minkowsky believe, a statement which is supported by the experimental research of Walter on the action of acids on certain animals, remains yet to be seen. Certainly, in the very last case of diabetic coma, the case of Dr. Morgan's quoted above, the urine increased nearly double in acidity during the progress of the coma; thus, at the onset, 100 cubic centimètres required 13.4 cubic centimètres of one-tenth normal soda solution, and, towards the end, the same quantity of urine required 26 cubic centimètres of normal soda solution for neutralisation. I may say, however, that in this case, no oxy-butyric acid was found by Dr. Liebmann.

I can only compare this third form of diabetic coma to uræmia, though the toxic agents here are totally different, and the symptoms not less so. We have an acute form of uræmia as we have an acute acetonæmia, if I may be allowed (for want of a better expression) to use this term, and we have also a chronic form corresponding to acetonæmia; again, we may have an accumulation of urea, uric acid, and the extractive matters of urine with no fatal result, and occasionally with

but few symptoms, if these bodies can again soon be eliminated; and, lastly, the injection of urea into the blood of animals, owing to its rapid elimination, produces even less toxic effects than the administration of acetone, though the retention of urea plays undoubtedly an important part in the causation of uræmia. How and where these bodies are formed is as yet a matter of speculation. It is not easy to see how they can be formed from oxydation, or further, fermentation of sugar. It seems more likely, especially according to the observations of Jaksch and Rosenfeld, that acetone at least is formed from the albuminous bodies; and if so, we can somewhat understand why the sudden change from a mixed to a pure nitrogenous diet should bring on the symptoms of coma.

There remain yet, however, a number of cases where the symptoms of diabetic coma with marked dyspnœa appear, and where yet no acetone is contained in the exhaled air, and no aceto-acetic acid is found in the urine. These cases I would relegate to our first group—the diabetic collapse—from which they seem to differ only in one additional symptom—dyspnœa. I cannot help feeling that rather too much stress has been laid on this "Kussmaul's symptom," which simply indicates, I think, that the respiratory centre is profoundly implicated. We miss the dyspnœa in otherwise typical cases of diabetic coma; and that it may be present in collapse or coma, independent of diabetes, is seen in the cases of pernicious anæmia related by Riess. Whether some of these cases may not be due to an intoxication by an alkaloid, a ptomaine, produced by fermentative changes in the body, is a point about which at present we have but too little positive evidence; but about which, considering the activity displayed in that line of research by Brieger, Bouchard, and others, we shall, no doubt, hear more before long.

And now a few words as to treatment. However much physicians may differ as to the pathology of diabetic coma, I think it is admitted generally that the appearance of the acetone breath and the presence of perchloride of iron reaction always indicate that we have a severe case of diabetes to deal with, and that in these cases a slight cause may bring on a fatal coma. Such patients should be forbidden active exercise; they should avoid mental worry and excitement. As obstinate constipation has occasionally been assigned as an exciting cause, the condition of the bowels should be attended to, but only gentle laxatives be given. If the symptoms come on soon after a course of an exclusive nitrogenous diet, a mixed diet should be at once recommended. We may in this way succeed in averting the symptoms of coma, for when once these are present, our therapeutics are powerless. Intravenous injection of phosphate of soda and chloride of sodium, recommended by Fagge, only delayed the fatal event for a few hours; not more success was obtained by transfusion. Stadelmann believing, as we saw, that the symptoms of diabetic coma depended on the presence of increased acid in the blood, gave in one case large doses of bicarbonate of soda; there was some slight temporary improvement, but the fatal result followed a few hours later. The different antiseptics have been tried, but with no better result; in fact, several cases of diabetes died from coma during a course of treatment with carbolic acid. The inhalation of oxygen, and the administration of stimulants, such as ether and camphor, gave no better result; the latter are, however, indicated in diabetic collapse. Very gloomy indeed is thus the progress of diabetic coma, and only too true the saying of Prout, who compares a person with diabetis to one who is walking on the brink of a precipice.

THERAPEUTIC MEMORANDA.

TREATMENT OF TWO FORMS OF DIARRHŒA IN CHILDREN

Drs. Braithwaite and W. W. Millard have recently contributed interesting notes on the subject of one form of infantile diarrhœa.

My own ideas regarding that and another form have been inspired by the valuable observations to be found in Dr. Ringer's book (seventh edition, 1879, pp. 246-248), to which I may be pardoned for referring my brother practitioners, who have not hitherto followed his line of treatment in these diseases.

There is no greater certainty in therapeutics than that "infantile cholera"—profuse watery diarrhœa—will be cured if treated within the first few hours by one-sixth of a grain of grey-powder given hourly even by itself. But I give usually one-sixth of a grain of hydrargyrum cum cretâ, with two grains of lactopeptine; and in some cases I administer as another *adjuvans* a vegetable astringent, such as krameria. Again, when the stools are slimy with, it may be, blood-streaks, I give liquor hydrargyri perchloridi, 2½ drachms in 2 ounces of water, of which a teaspoonful given every hour meets the case.

The diet should be cold, consisting of arrowroot made with water, and very slightly sweetened; barley or rice water to drink. One case which was baffling the grey-powder was explained by the presence of a piece of undigested beef on a napkin. Maternal ideas of feeding have sometimes to be sharply enlightened.

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REVIEWS AND NOTICES.

Climate and Health in Australasia. Edited by James Bonwick, F.R.G.S. New Zealand, New South Wales, Victoria, Tasmania. Four Pamphlets. 12mo. London: Street & Co. 1886.

We have to thank Mr. Bonwick for bringing together a quantity of information about the climate and health of our Australasian colonies, which will be useful to physicians as well as to emigrants. The varieties of climate in those regions are very numerous. One may say generally, that New South Wales and Victoria are hot and dry; Western Australia has a humid climate, while Northern Queensland has a tropical one. Tasmania has a medium excellent climate, while New Zealand has a breezy colder one, in many ways resembling that of England. But besides such generalisations, we have to consider locality. There are coast and inland climates, and differences of altitude from the sea level up to the colonial high Alps, with their snow. Some of the most favourite climates are those of the highlands of the north, or New England in New South Wales, of Rivenna in Victoria, and of Tasmania. We are told that consumptive patients in Tasmania or New Zealand, seek the dry plains of the Rivenna, or the sea-side Brisbane, in Southern Queensland. In short, there is a great variety of climates in those regions, as might have been expected, and we are beginning to distinguish them. The balance of evidence would seem to show, that phthisis is benefited by well-chosen Australian climates. In such cases, where patients are sent from England, the effect of the sea-voyage has to be taken into account. We have only space to add that Mr. Bonwick's book confirms the singular fact of the very great prevalence of rheumatism in all those colonies, though Victoria is said to suffer less from it than the others. The fact of the great heat not being so injurious in Australia as in other hot countries, and of its rarely producing sunstroke, continues to be accepted. We could mention many other interesting topics. Meantime, we are glad that Mr. Bonwick has presented, in a concrete form, much matter which, we hope, will be subjected to examination and correction in the future.

NOTES ON BOOKS.

South Africa as a Health Resort. By Arthur Fuller, M.B.C.M. Edin., M.R.C.S.L., 12mo., pp. 70. (London: W. B. Whittingham and Co. 1886).—Those who think of sending phthisical patients to Southern Africa, may gather many useful practical hints from this little volume. It shows the facilities, not only of reaching the Cape, but of arriving at various excellent health-stations in the interior, by the aid of railways. Long journeys, of many days' duration, in bullock-carriages, need not now be necessarily undertaken.

Remarks on the Climate of Dublin. By John William Moore, M.D. 8vo., pp. 19. (Dublin. 1886).—Dr. Moore thus sums up the results of twenty years of laborious observations by himself, and by his father: "The climate of Dublin is, in the fullest sense, an *insular* one, free from extremes of heat and cold, except on very rare occasions, and characterised by a moderate rain-fall (about 28 inches) annually, which, however, is distributed over a large number of days (about 195 in each year). Clouded skies, a high degree of humidity, and a prevalence of brisk winds, chiefly from westerly points of the compass, make up the climatology of the Irish capital."

Bright's Illustrated Guide to Bournemouth. 12mo., pp. 182. (Bournemouth: F. J. Bright. 1886.)—This guide, consisting of 182 closely printed pages, compiled by Mr. C. H. Octavius Curtis, contains ample information on all general subjects for visitors to Bournemouth—we would say almost too ample, for fifty-eight pages is an unconscionable amount of space to devote to a description of the modern churches in that place. Dr. Davison has contributed a judicious chapter on the climate of Bournemouth.