DELAYED CHLOROFORM POISONING

being

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AN INTRODUCTION TO THE STUDY OF

DELAYED CHLOROFORM POISONING.

INTRODUCTION.

The subject of Delayed Chloroform Poişoning has attracted considerable attention in this country since Dr Leonard Guthrie[1] in 1894, published a series of nine cases in which death occurred from ten hours to six days after operations performed under chloroform anaesthesia. Since the condition was recognised, a considerable number of cases have been reported, and the importance of the subject cannot be over-exaggerated. For instance, three cases[2] are reported as occurring within fifteen months, in the practice of the Manchester Hospital for Sick Children; Guthrie[1 & 3] alone has reported thirteen fatal cases. One anaesthetist[4] has reported three cases which occurred in his practice, but were not fatal, the symptoms of the cases being strongly in favour of their being due to delayed chloroform poisoning.

After careful investigation of the urines of cases after chloroform anaesthesia, one writer[5], who has given a great deal of attention to the subject, found that every patient showed signs of the disturbance of metabolism produced by chloroform, definite acetonuria being present in each case. Another observer[6] reports that acetonuria occurs

in sixty-six per cent. of chloroform cases, and from my own observations I found acetonuria present in fifty per cent. of the cases where a qualitative examination was made, and in every case where a quantitative estimation was performed.

That sufficient attention has not been drawn to delayed chloroform poisoning in former years is due to the fact that the condition was not recognised. In the various Medical and Surgical Journals of the past seven years, numerous cases have been annually reported. Previous to Guthrie's[1] first paper in 1894, there had been only eleven fatal cases reported as due to the toxic after effects of the chloroform. We must therefore conclude that probably many deaths occurring after chloroform anaesthesia, and due to this cause, were formerly attributed to other causes.

It is now fully recognised that the effect produced by a general anaesthetic is a disturbance of metabolism, resulting in an auto-intoxication, having very definite symptoms. Delayed chloroform poisoning is best studied in a children's hospital, amongst whom, as I will show, the great majority of the cases occur. General anaesthesia is, however, not the only cause of those definite symptoms of auto-intoxication, which we observe to be associated

with acetonuria.

(i.) It has long been known that acetone and diacetic acid appear in the urine of diabetics under certain circumstances; and that these are a better guide to the patient's condition than is the amount of sugar present. If a diabetic has 'bilious attacks' accompanied by restlessness, followed by drowsiness, acetone and diacetic acid will usually be found in the urine, though previously absent. These symptoms are also prominent in the auto-intoxication of delayed chloroform poisoning.

(ii.) Acetone, diacetic acid and B-oxybutyric acid have been found in the urine, breath and vomit of children, usually between the ages of 3 and 11 years, who are suffering from recurrent or cyclic vomiting. The average duration is from 5 to 6 days, and the condition may be fatal.

(iii.) It is now recognised that some of the serious forms of pernicious vomiting of pregnancy are due to a toxaemia. In these cases the post-mortem examination reveals a state of things in the liver and kidneys which closely resembles the morbid changes observed in these organs in delayed chloroform poisoning. The symptoms also resemble those of the latter condition.

(iv.) Anyone can produce acetonuria in himself by starvation; and therefore the fact that acetonuria occurs in such conditions as carcinoma of the digestive organs and certain febrile conditions may be accounted for. Of all tissues, fat loses most in starvation, the noble organs being fed at the expense of the less essential ones. To effect this the fat must be broken down, in the course of which we get the fatty acids set free.

Oxygen starvation can also produce acetonuria, as seen in mountain sickness, and oxygen starvation is obviously at work in the acetonuria of bronchopneumonia.

(v.) Again, in alkali and ash free dietaries we can produce acetone, with diacetic and B-oxybutyric acids in the urine of otherwise healthy persons.

(vi.) In certain poisons we get an exaggeration of protein catabolism with acetone and diacetic acid in the urine, e.g. Phosphorus, Arsenic and Phloridzin poisoning; and also in some cases where Soda Salicylate is being administered. The post-mortem changes in phosphorus poisoning closely resemble those found in delayed chloroform poisoning.

(vii.) In fatigue, we get excessive catabolism of fats and acetonuria.

(viii.) We also get acetonuria in the convulsive stage of eclampsia, and after the advent of a fit in an epileptic. In the same category may be placed strychnine and antipyrine amongst poisons.

(ix.) An interesting observation is the fact that the stoppage of morphia in a morpho maniac causes an acetonuria, and on morphia being resumed the acetonuria ceases.

(x.) Various gastro-intestinal derangements, especially in children, may produce a well marked acetonuria.

(xi.) It has been shown that in acute infective conditions acetonuria is readily formed. This fact is highly important; as so many cases of this nature are submitted to chloroform anaesthesia, and eventually prove fatal. It is extremely difficult, in fact almost impossible, to say how much the one or the other factor has contributed to the fatal result.

The study and investigation of the conditions enumerated above has led to a better understanding

of the subject, but still there remains a great deal to be done. The mechanism by which these exaggerations of protein metabolism are carried out in the various conditions requires further exploration.

In discussing the subject of delayed chloroform poisoning, no paper would be complete which did not deal with its historical aspect.

I will deal first of all with this aspect of the subject, from the year 1850, when Caspar(7) reported the first fatal case of delayed chloroform poisoning, up to the present time. The different papers and cases will be mentioned in chronological order, as nearly as possible, with the dates of each. It will help us greatly in the better understanding of the subject, if the action of chloroform upon the various tissues and organs of the body is included in this sketch.

I will next deal in detail with practically all the reported cases of delayed chloroform poisoning. I will give an exhaustive analysis of the symptomatology of the condition, and describe the symptoms in two cases which occurred in patients under my care and which have so far not been published. I will follow this up by a minute description of the findings in the urine of patients suffering from delayed chloroform poisoning, and give the results

of my examination of thirty urines after chloroform anaesthesia, both by qualitative and quantitative estimation.

I will deal next with the pathology of the condition; both the naked eye appearances and microscopic changes will be described in detail. Many causes, other than the toxic after effects of the chloroform, have been ascribed as producing the characteristic symptoms of delayed chloroform poisoning. I will criticise each cause separately, and show that chloroform anaesthesia of itself is responsible for many of the disastrous results, preceded by a characteristic set of symptoms, which may follow even the simplest operation.

I will next go carefully into the chemistry of the acetone bodies.

The following chapter will be taken up with a consideration of other conditions in which acetonuria occurs. I will here refer to other general anaesthetics, and show that these also may be followed by toxic after effects, and even death.

The treatment of delayed chloroform poisoning will next be dealt with in detail, along with a suggestion of my own.

Finally, a summary of the whole subject, embodying all the important points of the thesis, will

be followed by the bibliography.

A HISTORICAL SKETCH

of

DELAYED CHLOROFORM POISONING,

1850 - 1911.

HISTORICAL SKETCH.

Stiles and McDonald[8], in their extremely valuable addition to the subject of delayed chloroform poisoning, published in 1904, gave a very full historical sketch of the subject prior to the appearance of their paper.

I will include several papers which will help us the better to understand the signs, symptoms and post-mortem appearances which contribute to the condition we are about to study.

Caspar[7], in 1850, was the first to direct attention to the dangerous after effects of chloroform. He maintained that signs of poisoning may be seen hours, days, or even weeks, after its inhalation. Caspar speaks of the condition as chronic chloroform poisoning. He records a case of a woman who died nine days after amputation of the leg, with symptoms referable mainly to the brain. Langenbeck[9] in the same year published a case of a patient who had had his scapula excised and died seventeen hours after the operation. He attributed his patient's death to the after effects of chloroform. The patient's condition on the evening of the operation was quite satisfactory, but during the night vomiting set in and persisted all night. The following

morning he was pale, pulse small and frequent, and the vomiting continued. The respirations were free and regular; the pulse became progressively more rapid and feeble, and the patient died at 8.30 p.m. on the night after operation. At the post-mortem the liver was found to be fatty. Petters[10] in 1857, noted that the quantity of urine excreted by the patient did not diminish as the end approached and contained a normal amount of solids. Petters was the first observer to note acetone in the urine after chloroform anaesthesia.

No further evidence in support of the views of Caspar and Langenbeck were brought forward until 1866, when Nothnagel[11] published the results of his experiments on rabbits. Nothnagel introduced the chloroform by subcutaneous injection in some of his rabbits and into the stomach of others. On examining the organs some days later he found fatty degeneration of the liver and heart in both instances. When the chloroform had been introduced subcutaneously, the kidneys also shewed fatty degeneration; and urine expressed from the bladder four hours after injection contained red blood corpuscles and fibrinous casts. In these experiments the chloroform was probably carried direct to the kidneys by the blood stream, and set up an acute in-

flammatory reaction. Nothnagel had not the benefit of the modern microscope, otherwise he would have found, in the cases where chloroform had been inhaled, fatty changes in the kidneys as well. Stuart McDonald[12] remarks that a kidney which to the naked eye does not look fatty, under the microscope may contain a considerable degree of fat. In one of his experiments Nothnagel excised a small piece of the liver for the purpose of comparison before injecting the chloroform. Nothnagel concluded that the fatty degeneration was not due to pre-existing disease, but that chloroform produced fatty degeneration of liver, heart and kidneys, by destroying the red blood corpuscles. Nothnagel also demonstrated that ether could produce similar changes, but to a much less extent.

In 1883, Ungar & Junkers[13] were the first to demonstrate in animals the fatty change produced by chloroform when administered by inhalation. In the first set of experiments rabbits were used, but it was found that they could not be kept under the influence of chloroform continuously without a fatal result. In a second series of experiments dogs were used, and it was found that in these animals anaesthesia can be kept up for a much longer period, with less danger of causing sudden death. In their

experiments upon rabbits they failed, even on microscopic examination, to detect any fatty change whatever. Stiles & McDonald[8] state that in their opinion the animals were killed too soon after the administration of the anaesthetic. Ungar & Junkers in their experiments upon dogs, were able to demonstrate extensive fatty change in the liver, heart and voluntary muscles in an animal killed forty-eight hours after a single prolonged administration. After repeated administrations they demonstrated fat in liver, heart, spleen and mucous membrane of the respiratory and alimentary passages. By excising one kidney at the beginning of an administration of chloroform, they were able to show that it contained much less fat than did the other kidney which was excised after a prolonged administration. Stiles & McDonald[8] confirmed this observation in 1904. Ungar & Junkers argued that a previous administration of chloroform rendered the organism less likely to successfully withstand subsequent administrations. Schenk[14], in 1898, repeated this warning, as did Guthrie and others later. Ungar & Junkers suggested that in anaemic, alcoholic, or cachectic patients an ordinary dose of chloroform might prove fatal. This has not been borne out by subsequent experience. Discussing the modus operandi of chloroform in pro-

ducing fatty changes, they believed it to be a direct tissue poison setting free into the tissues, chlorine, which acts in the same way as iodine in iodoform poisoning. Kast[15], in 1888, agrees with Ungar & Junkers that chloroform sets free chlorine in the blood and is excreted in the urine. Strassman[16], in 1889, experimenting on the same lines as Ungar & Junkers, concluded that the fatty change was a degeneration and not an infiltration, caused by the destruction of proteids. It is important to note that in two of Strassman's experiments, in which the animals had been anaesthetised for three and five days respectively, the organs were found to be free of fat sixteen and fourteen days later. In the same year Ostertag[17] made exhaustive experiments on rabbits, guinea pigs, rats, pigeons, cats and dogs. He also confirmed the views of Ungar & Junkers. Ostertag regarded the fatty change as an infiltration. Thus we have a difference of opinion upon the nature of the fatty change, which is of interest in view of what I have to say on that point later. Ostertag believed in the theory of idiosyncrasy. He is also of the opinion that the fatty change in the liver is derived from the fatty metamorphosis in heart and kidneys. Theim and Fischer[18], in 1890, reported a fatal case of delayed chloroform poisoning, and

found post-mortem, fatty degeneration of liver, but the kidneys were normal. In the following year, 1891, Bastianelli[19] described three fatal cases of delayed chloroform poisoning, and describes the symptoms, which are now known to be common to all such cases. In his cases death occurred from three to ten days after the administration of chloroform. The liver was found to be fatty, and, to a less extent, the heart. Kast & Mester[20] examined a large number of urines after anaesthesia and found a condition of hyperacidity, the cause of which they were not able to determine. Fraenkel[21], in 1892, was the first to give a detailed description of the naked eye appearances which may result in the human subject from the inhalation of chloroform. He carefully investigated five cases in which death took place from forty hours to twenty days after the administration. Fraenkel regards the fatty change as a degeneration, and demonstrated a similar change in the heart, liver and kidneys, voluntary muscles and ascending aorta. Fraenkel concluded that these changes were specific in chloroform poisoning as apart from sepsis. He holds that chloroform destroys the red blood corpuscles, and he also believes in idiosyncrasy.

The first contribution on delayed chloroform poisoning, in this country, was published in 1894

by Dr Leonard Guthrie[1] in a paper entitled 'Some fatal after effects of Chloroform in Children'. He reported nine cases in which death was attributed to the after effects of chloroform, and one case in which recovery took place. Guthrie supposed that death was due to (i.) an auto-intoxication, (ii.) a fatty condition of the liver, which he then maintained, and still does, must be pre-existent to the administration of the anaesthetic, and (iii.) that chloroform plus shock aggravated the condition already present and loaded the organism with toxic alkaloids which, in some of his cases, the kidneys were unable to eliminate. Guthrie warned surgeons against giving chloroform in cases with a pre-existing fatty liver; and held that the only way to diagnose this condition was the presence of alkaloid substances in the urine. The nature and the best methods of detecting these alkaloidal substances Guthrie left for further investigation. These conclusions were not accepted in this country, but no further reference was made to the subject until Guthrie[3] published in 1903 further observations in support of his thesis. The title of this paper, viz.: 'On the fatal effects of Chloroform on Children suffering from a peculiar condition of Fatty Liver', differs from that of the first paper in

order to emphasise his contention that the liver is already fatty before the administration of the chloroform, and that the latter only acts as the 'last straw'. Guthrie also maintains that the post-mortem appearance of the liver is absolutely characteristic, being of a 'pale fawn' colour. Ambrosium[22], in 1895, reports a fatal case after chloroform, in a woman suffering from a pyosalpinx. He describes fatty degeneration in the tubules of the kidney and in the heart. In his opinion the cardiac nerves are affected, and also the ganglion cells of the central nervous system. It is interesting to note that this case is not the only one in which a fatality has occurred after the administration of chloroform in a patient suffering from a pyosalpinx. In fact, it has been stated that all the reported fatal cases of delayed chloroform poisoning followed abdominal operations: this, of course, is quite erroneous.

From what I have to say later, it will be seen that these septic cases are more prone to signs of toxic poisoning than are cases in which there is no septic element. Becker[6], in the same year, examined the urines in a large number of cases after anaesthesia, and found an increase in the amount of acetone after chloroform administration. The amount

of acetone was not found to be proportional to the amount of the anaesthetic used. Becker (Deutsch Med. Woch,1894,p.359) also published three cases of diabetics who died - two after the administration of chloroform, and one after ether, for the purpose of operation. In each case coma set in soon after the completion of the operation, and persisted till death. Luzatti[23] confirms Becker's observations, but says the amount of acetone excreted is proportionate to the amount of chloroform used. Nachod[24] also examined a large number of urines and found albumen and casts to be present after chloroform anaesthesia. He describes a parenchymatous condition of the kidney. According to Nachod, pre-existing albuminuria is not increased after chloroform. He never found glucose in the urine after chloroform, but may have found other reducing substances. Nachod relates four cases illustrating the danger of chloroform in diabetics. Referring to the excretion of acetone, he found acetonuria present in thirty out of fifty-seven cases, and in fourteen cases aceto-acetic acid occurred along with the acetone. Urobilin was frequently demonstrated in the urine, but no bile pigments were seen. Hill Abram[25] in 1896, demonstrated the presence of acetonuria in sixty-four per cent. of his cases after anaesthesia.

He agrees with Becker that the amount of acetonuria bears no relation to the amount of chloroform used.

It is well to point out here that these observations on acetone were made by qualitative tests only, as quantitative tests would have demonstrated acetonuria in every case, as will be seen later.

Babaci and Bebi[26], in the same year, investigated the urine after anaesthesia and found albumen present in 18.89 per cent. of the chloroform cases, and 36.6 per cent. of cases who had been etherized. They found that when albumen did occur, it was associated with parenchymatous changes in the kidney of a chronic type. Steinthal[27] describes a typical case of death after chloroform anaesthesia. The patient developed jaundice on the second day after operation, death being preceded by coma. Steinthal describes fatty degeneration of the liver, heart and kidneys. From the morbid changes, one would expect jaundice to be a frequent symptom of delayed chloroform poisoning, but on looking over the reported cases it is by no means invariably noted. Ajello[28] examined a large number of urines after chloroform and found albumen present in 80 per cent. of his cases. He states that the after effects of chloroform may be severe in organic disease. Ajello concludes that the degenerative

changes in the various organs are not definitely characteristic of chloroform poisoning, and are in proportion to the amount of chloroform used. Chiarleoni[29] has seen bile pigments in the urine which he considers to be directly due to the chloroform. In my own cases, I never saw bile pigments in the urine after anaesthesia. Grube[30] has noted the injurious effects of repeated administration of chloroform on the kidneys. He considers the symptoms of poisoning after chloroform are due to deficient oxygenation, and also to the destruction of red blood corpuscles. He regards death as due to an auto-intoxication. Zachrissen[31] reports five cases of delayed chloroform poisoning. He found albuminuria in from 24.5 per cent. to 38 per cent. of cases after chloroform anaesthesia. He attributes this to degeneration of renal epithelium. He also finds the amount of albumen to be proportionate to the amount of chloroform administered. Eisendrath[32] also examined the urine of a large number of cases after anaesthesia. He found casts and albumen in the urine after chloroform and to a less extent after ether anaesthesia. He describes a fatal case of pulmonary embolism after operation. Bandler[33] deals especially with the action of chloroform on the liver. He reports a death after

operation on a strong man where chloroform anaesthesia had lasted one hour. The symptoms resembled those of acute yellow atrophy of the liver. He describes the symptoms and gives a detailed account of the examination of the urine. The patient became jaundiced on the second day, as in Steinthal's case, and the urine contained bile pigments, much albumen, with granular and hyaline casts. A detailed description of the post-mortem and microscopical appearances follow. Bandler also gives the results of his experiments on animals: he found that ether causes less fatty change than does chloroform.

Marthen[34], in 1896, reports a fatal case in a woman, aet. 34, in which death occurred on the fourth day from heart failure. The symptoms are described and the results of the post-mortem and microscopic examination noted. Marthen emphasises the occurrence of jaundice, and remarks that the condition of the urine in no way indicates the extent of the parenchymatous change in the kidneys.

Heintz[35], in the same year, reports the results of his experiments on rabbits. He describes fully the post-mortem changes and supports the theory that idiosyncrasy plays a prominent part in poisoning by chloroform. He believes with Ungar that the degenerative changes are due to the direct

toxic action of chloroform, and that the fatty change is a degeneration and not an infiltration.

Schenk[14], in 1898, published the results of his investigation on apes and dogs to determine how soon the fat disappears from the organs after chloroform anaesthesia. His experiments show that the fat in the liver disappears, in some cases in a few days, in others, weeks after the administration. In all his cases fat was demonstrated in the liver fourteen days after chloroform: he was thus unable to confirm Strassman's observations previously mentioned.

Salen & Wallace[36], in 1899, reported two cases very similar to that reported by Bandler. The post-mortem changes are described.

Dormer[37], in the same year, describes a case of a child, aet. 2½ years, who died forty-two hours after operation. The symptoms and the results of the post-mortem are described. The patient had an enlarged thymus and hyperplasia of the lymphatic glands. This fact will be gone into more carefully later.

Poroschin[38], in 1902, describes his experiments on dogs. He found changes in the cardiac ganglia and respiratory centre, as well as the usual fatty change. Poroschin also found hyaline de-

generation of the small arteries of the heart, stomach and malpighian bodies of the spleen.

Cohn [39] in the same year describes the case of a robust woman of 21, who died five days after an operation for double salpingo-oophoritis. The symptoms, along with the post-mortem findings and the microscopical appearances, are described. The author remarks that death must have been due to the chloroform, which set up an acute intoxication.

Ballin[40] reports what he believes to be a recovery from acute yellow atrophy after an appendicectomy. In this paper Wersung[41] is mentioned as having collected sixteen recoveries from the disease. Mintz[42] regards post-operative cases of acute yellow atrophy as essentially septic. I shall point out later how difficult it is to differentiate between an acute septicaemia and the condition we are studying. No case of acute yellow atrophy after ether anaesthesia has been reported.

Rydgier[43], in a paper dealing with kryoscopic observations on the urine after chloroform anaesthesia, states that chloroform does not set up any renal insufficiency if the kidneys are healthy. Chloroform has a serious effect on diseased kidneys. Cohn[39] regards nephritis as a contra-indication to the use of chloroform.

Foerster[44] also in 1902 reports two cases which he considered were essentially due to the after action of chloroform. Both cases were those of children, aged 4 and 11 years respectively. The elder girl suffered from a localised appendix abscess. Foerster remarks upon the persistent coffee ground vomiting in each case. The results of the post-mortem examination are given and Foerster concludes that the changes found afford sufficient proof that death was due to the after action of chloroform.

Brewer[45] published a case of fatal acetonaemia following an operation for appendicitis. The patient was a boy of 12, and suffered from acute perforative appendicitis. Chloroform anaesthesia lasted twenty-five minutes. The symptoms and progress of the case is given, along with a differential diagnosis from meningitis, ptomaine poisoning and uraemia. Brewer describes a bright red colour of the mucous membranes and skin. This condition is also made mention of by another observer, (Flint) but it seems to be a rare addition to the clinical picture in delayed chloroform poisoning, and the following explanation by Brewer, so far, is the only one offered. Brewer concludes that the cause of death is due to rapid carbon dioxide poisoning of

the tissues, caused by B-oxybutyric acid, diacetic acid and acetone lowering the alkalinity of the blood, upon which depends its ability to absorb the carbon dioxide from the tissues. Dr Blue[46], at the Roosevelt Hospital, at the instance of Brewer, examined the urine in a number of cases after anaesthesia and found a pathological amount of acetone present in seven cases out of thrity-three different urines examined. Only one patient showed symptoms, and these were of so-called shock.

In 1903, as already mentioned, Guthrie[3] published his second paper. In the same year Montgomery[47] reported a fatal case of delayed chloroform poisoning. The patient was a boy of three years, who suffered from Inguinal hernia. Death, which was preceded by excessive vomiting and restlessness, occurred forty-eight hours after the administration of the anaesthetic. At the post-mortem examination, the brain and its membranes were found congested, the liver of a 'pale buff' colour, and the other organs are noted as being healthy.

In the following year, 1904, perhaps the most valuable paper on the whole subject of delayed chloroform poisoning was published by Stiles & McDonald[8]. They gave a full historical sketch of the subject. Two typical cases are fully described: both patients

were children. A minute description of the post-mortem findings, both naked eye and microscopical, is given. Owing to the fact that deaths occurring after chloroform administration are variously attributed to chemical poisoning by antiseptics, to fat embolism and to sepsis, the authors carefully investigated their cases from these different standpoints. A case which proved fatal from carbolic acid poisoning is described in detail, and compared with the cases they ascribed to delayed chloroform poisoning. The fat embolism theory is likewise dealt with, Stiles & McDonald being unable to find such a quantity of fat free in any of the vessels as might even remotely be the cause of death. Sepsis, as a probable cause of the symptoms and fatal result, is also dealt with. The organs of a child of 6 years of age, who died nine days after an operation for recurrent perityphlitis, are discussed microscopically. The authors agree that it is exceedingly difficult in some cases to tell how much sepsis had to do with the fatal result, and how much is due to the after effects of the chloroform. Vomiting as a symptom is dealt with in detail, as is also the nature of the operation.

The various points arising in the paper by Stiles & McDonald will be dealt with at greater

length later.

In the same paper are given the results of six experiments carried out on rabbits, chloroform being administered by subcutaneous injection in some and by inhalation in others.

In the same year Bracket, Stone & Lowe[48] published their paper entitled: "Acetonuria associated with Death after Anaesthesia". They describe the cases of six patients who died after operation; in all their cases ether was the anaesthetic used. They give a full description of the symptoms and course of the disease. It so happened that four of their patients suffered from Infantile Paralysis, and that fact, to them, is of special significance and they warn surgeons on operating on such cases. The authors also report cases following the same clinical course, but where no anaesthetic had been administered. The post-mortem appearances are described; and the etiology is discussed at length. Treatment is also discussed.

Wilbur[49] exhibited to forty animals, by intravenous infusion, certain acids, including B-oxybutyric acid and neutralised B-oxybutyric acid made in normal saline, at body temperature and at the uniform rate of 4 c.cs. per minute. The acids produced the characteristic symptoms of acid poisoning.

Wilbur concluded from his experiments that neutralised B-oxybutyric acid gives rise to the same symptoms as does the acid itself. He ascribed the coma to the diminished alkalinity of the blood, due to the union of certain acids with the alkali of the blood. Geelmuyden[50] in 1904 published a highly important paper on acid intoxication. In phloridzinised dogs with abundant glycosuria and acetonuria, he found only a small quantity of acetone in the blood from the arteries and veins. Geelmuyden found that the organs of diabetics contained more acetone than did the corresponding organs of non-diabetics. In diabetics the urine may contain much more acetone than the blood. The author goes deeply into the origin of acetone, and agrees with Waldvogel[51] that it arises from the imperfect metabolism of fat; and that the place of origin is in no particular organ.

In the following year, 1905, Guthrie[52] again contributes an article on delayed chloroform poisoning, but he does not shed any fresh light upon the subject. He still maintains that a pre-existent fatty condition of the liver is necessary, and that the chloroform acts as the 'last straw', causing the breaking down of the balance of metabolism.

In the same year Carmichael & Beattie[53] published the records of a fatal case of delayed

chloroform poisoning. The clinical course of the disease is minutely described. A very full naked eye and microscopical examination was made, even to the microscopic examination of the bone marrow. The authors are the only observers to describe a fatty change in the suprarenal capsules, which pervades the whole capsule. They favour the theory that chloroform destroys the red blood corpuscles, anaemia being a marked feature in their case. Carmichael & Beattie state that the symptoms are very like those in patients dying from intense septic infection. They concluded by observing that delayed chloroform poisoning is a primary condition and wholly due to the action of chloroform.

Bevan & Favill[54] describe a case of delayed chloroform poisoning which occurred in their practice. The patient, a girl of 12½ years, suffered from a gangrenous ovarian cyst with twisted pedicle. The amount of chloroform used was not noted, nor was the time taken. A full account is given of the symptoms, progress of the case, and the post-mortem examination. The case is discussed from a neurological point of view; and the fact of any circulatory derangement as a cause of the symptoms is put out of court. The literature is reviewed, as is also the clinical side of the case. The paper is

illustrated by photographs of sections of the liver from rabbits after chloroform and ether anaesthesia. The reported cases of previous observers are fully quoted. In conclusion, they are of opinion that the amount of injury to the liver cells is in direct proportion to the amount of chloroform used. The authors believe that idiosyncrasy plays an important part in the above condition.

Bajardi[55], in speaking of the elimination of chloroform from the stomach with vomiting after anaesthesia, observes: - that the quantity of chloroform found in the gastric juice is small and can only be detected by reagents, and that the quantities of chloroform found do not appear to have any effect on the production of vomiting. His other conclusions will be dealt with later.

Sick[56] reports a case of haematemesis in appendicitis, in which the haematemesis was such a prominent symptom that a diagnosis of gastric ulcer was made. In similar cases, various pathological changes have been observed in the gastric mucosa, which several investigators regard as due to the action of a toxic agent. Haematemesis being such a prominent feature in delayed chloroform poisoning, which is due essentially to an acid intoxication, I am of the opinion that Sick's case comes under the

same category, and had the urine been examined for acetone I feel sure its presence would have been detected. This case might be considered as outside my subject, but I am of the opinion that it comes under the head of an acid-intoxication similar to the subject of this thesis.

Richardson(57) reports a case of delayed chloroform poisoning occurring in a fat rachitic child. The operation, for genu-valgum, lasted thirty minutes, and the anaesthetic used was the alcohol, chloroform and ether mixture. The symptoms are described, and oxygen inhalations tried, but the child died thirty-three hours after the operation. The result of the post-mortem examination is given.

Kelly(58), in an important paper on the subject of delayed chloroform poisoning in 1905, gives a historical sketch of the subject, though by no means a complete one. He mentions various conditions in which acetonuria is found. Kelly states that acetone is excreted in small amounts in the foeces. He also believes that the amount of acetone excreted is no indication of the severity of the case, thus agreeing with Bracket, Stone & Lowe. This detail is dealt with later. Kelly compares the symptoms to those of cerebral pressure. He describes the treatment by alkalies, but in his experience has

found them only to give temporary relief. Kelly has found the greatest benefit from the use of an adrenalin chloride solution given every eight or twelve hours. In the case of children, 200 c.c. of a 1 in 50,000 adrenalin solution is used, and in adults, 500 c.c. of a similar solution. He finds it difficult to say if any treatment has any direct effect. From my own experience and from the results of treatment in the literature of delayed chloroform poisoning, I am forced to the same conclusion.

Hubbard[59], after dealing with the presence of 'Acetonuria in non-diabetic Surgical Cases', concludes :

1. Acetonuria is present more frequently than thought.

2. The presence of acetonuria without symptoms has no effect on operative treatment or on the prognosis.

3. The presence of acetonuria with moderate symptoms is of only slight importance in the future progress of the case.

4. Acetonuria with severe symptoms, makes the prognosis most grave.

I thoroughly agree with the first and the fourth sentence of the above conclusions, but I am unable to agree with Hubbard in his contention in

his second and third conclusions. These points will be dealt with later when I come to mention Beesly's paper.

Hubbard also gives the ages when acetonuria is most common. I will state when I deal with the urine in delayed chloroform poisoning, the ages, taken from practically all the reported cases of this condition, at which fatalities most frequently occur. It will be found that my deductions are very similar to Hubbard's. I deal more definitely with the ages of the younger children.

Embley & Martin(60), in a paper on the action of anaesthetic quantities of chloroform upon the blood vessels of the bowel and kidney, showed that the inhalation of a 1 to 3 per cent. chloroform vapour was sufficient to paralyse the blood vessels of the bowel and kidney, and suggested that the fall of the blood pressure might thus be accounted for.

Burton-Opitz(61) (in the Journal of Physiology for 1905) contributes a paper on 'The changes in the viscosity of the blood during narcosis'. In this paper the author, from experimental observation, states that the viscosity of the blood is increased by deep anaesthesia and lessened during light anaesthesia. Similarly the specific gravity of the blood is increased by deep and lessened by light narcosis.

Karawski[62], in dealing with the 'Reciprocal actions between diabetes and surgical interventions' notes that coma sometimes occurs after incision, and advises the reducing of the amount of sugar present and raising the patient's resisting power prior to operation.

I now come to the year 1906, when several important papers on the various aspects of delayed chloroform poisoning were published. I will first of all deal with Beesly's[5] valuable paper on 'Post-anaesthetic Acetonuria'. Beesly throughout his paper estimates the amount of acetone present quantitatively; and expresses his results in milligrams of acetone per 50 c.c. of urine. Beesly's paper will be more fully dealt with in the section upon the urine in delayed chloroform poisoning. Acetone was generally found in healthy urine by quantitative estimation, when colour tests were negative. Colour tests showed acetonuria to be present in every case after operation, except in one fatal case. I thoroughly agree with Beesly when he says that besides the fatal cases of delayed chloroform poisoning, every degree of intoxication is met with. As I look back upon the after course of several children after operation, many of the symptoms which were difficult of explanation, appear now, in the

light of delayed chloroform poisoning, to be only milder degrees of the same intoxication.

The first section of Beesly's paper is taken up with 'apparently healthy children whose urine before anaesthesia contained no acetone or only the faintest trace of it'. He illustrates by means of charts the degree of acetonuria in four cases, two after chloroform anaesthesia and two after ether. The chloroform cases do not show such a degree of anaesthesia as do the cases after ether, but the ether cases excreted their acetone more quickly than did the chloroform cases.

The second section is taken up with 'Children whose urine before anaesthesia contained an appreciable quantity of acetone, and who usually suffered from some constitutional symptoms, more or less severe.' The cases in this group are divided into Acute Acetonuria and Chronic Acetonuria. I regard this as an extremely suitable division. Beesly proceeds to show that after anaesthesia the excretion of acetone is usually greater than in previously healthy children. In chronic acetonuria, symptoms of poisoning, if any, are slight; while after acute acetonuria, the symptoms of poisoning are alarming, the case practically always proving fatal. Beesly lays stress upon what he terms 'delayed

acetone excretion', and proves that the danger lies not in the degree of acetonuria, but in the rate and time of its excretion.

Beesly concludes his paper by remarks upon treatment.

Telford & Falconer(2), in the same year, reported three fatal cases of delayed chloroform poisoning. They gave a short historical sketch, and after describing their cases with the post-mortem examination of each, proceed to give the results of their examination of the urines of one hundred and eighteen cases after anaesthesia. The authors varied the anaesthetic, but found that aciduria was generally, not invariably, produced after every anaesthetic. Telford & Falconer's observations upon acetonuria after ethyl chloride anaesthesia, will be dealt with when speaking of that condition.

Diet seems to have no effect on the production of aciduria. The authors err, however, in saying that no death has occurred after ether anaesthesia, as Bracket, Stone & Lowe have reported several. Telford & Falconer are strongly of opinion that rickety children are specially liable to the after toxic effects of chloroform.

Thompson(63), in a paper entitled 'Anaesthetics and Renal Activity', gives the results of his

experiments on dogs, using chloroform anaesthesia. A summary of results at the end of his paper clearly states Thompson's views, and will be dealt with in future sections.

An extremely interesting critical review of delayed chloroform poisoning is contributed by Tuffier, Maute & Auburtin(114). The whole subject is carefully studied, though nothing new is elucidated. Further, in 1906, we have other papers published and cases of delayed chloroform poisoning reported.

Cushing(64) describes a case of what he calls 'Acute atrophy of the Liver from Chloroform Poisoning'. The patient developed jaundice on the third day, along with haemorrhagic spots on the abdomen. Death occurred in a hundred hours after operation. Madison(65) reported three cases.

Wells(66), in a paper on 'Delayed Chloroform Poisoning and allied conditions', wherein he deals with the cause of these conditions, maintains that they "all depend on the effect on the liver of poisons that destroy the synthetic function of the liver cells without destroying their autolytic ferments." In Delayed Chloroform Poisoning, Wells is of opinion that it is the oxidising ferments that are particularly involved, accounting for the marked

fatty changes present in this condition.

Coming now to 1907, Langdon Brown[67], in a most excellent paper on Acetonuria, among other conditions deals with 'acetonuria in delayed chloroform poisoning'. The characteristic symptoms are mentioned and several previous papers noted. Langdon Brown states that after examining the urines of forty patients after chloroform anaesthesia, one of the house surgeons of St. Bartholomew's Hospital found diacetic acid present in only one case. Langdon Brown considers that such discrepancies as result between these results and those of Telford & Falconer where 84.2 per cent. of the cases showed diacetic acid to be present in the urine, perhaps depend on some difference in the method of administration. He believes that acetone and diacetic acid frequently appear in the urine after anaesthesia without the presence of any symptoms. Langdon Brown believes with Guthrie that a pre-existent fatty condition of the liver must be present before toxic symptoms of poisoning can occur. The paper is concluded by remarks on the treatment of acetonuria.

Ramsey[68] describes two fatal cases of delayed chloroform poisoning, both occurring in adults. The first, a woman aet.66, was operated upon for an umbilical hernia. The usual symptoms are described,

death taking place on the sixth day. No post-mortem was allowed. The second case is that of a man, aet.40, suffering from a suppurating ear. Two operations were performed within a few days of each other. At the post-mortem, the most characteristic change was the fatty liver. The most prominent symptom in both these cases was haematemesis.

Again in 1907 we find Guthrie(69) publishing a paper on 'Delayed poisoning by Anaesthetics'. A most excellent review of the whole subject is given. The nature of the operation and the condition of the patient at the time of operation is dealt with, but nothing new elucidated. The symptoms and post-mortem findings are given in some detail. The various suggested causes are criticised. Guthrie does not agree with Lengeman's contention that the amount of chloroform given to animals makes little difference in the extent of the fatty degeneration produced in different organs. Lengeman decided that a certain amount of chloroform must be in the circulation before fatty degeneration can be produced, 'yet this quantity is always present when sufficient chloroform has been given to produce narcosis'. Guthrie holds that if such be the case, chloroform, when given in large doses and over long periods, must invariably be fatal. Guthrie still firmly

maintains that a pre-existent fatty condition of the liver is necessary before symptoms of poisoning can arise; and that in these cases the chloroform acts as the 'last straw'. For the first time, venesection is recommended as a method of treatment in delayed chloroform poisoning.

Langmead(109) reported three cases of delayed chloroform poisoning, two of the patients being boys and the other a girl. Each case showed a hyperplasia of the lymphatic tissue in varying parts of the body. Jaundice developed in the first case, that of a boy of twelve years who suffered from recurrent lymphadenomatous glands on the right side of the neck. The girl had had previous bilious attacks, and her symptoms so closely resembled those of intestinal obstruction that an operation was considered. She eventually recovered. The post-mortem examinations in the cases of the two boys are given. In each instance the liver was 'buff coloured'; the other organs were apparently healthy. Langmead in his paper considers some other acetonaemic conditions in children, and dwells especially on recurrent vomiting. In summing up, Langmead states that the 'buff or canary coloured' liver is characteristic of cases suffering from the latter condition, as well as those who succumb to delayed

chloroform poisoning.

Campbell[70] reports three cases of delayed chloroform poisoning occurring in children between the ages of 4 and 6 years. All the patients were boys; two suffered from inguinal hernia, and one from cleft palate. In one of the cases, that of the boy of 4, who suffered from an inguinal hernia, the symptoms, which, to one familiar with delayed chloroform poisoning, were typical of the condition, so closely resembled those of intestinal obstruction that the surgeon again opened the wound under chloroform, thus, instead of relieving the patient, accelerated the fatal termination. The patient died fifty hours after the first operation. The post-mortem examination in each case revealed an intensely fatty liver. The symptoms in these cases are described, and various causes suggested as the cause of the symptoms. The paper is concluded by remarks on the treatment of such cases.

M'Arthur[71], in a paper on acidosis, reports a fatal case of delayed chloroform poisoning, and asks if by some means oxygen could not be set free in the tissues, as a method of treatment. Lengeman[72], after experimenting on the 'Influence of Oxygen on the after effects of Chloroform', concludes that the admixture of chloroform and oxygen

is less toxic than is the mixture of chloroform and air, but that the admixture of chloroform and oxygen is still of sufficient toxicity to compel caution in its universal use.

Guleke[73] published the case of a robust young woman upon whom a herniotomy was performed. Twenty-five c.c. of chloroform were used, and the duration of the anaesthetic was half-an-hour. The patient exhibited jaundice and profound cholaemia within twenty-four hours of the operation: she next became delirious, had several convulsions and died ninety-two hours after the administration of the anaesthetic. The post-mortem findings are described in detail.

In 1908, many papers were added to the existing literature of delayed chloroform poisoning. Taylor[74] reported a fatal case of a boy aged 2 years and 9 months, who suffered from inguinal hernia. The duration of anaesthesia was twenty minutes, and its course was normal. Twenty-four hours after operation, a deep cherry-red colour appeared over the area of skin prepared for operation. Vomiting was a prominent feature of the case, and consisted of mucus containing brownish flecks. Death took place thirty-eight-and-a-half hours after operation. At the post-mortem, the thymus weighed seven grammes,

and there was distinct hyperplasia of all the lymphatic glands. This latter fact is emphasised in the remarks on the case, as is also the 'cherry red' appearance of the lungs and over the area prepared for operation. As I have mentioned, Brewer(45) lays stress upon the same 'cherry red' appearance of the lungs.

Bride(75) reported two cases, the one a girl of three years who had a previous history of diarrhoea and vomiting and had been discharged from hospital on previous occasions as unfit for operation. This previous history is certainly suggestive, and demanded caution. The patient was rickety and suffered from equinovarus. According to several authorities, especially Telford, here was a combination of affairs specially liable to be followed by the toxic after effects of the anaesthetic. The symptoms, ushered in by a convulsion thirteen hours after operation, continued until the patient's death nineteen hours later. Air-hunger was a prominent feature just prior to death. The post-mortem findings are described in some detail. The liver, kidneys and heart were pale, and on section the liver was pale yellow and showed intense fatty change. The convoluted tubules of the kidney showed necrosis. The lungs showed a state of passive congestion.

The second case was also that of a girl, aet. 14, who suffered from genu valgum. An osteotomy was performed, and chloroform anaesthesia lasted fifteen minutes. Twenty-four hours after operation 'coffee ground' vomiting set in, and the patient vomited twenty-six times in the next twenty-four hours. The urine showed acetone and diacetic acid. Next day the patient vomited thirteen times, and acetone and diacetic acid were still present in the urine. The condition, from this date, gradually improved, and the patient was discharged ten days after the operation.

Wilson[76] reported a fatal case of delayed chloroform poisoning occurring in a girl, aet. $6\frac{1}{2}$, who suffered from a tuberculous hip. Two previous operations had been performed, some time before. The patient had a previous history of attacks of sickness and vomiting. The great trochanter was removed, one and a half ounces of chloroform being required, the operation taking one and a half hours. The symptoms of delayed chloroform poisoning began to show themselves definitely on the third day, the patient being apathetic, and a distinct smell of acetone being present in the breath. Next day patient was jaundiced, and though no acetone was found in the urine, bile was demonstrated. A

curious feature of this case was the occurrence of oedema and anasarca of the limbs, trunk and face. Coma set in one hour before death, which occurred on the eighth day after operation. At the post-mortem the liver was large and of a light yellow colour. It is stated that there was fatty infiltration, but no fatty degeneration of the liver. Slight oedema of the pia arachnoid was also noted. Stress is laid in this case on the delayed excretion of acetone and the previous history of sickness.

These two cases are extremely interesting from the point of view of the previous history of sickness, which all observers are agreed is a predisposing cause of delayed chloroform poisoning.

Beddard(77) deals with the treatment of delayed chloroform poisoning. He believes in certain individuals being more susceptible to the after toxic action of chloroform than others. The cause of the condition is gone into. By experiment, Beddard has shown that the exhibition of dextrose to animals prevents the transportation of fat. In delayed chloroform poisoning the liver cells call for fat more greedily than they can metabolise it, therefore while the transference of fat is increased, metabolism is decreased. By giving dextrose in this condition, though it cannot prevent the poison from

damaging the cells, and has been found useless in cases where the protoplasm has been too severely damaged, it provides the cells with the energy they can best utilise and so prevents them dying from inanition, and thus gives them time to recover. Beddard's method of exhibiting dextrose in cases of delayed chloroform poisoning is dealt with in the chapter on treatment.

Hill Abram[78], in a paper on 'Acetonuria and General Anaesthesia' quotes Jaksch as having found acetone to be a normal constituent of the urine. Abram examined the urines of twenty-five cases before operation, and daily after the operation until the urine was normal. In sixteen cases acetonuria was present, that being equal to sixty-four per cent. Becker, in his investigations, found acetonuria present in sixty-six per cent. of cases after chloroform anaesthesia. In these tests only qualitative examination of the urine was performed. Abram states that acetone invariably occurs after anaesthesia, and that the quantity and duration of the anaesthetic does not matter. Becker found that acetonuria follows anaesthesia, and if it be already present it is increased thereby.

Hunter[79], who has contributed largely to the literature on the metabolism of delayed chloroform

poisoning, deals in one of his papers, published in 1908, with the nature and prevention of the condition. Hunter points out that the acidosis accompanying increased fat metabolism becomes of grave pathogenic significance when combined with diminished proteolytic activity, owing to inanition, deprivation of food, or recurrent vomiting. Owing to the diminished absorption of ammonia in the portal blood, the intracellular alkalinity of the liver cell is at a low level. There then results first of all a serious interference with the proteolytic, antitoxic and glycogenic functions of the liver, and the transference of fat to that organ takes place in increased quantities. We now get the severe toxic cerebral symptoms of delayed chloroform poisoning, which may rapidly prove fatal. The physiology of fat metabolism is next gone into. The effect of disturbances of the proteolytic and antitoxic functions of the liver are then explained, and in conclusion Hunter states that if the patient had a sweet, nutritious, easily digested meal two or three hours prior to operation, the condition of delayed chloroform poisoning might be entirely prevented.

In the same year, at the British Medical Association's[80] Annual Meeting, the subject of fatty

acid intoxication was discussed. The opening paper was read by Leonard Guthrie. In this paper the results of the analysis of a large number of urines, for acetone, are given. The whole subject of acidosis is dealt with, but as far as delayed chloroform poisoning is concerned no fresh facts were forthcoming. In the discussion that followed, many leading authorities took part, including Stiles & Stuart M'Donald(12). The latter pointed out that in cases of acute yellow atrophy the liver never presented the 'intense and practically uniform yellow colour' which was so characteristic of the chloroform cases. Professor Leathes(81) maintained that it was erroneous to speak of fatty liver as a cause predisposing to delayed anaesthetic poisoning. Wells(82), another observer, who has contributed largely to our knowledge of the subject, divides cases of delayed chloroform poisoning into two classes: (1) 'Acidaemia' or 'Acetonuria' without jaundice; in these cases, he states, the changes in the liver are not marked. It is difficult - in view of the numerous cases published where jaundice has been absent and where there has been extreme fatty change in the liver - to take this statement of Wells' as correct. It is doubtless what one should expect, but jaundice is by no means an invariable sign in delayed chloro-

form poisoning, while extreme fatty change in the liver is the rule. (2) Acetonuria with profound jaundice: these cases occur mostly in young adults, with intense colaemia, haemorrhage, and the usual symptom complex. Cases of this nature rapidly prove fatal, and post-mortem the liver appears much as it does in acute yellow atrophy.

Intermediate cases occur which do not fall into these groups. Cunningham(83) reports a case of acid intoxication following ethyl chloride anaesthesia, with symptoms extremely like those which occur after chloroform. The patient recovered. This case will be gone more fully into when speaking of acetonuria following ethyl chloride anaesthesia.

Thorp(84) reported a fatal case in a boy of 3 years and 10 months who suffered from phimosis. Two drachms of chloroform were used, the patient being under the influence of the anaesthetic for only seven minutes. The symptoms, which are described in detail, clearly suggest this case as one of delayed chloroform poisoning. Death occurred thirty-six and three quarter hours after the operation, and twenty-three hours after the onset of symptoms. The urine contained acetone and diacetic acid. Unfortunately, no post-mortem was allowed. This case is important in respect of the small amount of

chloroform used and the extremely short time the patient was under its influence.

Telford[85] again reports three cases, two of which were fatal within forty-eight hours. Each of these three cases suffered from rickets, as did two of the previous three cases reported by him. Each of the three cases reported in 1908 had 'coffee-ground' vomiting. As against Wells' statement, that cases which showed no jaundice had only slight fatty change in the liver, each of the two fatal cases now reported by Telford had extremely fatty livers, post-mortem, and neither of them had jaundice. The symptoms in each case are detailed. In the two fatal cases, the post-mortem appearances, both naked eye and microscopical, are described. Telford does not believe that a pre-existing fatty condition of the liver is the necessary cause of delayed chloro-form poisoning. He strongly maintains that rickets is a predisposing factor; but surely rickets can have no effect in the cases of adults who have suc-cumbed to this condition.

Forsyth[86], in 1908, published an extremely interesting case occurring after child labour: the patient exhibited acetonuria, with delayed excretion of acetone. The patient was a dyspeptic, and the liver prior to anaesthesia reached two finger

breadths below the costal margin. The symptoms did not set in until the third day, when headache and drowsiness were evident. Next day the patient showed slight general jaundice. On the fifth day, and not till then, was the smell of acetone recognised in the breath, and the same day the urine contained acetone and diacetic acid. Next day the patient was delirious and vomited bile and mucus. There was no 'coffee-ground' vomiting throughout the course of the case. From this time the patient gradually improved. This case is interesting from the fact, which has been already observed, viz. that a fatty condition of the liver is concomitant with pregnancy, and therefore one might say a predisposing cause of delayed chloroform poisoning.

Wallace & Gillespie(87) published a valuable work on the effect of prophylactic treatment upon post anaesthetic acetonuria. They divided their cases into three series. In the first series, no treatment was administered; in the second series, soda bicarbonate was given; and in the third series, glucose was exhibited before operation. From their investigation they concluded that the administration of glucose in quantities of half-an-ounce every four hours, for six doses prior to operation, successfully prevented the occurrence of delayed chloroform poisoning.

Wallace & Gillespie quote Ladd & Osgood[88], and Young & Williams[89], as proving that ether, given by the open method, is followed by much less acetonuria than when given by means of a cone. Shoemaker[90] and Corbett[91] have each reported a case of delayed chloroform poisoning.

In 1909, we find a lively interest taken in the acid intoxication after anaesthesia, especially by American surgeons; several articles appeared in the Journal of the American Medical Association. As a whole the cases are very thoroughly dealt with.

Weill, Vignard & Mourignand[92] encountered a series of fatalities after operations for appendicitis, due to the injurious effects of chloroform on the liver. The symptoms are described, jaundice and black vomiting occurring in each case. All their patients died in from two to three days.

Heysett[93] reports a fatal case of acute toxaemia after chloroform anaesthesia. He finds fatalities occur more frequently in females than in males. Heysett reviews briefly the symptoms and the pathology.

Spriggs[94] gives an admirable critical review of acidosis as a whole. The subject we are now studying is also briefly reviewed. No new light upon the subject, however, is forthcoming.

Howlands & Richards[95] studied the metabolism and pathology of delayed chloroform poisoning experimentally. They found that in dogs, after chloroform anaesthesia lasting one and a half hours, fatty changes in the liver were produced in the intermediary zone of the lobule. More prolonged and repeated anaesthesia gave rise to a necrosis, beginning in the centre of the lobule and extending until all the cells were necrosed. They regard death as due to toxic substances of an unknown nature.

Williams & Becker[96] describe the symptoms and post-mortem appearances in the case of a man aet.19 which proved fatal. Here again we have a previous history of indigestion. The liver in this case was the only organ which was not healthy. It was softer than normal, pinkish-gray in colour, and on section was friable and of a yellowish-gray colour. The authors agree that neither the degree of toxicity, nor the extent of destruction of the liver, bears any relation to the amount of chloroform used. They regard death as due to a perverted metabolism of the liver.

Whipple & Sperry[97] contributed a valuable paper on'Chloroform poisoning - Liver necrosis and repair'. They state that chloroform anaesthesia for a period of one to two hours invariably causes

some central liver necrosis, and may cause a fatal result in dogs. Young animals are more susceptible to the toxic action of chloroform than are adults. The authors describe the essential change as an extensive necrosis and fatty degeneration. There may be numerous ecchymoses and haemorrhages into the peritoneum and upper intestinal tract. The pancreas may show fat necrosis and ecchymosis. The kidneys and heart may show fatty degeneration. The post-mortem findings, according to Whipple & Sperry, are identical in dogs and man. Talking of repair after liver necrosis, they state that, should the patient recover, the liver returns to normal in two or three weeks. Repair is effected by solution of the necrotic cells and rapid multiplication of peripheral cells.

Sommerville[98] reports three fatal cases of delayed chloroform poisoning. In each of these cases, 'coffee-ground' vomiting and jaundice were present, though the latter was not intense. The symptoms and pathological changes are described. In one of the cases, that of a male aet. 18, no acetone was found in the urine on qualitative examination. The temperature in each case rose prior to death, in one case reaching 106°.

Weir[99] reports a case, which appears to be

one of delayed chloroform poisoning, which recovered after the exhibition of large doses of glucose. The paper is entitled so as to indicate that dextrose was used, but in the report, glucose alone is mentioned. One interesting feature of this case is the fact that the face became of a 'rich plum colour'.

In the Indian Medical Gazette(100) of July 1909 appears a leading article on acidosis and acid intoxication, which draws attention to the relationship between acidosis and scurvy. It is pointed out that a diet composed wholly of tea and beef, such as is taken by the Pathans in Calcutta, is peculiarly favourable to the production of acidosis and acid intoxication, and that this diet is also favourable to the production of scurvy.

Gillman Moorhead(101) reports two cases of acid intoxication. He found acetonuria present in six out of twenty-one cases operated upon. In one case, diacetic acid also appeared in the urine. Moorhead reports a most remarkable case after removal of the right lobe, the isthmus and a part of the left lobe of the thyroid gland in a patient suffering from a cystic goitre. The operation lasted one and a half hours. Symptoms of poisoning did not appear until one month after the operation. Between the operation and the onset of symptoms, no factor, it is

stated, which might have determined such a condition, was observed to be present. Whether this case is to be looked upon as due solely to delayed chloroform poisoning is exceedingly doubtful.

Carey(113) reported a fatal case of delayed chloroform poisoning. The symptoms are described in detail, as is also the microscopic appearance of the liver. A note at the end of the case states that no carbolic acid was used at the time of operation.

During 1910 few papers on the subject under consideration were published. At the British Medical Association's Annual Meeting(102), the subject of acidosis was discussed. The opening paper was read by Professor Edsall of Philadelphia. Edsall has paid a great deal of attention to the condition known as acidosis, and has written largely upon the subject. Various workers on the subject took part in the above discussion, but apart from a clearer definition and exposition of the cause of the symptoms as far as this is known to day, no fresh light is thrown upon delayed chloroform poisoning.

Goodhart(103), in a paper on 'Chloroform necrosis of the Liver', deals with the condition of that organ in rabbits. After comparatively short periods of anaesthesia, it was found that in a rabbit, killed

at the end of forty-eight hours, after sixty minutes chloroform anaesthesia, there was definite necrosis at the centre of the lobules. Anaesthesia for a shorter period than one hour produced no central necrosis, although the fatty change generally throughout the lobule was marked. In a rabbit anaesthetised on two separate occasions for periods of twelve minutes and thirty minutes respectively, there was marked central necrosis of the liver lobules. In the majority of the experiments where the rabbits were injected subcutaneously, the centre of the lobule was represented by a mass of red blood cells, with the remains of isolated liver cells scattered amongst them. The method of repair of the liver cells has not been gone into by Goodhart.

Telford[104] has published an extremely interesting case of delayed chloroform poisoning. The patient, a woman aet.47, required a posterior gastro-enterostomy performed. During the operation the liver was seen and handled, and found to be normal in every way. Thirty-six hours after operation, vomiting began, and was persistent, ultimately taking on the typical 'coffee-ground' appearance. The patient died on the fourth day after operation. Post-mortem the liver showed extreme fatty degeneration, was larger than normal, and greasy to the feel.

This case is quite contradictory to Guthrie's 'last straw' theory, and is an extremely valuable addition to our knowledge of the subject.

Telford, in the same article, reports a case of Recurrent or Cyclic vomiting brought on by the chloroform anaesthesia. The patient had previously suffered from recurrent vomiting. The case recovered.

Wallace & Gillespie[105] published a paper on 'Acidosis in relation to Anaesthesia' in which they review the whole subject. They deal at some length on the site of origin of the fatty acids, and after discussing the effect of the anaesthetic on the organism, describe the symptomatology in delayed chloroform poisoning. The authors divide the post-anaesthetic condition into two groups, viz., acute or acid intoxication, and subacute or acidosis. They describe the symptoms in each variety, and conclude their article with remarks on treatment and the pathological findings. No new facts are revealed in this paper.

Turning to the description of acidosis, and especially delayed chloroform poisoning, in the medical text books, we find in Osler & Macrae's System of Medicine[106], 1909, a note to the effect that 'it is doubtful whether the symptoms are really due to acetone.' In Allbutt & Rolleston's System[107]

we find a much more graphic picture of the subject. This article is written by Hunter, whom I have already had occasion to mention. The pathological changes in delayed chloroform poisoning are described, and the causes of the condition are, as far as is known, explained. In Hunter's article, we get a very good introduction to the subject we are now studying.

This year I have so far found three cases of Postanaesthetic acid intoxication reported. Two are published by Gilbert Brown(111), and occurred in the Children's Infirmary, Liverpool. The first is that of a boy, aged 6 years, who suffered from a chronic intussusception. The anaesthetic employed was ethyl chloride, followed by ether. The second case was that of a child, aged 1 year, who had an inguinal hernia. Two drachms of the chloroform-ether mixture were used, as well as half an ounce of ether. The symptoms in each case were similar to those in delayed chloroform poisoning. Treatment by soda bicarbonate was instituted, without avail in the latter case. The liver in this case was slightly paler than usual. The third case this year was reported by Woodforde(112) at a Meeting of The Royal Society of Medicine on February 24th. The patient, a boy of 9 years, suffered from glands

in the neck. Anaesthesia lasted fifteen minutes. It was not until the third morning after the operation that any disturbing symptom was noticed. The patient was then in a collapsed state, but reacted well to restoratives. The same evening vomiting set in, and later unconsciousness; respiration ceased two hours later. With artificial respiration the heart continued to beat for five hours after breathing ceased. There was abundant acetonuria just before death. The liver, post-mortem, was of a 'golden yellow' colour, and fatty degeneration was present in the heart, kidneys and spleen. A few submucous haemorrhages of small size were seen in the stomach.

This last case concludes my historical sketch of delayed chloroform poisoning. I have been particular in reporting cases where there was practically no doubt as to this condition being present. Cases in which elements, other than the after toxic effect of the anaesthetic, might reasonably have produced the symptoms, have been excluded. Numerous cases, especially in later years, have succumbed after anaesthesia, but many of them to my mind do not justify the diagnosis of delayed chloroform poisoning.

An Analysis of the

SYMPTOMATOLOGY

in

DELAYED CHLOROFORM POISONING

with a detailed description of the Symptoms
in two cases which I personally observed.

SYMPTOMATOLOGY.

In dealing with the symptoms of Delayed Chloroform Poisoning, one recognises most of them as occurring at some period or other during the post operative progress of many surgical cases. The symptoms as a rule, however, in no way approach in severity those we find in a case which eventually proves fatal from the toxic after effects of the chloroform. Before one fully realised delayed chloroform poisoning as a very real condition - which cannot fail to impress anyone who has once seen a case - one was apt to attribute the symptoms to anything but the toxic after effects of the anaesthetic. One attributed the immediate symptoms to the effect of the anaesthetic on the stomach in case of sickness: shock accounted for the pulse, and for any pallor there might be. The temperature, if any, generally fell just after the operation, and a subsequent rise was regarded as of septic origin. Restlessness was put down to the mental condition of the patient, and a slight icteric tinge was an interesting observation and must have something to do with the effect of the anaesthetic or some other cause on the liver.

Having once seen an undoubted case of delayed

chloroform poisoning, the surgeon does not treat such symptoms lightly. Symptoms, though frequently occurring apart from the severer condition of delayed chloroform poisoning, may yet be forerunners of that condition. Having seen two cases of delayed chloroform poisoning, the feature that struck me most was, how very ill the patient looked, and even in the case that recovered, I could not but think that the end was not far off.

Having collected over eighty cases which appear to me to be undoubtedly due to delayed chloroform poisoning, I will proceed to give a detailed analysis of the different symptoms.

I will first of all describe a typical case 8(Case 2). The case is that of a girl of 8 years of age, well nourished, and with no evidence of any organic disease whatsoever. The patient suffered from Genu Valgum, and a wedge of bone was removed from the inner side of the lower end of the diaphysis of the femur. This was done at 11 a.m. on October 21st, 1902. There was no difficulty about the operation and no shock. The total duration of the anaesthesia, including induction, was twenty-two minutes. The amount of chloroform used is not mentioned, and I do not think matters.

The patient was a little sick after her return

to consciousness. No further vomiting took place the whole of the afternoon, and her condition was in every way satisfactory.

Later in the evening vomiting again set in, and continued at intervals throughout the night. The vomited matter, which consisted at first of gastric juice mixed with a little bile, became more copious and of a dark green colour, and finally presented the characteristic 'beef-tea' like appearance seen in this condition.

She complained of great thirst, cried out for drinks, and became very restless. Every now and then she attempted to throw off the clothes, and would frequently clutch hold of the bars of the crib and pull herself into awkward positions. In the intervals between these excited periods she appeared to be listless, and did not complain of pain.

The pulse became increasingly rapid and feeble. The breathing was natural. There was no involuntary passage of urine or foeces.

The following morning the vomiting ceased, and her condition was more satisfactory. She was, however, a little flushed, and the pulse was small and quick.

At 1 p.m. she asked for and received a drink. An hour later, the child was looking collapsed, grey

and slightly cyanosed. The pulse was almost uncountable, unconsciousness rapidly supervened, and the patient died suddenly at 2 p.m., twenty-six hours after the operation.

The above case, as I have said, is very typical and gives most, but not all, of the classical symptoms.

The symptom which perhaps most of all impresses itself upon one is vomiting. I will now deal with this symptom in detail.

Vomiting.

The point about the vomiting which strikes one most is its nature - by that I mean the large number of fatal cases whose vomit ends in the same manner, viz., like 'beef-tea'. Guthrie(1), in 1894, first pointed out how characteristic was this sign; since then, his experience has been fully borne out by other observers.

Many cases after the administration of an anaesthetic are sick to a more or less degree - quite apart from the subject of this paper. On the patient being returned to bed after the operation, there is nothing in the initial sickness which warrants one to say the case is one of delayed chloroform poisoning. In fact, cases of this condition

which eventually prove to be fatal, have had no sickness at all just after the operation. Many of the cases, notes of which I have, did not vomit at all until ten hours to twenty hours, and even longer, after operation. This shows that cases which eventually prove fatal from the after effects of the chloroform pursue the same course immediately after operation, that is up to two hours at least[1(Case 2)], as any ordinary post anaesthetic case. The case I have just mentioned showed carboluria as a complication, and death ensued in five hours ten minutes, and as carbolic poisoning, of itself, may cause death[(8)], with symptoms very much akin to delayed chloroform poisoning, I can hardly base my deductions upon that.

Again, I see, a case - which proved fatal in eleven hours[5(Case 2)], the patient bringing up 'coffee-ground' material three hours after operation - was complicated by sepsis, it being a case of osteomyelitis.

Both the above conditions, viz. carbolic poisoning and sepsis, have been proved[(8)] to intensify the condition. Taking a case of delayed chloroform poisoning which, as far as reported, had no other condition present to intensify or accelerate the symptoms, I find the first indication that the above

condition was probable appeared ten hours[85(Case 1)] after operation, and death ensued four hours after commencement of symptoms. In this case, 'coffee-ground' vomiting was the first symptom, and to one acquainted with delayed chloroform poisoning was very ominous.

One can therefore say, after an analysis of practically all the reported cases of delayed chloroform poisoning, that the first definite symptom of the condition may not be expected, that is, in an uncomplicated case, for about ten hours, but in cases complicated by conditions which give rise to very much the same pathological processes, symptoms may appear as soon as two hours, and the symptom beyond all others to make one extremely suspicious is vomiting; and the particular nature of the vomit 'coffee-ground' or 'beef-tea'.

From the operation up to the time when the above characteristic vomit is noticed, the contents of the stomach which are brought up consist of gastric juice, bile stained fluid, in some cases large quantities of colourless fluid[98(Case 1)], though usually, however, the vomit is not so copious, sometimes a very dark green material, or even a dark brown fluid 3(Case 3) 5(Case 1) 108 distinguishable from the 'coffee-ground' material. In one case[85(Case 1)],

condition was probable appeared ten hours[85(Case 1)] after operation, and death ensued four hours after commencement of symptoms. In this case, 'coffee-ground' vomiting was the first symptom, and to one acquainted with delayed chloroform poisoning was very ominous.

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one hour before death, the vomit was black.

We have now to ask ourselves, that given this vomit, is the case invariably fatal? and, if so, can we forecast within limits the time of death?

The fact that the vomit is like 'beef-tea' or 'coffee-grounds' in no way entitles us to look upon the case as necessarily fatal. I have collected four cases which showed this symptom but recovered completely[4](Cases 1 & 2) 85(Case 3) 75(Case 2). In those cases which have proved fatal, one of them 85(Case 1), I have already mentioned, terminated four hours after the 'coffee-ground' vomiting commenced: another[2](Case 2) did not show this symptom until twenty-six hours after the operation, and died one hour later; while still another[8](Case 3) had 'coffee-ground' vomiting twenty-four hours after operation, but the fatal termination did not take place until the fourth day.

Considering that among the fatal cases I have collected death was never longer delayed than ten days[(7)] from the day of operation, one is led to assume that once 'coffee-ground' or 'beef-tea' like vomiting has commenced, if the case is to prove fatal, the end will not be more than three days distant and may take place within an hour.

Does the vomit once having been like 'beef-tea'

continue so until the end? By no means, the cases which recovered make that clear: and also in the fatal cases some of the patients had longer or shorter periods of either no sickness at all[8(Case 2)] or sickness which perverts to the milder types I have already indicated. In a true case of delayed chloroform poisoning, vomiting having once begun is generally persistent and severe, and sooner or later reverts to the characteristic 'beef-tea' type.

From a study of practically all the cases of delayed chloroform poisoning, I am forced to this conclusion, viz., 'Beef-tea' vomit early in a case does not necessarily mean a fatal termination; on the other hand, the longer it is delayed the more grave is the prognosis.

One accompaniment of the vomiting which is by no means always present is retching. Only in two of my cases[85(Case 2) 76] is retching mentioned as particularly distressing, and in only one[5(Case 2)] case is it mentioned that there was no retching, though the vomit resembled 'coffee grounds'. On these grounds one assumes that retching on the whole is not a distressing symptom of delayed chloroform poisoning.

The vomit at first has a sweetish odour, but later it loses this characteristic. One must not

confuse this with the sweetish odour of the patient's breath. In two of my cases[5(Case 1) 108] the vomit is described as 'blood stained', and in one[(42)] as containing blood; no mention is made in these as to retching.

One naturally asks oneself, how does this 'beef-tea', 'coffee-ground' or blood stained vomit come about? I think the answer to that question is made clear by Beattie & Carmichael[(53)]. They found that the peripheral lining cells of the capillaries of the gastric mucous membrane were filled with fat globules, the central cells showing only a moderate degree of fatty degeneration, and they thought that any strain on these capillaries in their weakened degenerated condition would easily rupture them; and hence the nature of the vomit.

Stiles & M'Donald[(8)] in their paper, point out after experiments on rabbits, that a local lesion of the gastric mucosa may be due to chloroform absorbed by the blood, and excreted into the stomach by the gastric glands. This they think is the most reasonable explanation of the petechial gastric haemorrhages and accounts for the nature of the vomit. They also point out that it must not be forgotten that severe parenchymatous changes in the liver, by interfering with the circulation, will cause increased

hyperaemia of the gastric mucosa, and so in its turn favours the occurrence of capilliary ecchymosis.

Bajardi[55], on the elimination of chloroform from the stomach and its relationship to the vomiting after anaesthesia, concludes as follows:-

1. Chloroform is found fairly frequently in the gastric juice (16 times): the frequency is greater according to the length of the period of excitation (first stage of administration).

2. Among the above sixteen, eight suffered from post anaesthetic vomiting, and eight had no vomiting.

3. In the cases with vomiting, chloroform was only found in the first few hours after anaesthesia and disappeared after the first washing out of the stomach.

4. The quantity of chloroform found is small and can only be detected by means of reagents.

5. The fact of chloroform being found in greater quantity among those who had a relatively long stage of excitation and the fact that it disappeared after the first washing out of the stomach led the authors to suspect that the condition might be due to the swallowing of chloroform at the beginning of anaesthesia.

6. The small quantities of chloroform found in analysis do not appear to have any effect in the production of vomiting. This confirms the previous finding of the authors, that substances given to prevent the contact of chloroform vapour with the stomach wall were inefficacious.

So far as I can find, no further analysis of the vomit has been made.

Immediately prior to death, vomiting, as a rule, is not a prominent symptom, although one case 8(Case 3) is said to have vomited right up to the time of death.

So far as I can find, the characters of the motions have not been considered as playing any important part in the progress of cases of delayed chloroform poisoning. I think, however, it is convenient to deal with the faeces at this point.

Faeces.

In the large majority of the cases of delayed chloroform poisoning, no mention is made concerning the faeces.

In a few of the cases it is noted that the patient did not pass his faeces involuntarily, and in one case[74] it is stated that the faeces were black in colour and contained mucus, and in another case[50] the motions are described as tarry. In the case with 'tarry' motions, the patient recovered.

In a communication by Guthrie[69] in 1907, no mention is made of the faeces at all; nor do I find any reference to the faeces in the British Medical discussion on the subject in either 1908[80] or

1910[102]. We can therefore assume that, as a rule, there is no involuntary passage of faeces, and except when the motion contains altered blood, there is nothing to draw one's attention to them. The fact that the motions contain blood does not add to the gravity of the prognosis, as witnessed by the case that recovered[85(Case 3)]. We must, however, remember that operation cases are as a rule carefully prepared, and when an anaesthetic is being given the bowels are in a very empty state, and also subsequent to the operation, and especially if there are any disquieting symptoms, food is withheld.

I shall have some remarks to make later on the excretion of acetone in the faeces.

A symptom which impresses itself upon one, and in a large number of the cases even before the vomiting has taken on the 'beef-tea' appearance, is restlessness. I will now deal with that symptom.

Restlessness.

This symptom may be the first to arouse the surgeon's suspicion[3(Case 1) 70(Case 2)]. The restlessness in these cases is very much more severe than is often witnessed in many post operative cases, especially in acute cases. In delayed chloroform poisoning, we get wild excitement; the patient

utters wild screams at short intervals[1(Case 7)], tosses himself about the bed[5(Case 2)], pulls himself into awkward positions[8(Case 2)], tears off his dressings[(76)], grinds his teeth[2(Case 2)] and requires constant attention.

The initial phase is an inability to sleep [1(Case 3)]: the patient may start up with a look of terror on his face[(76)], and will not be pacified. He then becomes more and more restless, as indicated above, may become delirious[33, 34, 44(Case 2)], his face and limbs may twitch[5(Case 1)], or he may have a convulsion[3(Case 3)]. These symptoms generally pass off, and the patient becomes apathetic[1(Case 4) (39)], semi-unconscious[2(Case 2)], quite unconscious [8(Case 2)], or comatosed[44(Case 1)] and so dies. One case[85(Case 2)], however, is stated to have remained conscious till death.

During all this period of restlessness the patient's face is flushed, the eyes wild and sunken; he looks round and seems not to recognise anyone, though he will often answer questions: then, as suddenly as he started up, he sinks back to his pillow dull and listless[98(Case 1)]. His thirst is often intense[3(Case 3)], he gradually becomes haggard [85(Case 1)], emaciation is rapid[109(Case 3)], and his abdomen often retracted[1(Case 8)]. Consciousness

may be lost early and never regained(33), though even after being comatosed, the patient may recover 85(Case 3).

How long after the administration of an anaesthetic is this restlessness first noticed? From the cases I have collected, I find this symptom may appear immediately after the operation3(Case 1), and that case recovered.

Coming now to a fatal case of delayed chloroform poisoning, I find that restlessness has been noticed as soon as eight hours after operation, and this case is peculiar in not having any vomit at all. Two of my cases showed marked restlessness the same night as the operation85(Case 2) 109(Case 2), and these cases proved fatal in thirty hours and forty-six hours respectively. In the case that proved fatal fourteen hours after operation85(Case 1), the patient is described as having wakened up with a 'startled expression' ten hours after the anaesthetic. Again, in a case that proved fatal in eight days(76), restlessness was not marked until the fifth day. From this we may infer that the sooner restlessness occurs, the sooner will the case terminate, in recovery or otherwise, and that the presence of restlessness does not necessarily render the prognosis more grave.

There is no relationship, as far as I can make out, between restlessness and sickness. Some cases exhibit the one symptom more prominently, and some the other: neither does it happen that if sickness appears first, restlessness is necessarily retarded, nor vice versa.

Restlessness may quickly subside[109(Case 2)], and give place to drowsiness and coma, or, on the other hand, to recovery. In some cases the restlessness may last for twenty-four hours[(53)] or even longer[(76)].

It is an interesting fact that many of the cases reported showed apathy[(74)(76)], drowsiness [109(Case 3)], and even semi-consciousness[(39)] before restlessness manifested itself. In all these cases the restlessness was followed by a return of the drowsiness, considerably increased in degree. This drowsiness generally increases till death, which occurs in the majority of cases in coma.

Another symptom which may draw the attention of the surgeon to the case is convulsions. A general convulsion may be the first symptom[(75)]; in this case the convulsions occurred at one hourly intervals for six hours, and were then rapidly followed by coma and death. In another case, the convulsions occurred at half hourly intervals[70(Case 3)] and

were followed by coma as above. Another patient 3(Case 3) had a convulsion half-an-hour before death.

From amongst practically all the reported cases of delayed chloroform poisoning, we find only three in which there were convulsions: we therefore assume that this symptom is a more or less unusual one, but when it does occur the case is almost necessarily fatal, from half-an-hour to six or eight hours.

A fatal case of delayed chloroform poisoning terminates in one of three ways, viz., sudden collapse(36), increasing cardiac weakness(37), or coma 85(Case 1). A case having become comatosed, we must not say absolutely that it is bound to be fatal; Telford85(Case 3) reports a case of recovery, but that is the only case of recovery I can find.

How long does a case remain in a comatosed condition before death results? The shortest time reported is half-an-hour(74), and the longest time for a patient to remain in a state of coma is twenty-four hours3(Case 5).

Another symptom which I find reported, in only two cases, however, is twitching of the face and limbs. In both cases the patients were in a comatosed state. In the first case5(Case 1) the face and fingers twitched one hour before death, and in the other, the left arm and face twitched109(Case 2)

two hours before death. Beyond this, I do not think this symptom is of any special importance.

In all these various symptoms, restlessness, lethargy, drowsiness, semi-consciousness, the patient may vomit. No mention, however, is made of vomiting when the patient is comatosed.

I have mentioned thirst as a symptom: I will just touch on this in passing.

In many of the cases, thirst is a most distressing symptom and is very intense. From among my cases I find four[3](Case 3), 8(Case 2), 53, 109(Case 2) in which thirst is especially mentioned. I have been unable to find any article dealing particularly with thirst, though several writers mention it. In this connection it is interesting to note that Hurry Fenwick[(110)] states that thirst is the first symptom of disease of the kidney.

I will now deal with the colour of the patient.

From the immediate effects of the operation, many patients are pale, and I think at this time the colour, as far as delayed chloroform poisoning is concerned, does not convey much. During the period of excitement and restlessness, the face may be flushed, or, on the other hand, the patient may be

pale. Even without excitement the face may be flushed[1](Case 5), 8(Case 2). This is only noted specially in two of my cases. As the disease progresses the universal colour is pallor[2](Case 2), 85(Case 1), 53, though in one case a special note is made that the patient was flushed half-an-hour before death.

Another symptom which, though not characteristic, has been frequently noticed is cyanosis. In the four cases[2](Case 3), 8(Case 2), 39, 70(Case 2) where cyanosis is mentioned, two of them[2](Case 3), 8(Case 2) showed this sign, one hour and half-an-hour respectively before death.

Brewer(45) reports that in his fatal case the skin and mucous membranes took on a cherry-red colour. His explanation is given elsewhere.

Cyanosis has never been observed in a case which has recovered, and Bracket, Stone & Lowe(48) regard it as a sure sign that the end is near.

I will now deal with a symptom which so frequently occurs that it may be almost termed characteristic, and from the post-mortem findings we wonder it does not occur more often, viz.

Jaundice.

Among the cases I have collected I find no

fewer than almost one half of the patients exhibit this symptom. The degree of jaundice was in one case the slightest 'yellow tinge'85(Case 3), while in another, it was extreme(33). It is very remarkable that, but for one or two exceptions, all the cases I have collected, which exhibited jaundice as a symptom, were fatal. From this, one is justified in saying that the appearance of definite, or well marked jaundice makes the prognosis exceedingly grave.

Jaundice may develop at any time after the operation, depending upon the severity of the case. Three of my cases8(Case 1), 34, 108 developed jaundice the day after operation, and these proved fatal in sixty-eight hours, three days, and four days respectively. Four patients3(Case 2), 27, 33, 98(Case 2) developed jaundice on the second day, and death took place from eighty-four hours to five days. Four cases39, 42, 98(Case 3), 109(Case 1) developed jaundice on the third day and proved fatal in eighty hours to five days. One patient(76) developed jaundice on the fourth day and died on the eighth day, another44(Case 2) on the fifth day and died the same day. In several of the cases are notes to the effect that the jaundice deepened before death 8(Case 1), but in no case is it mentioned that the

patient regained his natural colour before the fatal termination.

In one case[44](Case 2) jaundice appeared on the day of death: in another case[98](Case 3) it appeared eight hours before death. On the other hand, one patient(42) developed a yellow colour on the third day after the anaesthetic, but death did not take place until the seventh day.

From this we see that jaundice may be only of a few hours' duration, appearing just before the fatal termination, or may exist for as long as four days. In one case which was markedly jaundiced 3(Case 2) the liver was two finger breadths below the costal margin and was tender, and remained so till death. In another case(76), the patient is said to have had pain in the epigastrium; in this case, though acetonuria is mentioned, no note is made of bile in the urine. In one case where there was no jaundice the liver is stated as being large and tender.

Itchiness is not mentioned in any of the cases, but one case(33), on the day after the appearance of jaundice, exhibited minute haemorrhages over the abdomen; this case died the next day.

From the above cases we may conclude that jaundice appearing soon after the operation need not be

looked upon as such an ominous symptom as when it occurs later in the disease. The causes at work in the cases of jaundice soon after operation, we may take it, are more acute than in delayed jaundice, and as soon as the primary cause, the anaesthetic, is removed, may pass off, while in the later cases, the direct causal agent has been in the system ever since the anaesthetic, and instead of diminishing in power has produced changes which are more harmful to life. One observer(54) says he has seen six cases of delayed chloroform poisoning, and in each instance there had been well marked hepatic insufficiency before an anaesthetic was administered, one patient having had catarrhal jaundice. As Dr Guthrie(52) says, the most typical cases are those in which jaundice has been a symptom.

It should be noted that bile in the urine has seldom been reported. In only one case(33) do I find it reported; in that patient it appeared on the second day, the same day as jaundice appeared.

I again repeat that considering the post-mortem changes in the liver, one is surprised that jaundice is not more common.

I will now deal with the Pulse in delayed chloroform poisoning.

In all reported cases where the pulse rate is mentioned, it is noted as being greatly increased 3(Case 3), 8(Case 1). In some cases, shortly after the operation, it has been noted as being rapid, e.g. 112 in one case(76), and also in this case the pulse is said to be of moderate strength. In another case(53), just after operation, the pulse was 132 and small, and in a third[1(Case 8)], it is spoken of as small and rapid.

With the first onset of symptoms, more attention is paid to the pulse, and here we find the rate mentioned as being 116 in one case[3(Case 2)] and in another, uncountable[98(Case 1)]. The pulse rate may be anything between these two extremes, and varies from time to time[3(Case 3)]. When symptoms of delayed chloroform poisoning set in, the pulse always increases in rate as the case progresses, except, of course, where the patient recovers, and has been noted to be, shortly before death, 'running'[2(Case 1)], 'rapid'[2(Case 2)], or even 'uncountable'[75, 85(Case 1)]. In two cases[3(Case 3) 98(Case 3)] the pulse, immediately before death, was 130 and 160 respectively.

Unusual rapidity of the pulse is, then, one of the signs in delayed chloroform poisoning. The pulse rate may be regular[5(Case 2) 8(Case 1)], but is more often irregular[1(Case 2) 2(Case 1)].

The character of the pulse is very constant, it is always weak. As already stated, it may be of moderate strength(76), but is variously described as 'feeble'2(Case 1), 'weak'98(Case 1), 'thready' 2(Case 3), 'small'53, almost imperceptible36, and imperceptible13. In one case1(Case 2) the pulse is said to have been 'intermittent'.

The great characteristic is increasing feebleness, which follows what I have already said, that death may occur from increasing cardiac weakness 44(Case 1).

It is convenient at this point to make a short note on the condition of the blood. Little has been done in this respect in delayed chloroform poisoning. In Bevan & Favill's(54) case, mention is made of the degree of leucocytosis which on the first day amounted to 12,800, on the third day to 15,200 and on the fourth day to 14,800, and I quite agree with them in saying it is 'evidently not specially significant'. The above case contained a gangrenous mass in the abdomen.

The reaction of the blood, noted by various observers, is confusing and leads to nothing definite. In speaking of Diabetes Mellitus, an allied condition to delayed chloroform poisoning, Spriggs(102)

states that the alkalinity was diminished. The blood never becomes acid. In Bevan & Favill's case above mentioned, the blood before death and after death was sterile.

I have already mentioned the effect on the viscosity and specific gravity of the blood, and also the effect on the neuromuscular mechanism of the blood vessels of the bowel and kidney during chloroform narcosis in a previous section (p.33). In the same section (p.36) I have quoted experimental results on the effect on the blood pressure during and after chloroform anaesthesia.

I will now proceed to deal with the Respiratory phenomena.

I find the first note on the respiration is made five hours after operation in a case that proved fatal in twelve hours[5](Case 1). It is here noted that a smell of acetone appeared in the breath. We may take it, seeing that no note on the respiration has been made at earlier periods in the progress of the cases, there was nothing noteworthy. As in the case of the other symptoms, changes in respiration may be noticed at any time from this onwards, according more particularly to the rapidity of other suspicious signs, as slight changes in

respiration alone would not put the surgeon on the qui vive for delayed chloroform poisoning.

In another case that succumbed in twelve hours [1](Case 6), no mention of respiration is made. In one case that proved fatal in twenty hours[1](Case 7) the respiration is noted as normal at the end of nine hours.

From what I have said, we need expect no change in the respiratory rate or rhythm to occur, and we will also not find any evidence of acetone in the breath, prior to at least five hours after operation. The actual time when any marked change is noticed in the respiration is seldom noted more precisely than on a certain day after the operation. In one case[(9)] which terminated fatally in seventeen hours, the respirations throughout were free and regular. This is the exception rather than the rule. Sooner or later, in every case of delayed chloroform poisoning, more or less marked changes in respiration are noticed. Any time after five hours, various changes may be exhibited. In one case[2](Case 2), no change was seen until half-an-hour before death.

The usual differences from the normal respiratory cycle to be noticed are, firstly, irregularity of the rhythm, and this is generally accompanied by shallow breathing[1](Case 1). The rate at this time

may or may not be increased. The 'shallowness' of the respiratory movement is sometimes more noticeable than the irregularity. Secondly, the rate from this time may quickly become rapid(22) and the shallow movement replaced by deep inspirations 3(Case 2). Thirdly, this rapid, deep and irregular respiratory movement is replaced, in many cases 1(Case 1), 2(Case 2), 3(Case 3) by sighing and moaning, and this in turn may rapidly give way to stertor(74). On the near approach of death, respiration follows no one type; it may be loud and rapid 3(Case 2), rapid, deep and laboured2(Case 1), sighing2(Case 2), much slower5(Case 1) than before, stertorous(74), or give place to what we term 'air hunger'. In one case just before death the patient was 'panting'(76). In several of my cases(34), 70(Cases 2 & 3), the respiration has ended in the Cheyne-stokes type.

Acetone may be noticed in the breath any time from five hours to shortly before the fatal termination. In one case it appeared ten hours after operation85(Case 1), in another the morning after 109(Case 2), in several cases(76), 109(Case 3) on the third day, one of these proving fatal in eight days and the other recovering. In the case that proved fatal the smell of acetone was much more

distinct on the fourth day.

I can find no mention in any case to the effect that acetone having once appeared ever disappeared, and that is what one expects. In another case 2(Case 1) acetone appeared for the first time five hours before death.

I will now deal with the Temperature.

The temperature just after operation is not of much moment as far as delayed chloroform poisoning is concerned. This fact coincides with all the other symptoms in that, immediately after the anaesthetic, there is a 'lull', in cases uncomplicated by diseases known to intensify the condition, of from eight hours to seven days. It is unnecessary to mention all reported temperatures, as all show the same tendency, that is, a gradual rise(37) towards the fatal termination. Some observers report a normal or subnormal temperature throughout3(Case 2); this is the exception. The temperature may vary from normal2(Case 2), or 99°(39) to 107° at death 3(Case 4).

As I have said, in very many cases the temperature rises as the disease progresses. Guthrie(52) says that pyrexia is uncommon; with that I cannot agree, from the cases I have collected. In many of

my cases the temperature is not noted at all, a few are noted as normal, and the rest exhibit various degrees of pyrexia, from 99°(39) to 107°3(Case 4).

Having dealt with all the common symptoms of delayed chloroform poisoning, there remain still one or two signs and symptoms to be shortly mentioned.

I will refer shortly to the state of the pupils in delayed chloroform poisoning.

Guthrie(52) mentions that the pupils are often dilated and may be unequal; with that I fully agree. In the first case where the pupils are mentioned 1(Case 8), I find they are noted as unequal, but whether dilated or contracted, the report does not say. I find the same note in another case[109(Case 1)] In three cases the pupils are noted as dilated and equal[5(Case 2), 53, 76]. In two other cases[2(Case 3)] (74), the pupils were contracted shortly before death.

While speaking of the eye, I may mention here that strabismus has been noted in one case[109(Case 1)].

Oedema has also been noted in delayed chloroform poisoning. One case(76) showed marked anasarca and oedema of lower limbs, trunk and face two days before death, and this condition continued till death. Another[1(Case 8)] showed well marked oedema of the abdomen.

But for these two cases I can find no other mention made of oedema. This sign points to a weakened condition of the heart and kidneys, as well as the liver.

The urinary phenomena I will deal with later (p.107).

Head retraction has been noted in more than one case[109(Case 1)]; in the case I mention, strabismus was also present.

Cold sweats have also been reported[1(Case 7)] shortly before death.

To one who is not fully alive to the condition known as Delayed Chloroform Poisoning, the great resemblance of some of the symptoms to Intestinal Obstruction is very close. In fact, one case[30(Case 1)] was anaesthetised a second time and operated upon, the surgeon feeling certain that intestinal obstruction was present. Needless to say the patient succumbed, the second administration helping to bring about the fatal result.

PERSONAL OBSERVATIONS.

I will now proceed to describe the symptoms which presented themselves in two cases under my care in the Queen's Hospital for Children, London, during 1909.

The first patient, a girl Ethel J., aged 5½ years, was found to be suffering from enlarged tonsils and adenoids. She lived some distance from town, so we decided to admit her to the wards, instead of operating upon her as an out-patient.

The patient was received into the ward the day before operation. The usual preparation for such cases was employed, viz., light diet the day before operation, castor oil at night and an enema in the morning, a little milk at 7 a.m. and again at 11 a.m.

The operation was performed on August 23rd, 1909, at 4.45 p.m. Chloroform was the anaesthetic used, the patient receiving a drachm and a half. She was under the influence of the anaesthetic for ten minutes.

She was returned to bed after the operation, and nothing amiss was noted. She vomited six times on recovering from the effects of the chloroform. No suspicious symptoms were noted during the evening and the patient fell asleep about 8 p.m.

About 1 a.m. she awoke suddenly and seemed fretful. At 2 a.m. she vomited a 'brown' material like altered blood. This of course was possibly due to her swallowing some blood which had trickled down the back of her nasopharynx. She continued to vomit at intervals of a quarter of an hour. The vomited matter for the most part was clear, with flakes of greyish material scattered throughout. She vomited thus three times, and on the last occasion the vomit was again brown and resembled more closely 'coffee ground' material.

I was sent for at 6 a.m., as the patient looked so very ill. She was lying on her back, with a malar flush on each cheek, the eyes were somewhat sunken, and she frequently tossed her arms about.

As I watched her, the restlessness increased, and she persisted in trying to rise up.

There was no jaundice present.

The smell of acetone was quite distinct in her breath, and that fact gave me an inkling as to what was the matter. I asked the nurse to keep a careful report of her condition.

During the morning I was informed the patient had been very restless, and the respirations had been sighing in character. No urine had been passed since the operation.

At 9 a.m. I again saw the patient and she looked so ill that I immediately wired for her parents to come. She was still very restless, the respirations were still sighing, and she looked extremely collapsed. No effort was made to answer any questions put to the patient.

The temperature was 99° and the pulse 160 per minute and feeble.

Infusion with one pint of normal saline was performed, and the patient for an hour seemed better. Soda bicarbonate grs.15 every four hours was ordered, and a rectal injection of a solution of the same drug administered also every four hours.

All those who saw her regarded her condition as extremely grave, and we all thought she would succumb.

At 11 a.m. the patient was again infused and a drachm of brandy administered. Again she seemed to pick up for a time.

At 12 noon she had a motion. The pupils were equal, of medium size, and reacted to light. There remained a strong smell of acetone in the breath. The above condition remained practically the same during the rest of the day.

When I saw the patient at 8 p.m. she was apathetic. She was not difficult to rouse, though she

would answer no questions and took no notice of her parents. The breath still smelt strongly of acetone, and the respirations were now rapid and shallow. The patient was very dark under the eyes and looked as though she had suffered from a severe illness. The temperature was still 99°, but the pulse was 150 and slightly better.

Shortly after 8 p.m. the patient began to retch, but did not vomit. During the evening she passed a small amount of urine.

About 10 p.m. she dropped off to sleep for two hours, and on waking she was much quieter but there was still a marked odour of acetone in the breath. The patient had a fairly quiet night, and next morning seemed decidedly better.

From this point she made an uneventful recovery and was discharged on August 30th.

The fact that struck me most about this case was how extremely ill she seemed. Vomiting was not a pronounced feature in the case. Restlessness was marked, but collapse was the most prominent symptom. Thirst was also very troublesome.

Although not exhibiting all the classical signs and symptoms of delayed chloroform poisoning, I consider the above case to be due to the toxic after effects of chloroform, and having once seen a case

it is not likely that one will overlook this condition in the future.

This case also proves my contention that the sooner the symptoms of intoxication commence, the earlier do they terminate, either in recovery or death. I do not think that any treatment had any effect upon the recovery in my case. In my opinion the intoxication was of a mild degree.

The findings in the urine in this case will be dealt with in the next section (p. 136).

One might note in connection with the above case that the operation was performed the day after admission, a proceeding which Guthrie does not recommend. The last time food was administered was five and three quarter hours before operation. Hunter(79) objects to this and thinks if cases had a nourishing, well sweetened meal two to three hours before operation, the toxic after effects of chloroform might be entirely avoided. The patient was evidently healthy in every way before operation, and on qualitative examination of the urine, neither acetone nor albumen was found. The patient did not suffer from rickets, and on enquiry afterwards, there had been no previous 'bilious' attacks.

In the operation itself, no chemical agents were used. The patient did not seem excessively

frightened or home sick prior to operation. There was no suggestion of ptomaine poisoning, and I think meningitis may be excluded. Patients anaesthetised from the same bottle of chloroform and by the same anaesthetist on the same day, developed none of the symptoms exhibited in this case. There was very little blood lost and no septic focus was discovered during patient's stay in hospital. Thus we exclude practically all the causes suggested as giving rise to the symptoms apart from the toxic after effects of the chloroform.

My second case is also that of a girl, Martha M., aged 8 years. This patient suffered from extensive Tuberculous Adenitis in the neck.

She was admitted to hospital on September 2nd, 1909. She was a well nourished child, rather tall for her years. She was particularly lively prior to operation, and such a thing as home-sickness or fright never for a moment suggested itself. Patient took her food well, and had no sickness during her stay in hospital prior to operation.

On the night of September 6th, the child had a bath, the part was prepared for operation, soap and water and ether were used to cleanse the skin, and a soak of 1-3000 perchloride put on over night.

This was changed in the early morning for another similar soak. Castor oil was administered and an enema given, as in the previous case. Milk was given at 7 a.m. and again at 11 a.m. on the day of operation.

At 3 p.m. on September 7th, chloroform was administered. Two and a half drachms of chloroform was used and the patient was under the anaesthetic for three quarters of an hour. There was no trouble during the administration.

The patient on recovering from the anaesthetic vomited three times. She was a little restless during the night, but caused the nurses no anxiety.

Next day, September 8th, patient was rather drowsy, and wished to be left alone. Towards evening she again became restless, but there was nothing to suggest the subject of this paper. The restlessness, however, increased as the night advanced, and at midnight - that is thirty-three hours after the operation - she had what the nurse called a 'brown vomit'. The restlessness increased, and the patient began to wear an anxious expression. After this initial vomit, there was some 'retching', but nothing was brought up.

At 3 a.m. the patient again vomited, and this vomit was typically 'coffee ground'. She looked so

ill that I was sent for. I found the patient lying flat on her back, with eyes widely open, and an anxious frightened look on her face. The temperature was 99.8°, pulse 130, and respirations 28 and deeper than normal. Both pupils were semi-dilated and reacted to light. The skin was cold and clammy. There was no pain complained of in the wound, or over the liver region. Patient had not had her bowels moved since the operation, although she had passed urine. Soda Bicarbonate ℥ij in two ounces of water was begun four hourly. Between this and 7 a.m. the patient vomited three times. On the first two occasions the vomit was clear, frothy and slightly bile stained; on the third occasion, however, it reverted to the classical 'coffee ground' type.

At 7 a.m. I again saw the patient. She was now pale, the eyes half closed and sunken, and she seemed only semi-conscious. The pupils were smaller than at 3 a.m. and still reacted to light. The temperature was now 100.2°, pulse 140, the respirations 33, and shallow. No pain was complained of, and the patient did not resist being examined. Dextrose was ordered, twenty grains every four hours, alternating with the soda bicarbonate.

At 10 a.m. the patient was in much the same state, but much more difficult to arouse. There

had been no vomiting since 7 a.m., but she had retched several times. The pulse had increased to 150 per minute, and she was evidently weaker. The breath for the first time now smelt of acetone. On passing a catheter, six ounces of urine were withdrawn for examination.

At 1 p.m. the patient was practically comatosed. The temperature was 100°, pulse 150 but very feeble and irregular. The respirations were 30 per minute and of the 'air hunger' type. Jaundice was absent throughout. The pupils were contracted and responded feebly to light. Cyanosis was absent. Two drachms of brandy were given, but seemed to have no effect. The patient became gradually weaker, and died comatosed at 3 p.m., forty-eight hours after operation and fifteen hours after the first 'brown vomit'. The temperature just prior to death was 100.6°, the pulse 150, and the respirations 30, very shallow, and smelt strongly of acetone.

The urinary phenomena will be discussed elsewhere (p. 136).

At the post-mortem, the liver was intensely fatty. There was a small septic focus in the wound, but certainly to my mind not sufficient to cause the symptoms and death. The pathologist, who was very sceptical about the condition of delayed chloroform

poisoning, attributed the post-mortem findings to sepsis, but I am strongly of the opinion that the case was one of undoubted toxic poisoning due to the chloroform. The only chemical agent used in this case was the 1-3000 perchloride soak. The small septic focus in the neck, where there was not more than half a drachm of pus, was the only condition which even remotely may have caused the symptoms and death.

THE URINE

in

DELAYED CHLOROFORM POISONING

with the results of the
Examination of Thirty Cases.

THE URINE

in

DELAYED CHLOROFORM POISONING.

The study of the urine in delayed chloroform poisoning is exceedingly interesting.

As long ago as 1857, Petters[10] observed that the output of urine did not diminish in quantity towards the end of chloroform anaesthesia, and that it contained a normal amount of solids. He also noted the presence of acetone after anaesthesia.

Nothnagel[11], in 1866, as the results of experiments on rabbits, showed that when chloroform was injected subcutaneously, fatty degeneration of the kidneys was produced, and that urine expressed from the bladder, four hours after the injection, contained red blood corpuscles and fibrinous casts.

Ungar & Junkers[13], in 1883, produced fatty degeneration of the kidneys in dogs, after repeated administrations of chloroform, by inhalation.

Kast[15], in 1888, showed that after the subcutaneous injection of chloroform, chlorine was excreted in the urine in an increased amount.

Zeller, quoted by Stiles & McDonald, found the same to be the case after administration by the mouth.

Guthrie[1], in 1894, argued that chloroform and shock aggravated a condition which was already present. Those loaded the system with toxic alkaloids, which the kidneys, in the case of a girl of 7 who had pre-existing albuminuria, and also in the case of a boy whose urine contained phosphates and pus before anaesthesia, were unable to eliminate. Since the morbid condition of the kidneys has been fully realised, similar observations have been made in a great many post-mortems after delayed chloroform poisoning.

Stiles & M'Donald[8] point out that kidneys which to the naked eye show no gross lesion, microscopically, exhibit manifest pathological changes.

Guthrie[1], in 1894, was the first who paid special attention to the urine in fatal cases of delayed chloroform poisoning in the human subject. He found albumen present in some of his cases. In one case[1(Case 1)] he remarks that the sulphates were normal; in another[1(Case 2)] that the urine was not smoky. In some of the cases where carbolic acid was used as an antiseptic, carboluria was present.

Becker[6], in 1895, pointed out that the amount of acetone in the urine was increased after anaesthesia, and especially after chloroform. He also pointed out that children are more susceptible than

adults; and existing acetonuria was greatly aggravated. The duration of narcosis seemed of no importance. Luzatti[23] found, however, that the acetonuria was in proportion to the amount of chloroform inhaled.

Nachod[24], in the same year, found sero-albumin, nucleo-albumin and casts. He never found glucose in the urine after chloroform. He reports, however, a case of a patient with sugar in his urine, some time previous to operation, becoming comatosed and glycosuria reappearing after the operation. Nachod also found acetonuria in thirty out of fifty-seven cases after chloroform, and in fourteen cases aceto-acetic acid occurred along with the acetone. Bile pigments were never found, but urobilin was frequently demonstrated, being usually first seen about the second or third day and continuing until the fourth day. Nachod concludes that the metabolic disturbances leading to the altered urinary excretion are directly due to the action of the chloroform.

Hill Abram[25], in 1896, found acetonuria present in 64 per cent. of cases after anaesthesia, and holds that the quantity of chloroform inhaled bears no relation to the degree of acetonuria. He again, in 1908, repeats this[78].

Other observers report albuminuria, haematuria

and casts.

Grube[30], in 1898, found an increased excretion of uric acid, chlorides, phosphates and sulphates.

Zachrissen[31], after a careful examination of the urine from one hundred cases, concludes:

1. Slight transient albumen was present in many cases.
2. Its frequency was in proportion to the length of the operation.
3. Casts were often seen.
4. If previous albuminuria and casts were present, the condition is aggravated after anaesthesia.

Other observers agree with these conclusions.

It is worthy of note that one observer[29] has frequently seen bile-pigments in the urine after chloroform anaesthesia, and two different cases are published[33, 2(Case 2)] in which bile was present in the urine.

Prior to the publication of Brewer's[45] paper, in 1902, most stress seems to have been laid upon the occurrence of albumen and casts in the urine after anaesthesia. This fact would indicate that delayed chloroform poisoning was not generally regarded as an acid intoxication.

Subsequent to Brewer's contribution, attention

has been concentrated upon the occurrence of acetone, diacetic and B-oxybutyric acids in the urine. The recognition of this fact has led to a closer study of the cause of acid intoxications as a whole.

Among the earlier observers who paid special attention to the presence of acetone in the urine in cases of acid intoxication following anaesthesia may be mentioned Brewer[45], Bracket, Stone & Lowe[48], Guthrie[52], Kelly[58] and Hubbard[59].

In 1905, Offergeld[115] published the results of his 'Experimental Beitrag toxischen Wirkung des Chloroformes auf die Nieren', in which he proved that fatty degeneration did not occur in the kidney if the renal artery to that organ was ligatured. But it occurred most rapidly if the ureter was tied.

The most valuable contribution to our knowledge of the urine in delayed chloroform poisoning was published by Beesly[5] in 1906. In the same year an interesting paper[63] on 'Anaesthetics and Renal Activity', by Thompson, was published.

In January 1908, Hill Abram contributed a paper on 'Acetonuria and General Anaesthesia'[78]. In the same winter, Guthrie's House Physician examined the urine in a large number of cases after anaesthesia, and his results were published during that year.

Wallace & Gillespie[87], after treating some patients before operations with soda bicarbonate and others with glucose, examined the urines for acetone. Their results are published elsewhere (p.214).

Having given this brief outline of the work done on the urine in delayed chloroform poisoning, I will now deal shortly with the urinary symptoms during the progress of the case. In only a small number of the cases do I find mention made of any urinary symptoms. We may therefore take it for granted that such symptoms were not prominent.

I find that in three of my cases, these special symptoms are mentioned. In one case[36] there was complete anuria before death, which took place on the second day; another case[108] also showed complete anuria on the second day, death occurring sixty-eight hours after the administration of the anaesthetic. The third case[8](Case 1), which proved fatal on the fourth day, showed suppression of urine. From these few facts it will be seen that anuria, or suppression of urine, is an ominous sign when occurring in delayed chloroform poisoning. No case has been reported in which suppression of urine began immediately after the operation, but according to the severity of the case, this phenomenon may set in

any time after the first twenty-four hours or so.

I will now deal with the action of chloroform on the kidney.

Thompson[63] has contributed a valuable paper on this subject. His experiments were performed on dogs.

THE EXCRETION OF URINE DURING CHLOROFORM NARCOSIS.

Thompson mentions Kemp and Buxton & Levy, who proved that the outflow of urine from the ureters in no way diminished until the general circulation became markedly affected. Thompson himself found that the volume of urine was affected in two ways during chloroform narcosis:

1. In the early stages, when the anaesthesia is light, the quantity is increased.
2. During full anaesthesia, it is always diminished and may be suppressed.

From this we see that during the period of deep anaesthesia, the chloroform with all its toxic properties is being taken into the system, and for a time at least, there is no adequate outlet for these toxines. We find, however, some hours after the administration has ceased, that the urine is invari-

ably increased in amount, and may reach to even four times the normal amount(63).

Thompson has also found that while the urine is diminished in quantity, it is also less concentrated.

It has also been proved that in prolonged narcosis with marked diminution of urine volume, there is a considerable exudation of leucocytes in the renal tubules, which subsequently escape with the urine. This may be due to more or less stasis in the glomerular vessels. The above experiments show us why many observers have noted albumen, and sometimes also the presence of blood in the urine in delayed chloroform poisoning.

NITROGEN EXCRETION DURING CHLOROFORM NARCOSIS.

Eulenburg-Strübing, quoted by Thompson, found a diminution of nitrogen metabolism. This coincides with Thompson's experience, viz., that as well as the amount of urine being diminished, the amount of nitrogen excreted is also diminished, even more so than the quantity of urine.

Salkowski, Strassman and Kast & Mester, quoted by Thompson, have all noted an increase of the excretion of nitrogen. In the minority of Thompson's experiments, the urine was increased in quantity, and also the nitrogen, but the latter increase was

much less in proportion to the amount of urine. He infers that not only does chloroform affect the blood flow through the glomerulus, but also the secretion of the nitrogenous solids through the tubules, which supports Bowman's theory.

THE EXCRETION OF CHLORIDES DURING CHLOROFORM NARCOSIS.

Zweifel, quoted by Thompson, found unaltered chloroform in the urine. Kast, quoted by Thompson, in 1887, found that the excess of chlorine which occurs after chloroform anaesthesia is excreted as organic chlorides. Thompson[63] found that the quantity of chlorides was much increased, both during and after chloroform narcosis.

THE BLOOD PRESSURE DURING CHLOROFORM NARCOSIS.

Looking at Thompson's tracings, we find a marked fall of blood pressure during the whole time of the administration, which does not rise again to normal for some hours after the narcosis has ceased. The outflow of urine does not correspond at all closely with the blood pressure, as complete suppression may take place with a comparatively high blood pressure.

Thompson, with many other observers previously

mentioned, shows that albumen, previously absent, frequently appears in the urine after chloroform narcosis. This coincides with what has already been stated, viz., existing albuminuria is aggravated. It is also mentioned in the above paper that reducing substances are invariably increased. This is what I often myself found when testing urines after chloroform anaesthesia, and was much puzzled as I was quite unable to arrive at the nature of these reducing substances.

Interesting as these facts are, we have had no further light upon the presence in the urine of acetone and diacetic acid, which, at some time or another in the course of a case of delayed chloroform poisoning, make themselves manifest when looked for.

I will now deal with the presence of these bodies, acetone and diacetic acid, in the urine.

ACETONURIA.

I have already mentioned Petters[10] and Becker[6] as pointing out the marked increase of acetone in the urine after chloroform anaesthesia.

The most valuable recent paper on this subject is by Lewis Beesly[5]. In healthy urine, acetone was generally found to be present, though not in large enough quantity to give a colour test, but its

presence was ascertained when a quantitative examination was made. In some cases as large a quantity of acetone as 25.0 milligrammes were passed in every 50 c.c. of urine, and yet no symptoms were present. Beesly recognises two conditions prior to an anaesthetic being administered, (a) Chronic acetonuria, where the production and excretion of acetone is constantly proceeding; and (b) Acute acetonuria, which develops most commonly during the onset of acute infective conditions.

I will first of all refer to cases in which there was no acetone present in the urine, or only the faintest trace of it, before anaesthesia. The amount of chloroform used has no direct parallel in the amount of acetone excreted in the urine.

As I have already stated, there is a great increase in the amount of urine passed from the end of the administration of chloroform for several hours, longer in some cases than others.

With regard to the amount of acetone excreted, Beesly has shown that the greatest quantity is passed twenty-four hours after the anaesthesia has ceased. From this time the acetone as a rule steadily diminishes in quantity. Various factors, such as constipation, may prevent the elimination of acetone, proving that acetone is excreted by the bowel

and passes off in the foeces. In such cases the acetone curve does not show a steady fall, and the period of acetone excretion is consequently lengthened. In cases where there has been no previous acetonuria, all the acetone may be eliminated by the third day, but with any condition which will hinder this elimination, acetonuria may be found six or even more days after the operation. The amount of acetone excreted in the urine varies greatly in individual cases. Beesly attributes this to idiosyncrasy. We may say that ten milligrammes of acetone per 50 c.c. of urine is a fair average quantity, at the end of twenty-four hours when the excretion is at its highest.

Compared with ether, chloroform does not produce such a severe degree of acetonuria, but on the other hand ether acetonuria is less dangerous. The amount of acetone excretion of which I am now speaking is rarely accompanied by symptoms of delayed chloroform poisoning.

Coming now to cases which Beesly designates as suffering from Chronic Acetonuria, we find several points of difference from the healthy cases we have just considered. Beesly has shown that the greater the amount of existing acetonuria, in these chronic cases, the less marked is the action of the chloro-

form on the amount of acetone already present. After anaesthesia, we find the acme of acetone excretion occurs at the same time - viz. at the end of twenty-four hours - as it does in healthy cases. As can be easily understood, acetone excretion is kept up much longer in these cases, compared to what occurs in previously healthy urine. It is an interesting observation, and helps to prove Beesly's contention that acetone is excreted in the foeces, that whenever a patient has had two motions in the same day, there is a greater drop in the amount of acetone excreted in the urine than when the patient has had only one motion, or none at all. The amount of acetonuria is much greater, in cases of previous chronic acetonuria, after the operation than is found in the previously healthy cases. Beesly remarks that among his cases of chronic acetonuria there were no symptoms of poisoning and no deaths. This fact would point to the organism accommodating itself to the deranged metabolism, and that even though this derangement is intensified to a considerable degree, no symptoms of poisoning occur.

The degree of acetonuria found in these cases where there is a chronic excretion of acetone, if produced suddenly in a previously healthy urine, would almost certainly give rise to symptoms.

From what I have said we have seen that after chloroform anaesthesia, we get acetone rapidly excreted in the urine, reaching its acme in twenty-four hours. We may now ask ourselves, what would happen if the acetone excretion is delayed? does such a thing as delayed acetone excretion occur?

Beesly has shewn that delayed acetone excretion does occur, and that when it does, just as we should expect, symptoms of poisoning shew themselves. In his valuable paper, Beesly reports three such cases 5(Cases 7, 9 & 10). The symptoms are characteristic of delayed chloroform poisoning. These symptoms begin to pass off as soon as the acme of excretion is reached. The fact that delayed acetone excretion does occur explains why, in a number of cases of delayed chloroform poisoning, acetone has not been detected in the urine at all, or only just before death. In many of the cases where no acetone was found in the urine, it was present in the breath, shewing that acetone was in the system.

Beesly does not agree with Bracket, Stone & Lowe(48) in their contention that the amount of acetonuria does not give any indication as to how the case is progressing. He, rightly, points out that it is not actually the amount of acetone that is excreted that is so important, but to know whether

the acme of excretion has or has not been reached.

I now come to Acute Acetonuria occurring before operation, developed during the onset of acute infective conditions, and the effect of chloroform anaesthesia in such cases. As one would suppose, this is a much more serious condition of affairs, as compared with those we have already studied.

The kidneys have already had a sudden strain imposed upon them, and are trying to eliminate the acetone, but when we get a substance introduced into the organism, which at one and the same time is a poison to the kidney tissue and causes an increased amount of acetone to be formed, we cannot be alarmed if the kidneys fail. The same effect is produced if one administration of the anaesthetic is quickly followed by another. As Beesly has shewn, this is exactly what takes place. The amount of acetone which was being excreted before operation, after operation suddenly falls. The acetone must therefore be retained in the system, the kidneys being unable to eliminate it. We may now expect symptoms of poisoning, and that is exactly what happens.

Beesly has clearly demonstrated this point by two cases[5](Cases 13 &14), the infective condition in one being acute appendicitis of three days' duration and in the other, acute osteomyelitis of about seven

days' history. In both these cases the amount of acetone excretion fell immediately after the operation, no subsequent rise being manifest prior to death, which took place twenty-four hours after operation in each case. Kelly(58) has also shewn the frequency of acetonuria in acute appendicitis after operation.

Beesly now goes on to compare the effect of ether anaesthesia with chloroform anaesthesia in acute infective conditions. The fact that acute acetonuria occurs in acute infective conditions is extremely interesting, especially from the point of view of chloroform anaesthesia.

I have already dealt with Hubbard's(59) conclusions from his examination of one hundred and twenty-five urines after anaesthesia (p. 32).

Sick(56) describes a case of haematemesis in appendicitis and considers the condition due to the action of toxins rather than to actual bacterial invasion. Haematemesis, as we have seen, is a prominent symptom of delayed chloroform poisoning.

Bevan & Favill(54) report that in their case the urine was highly concentrated two days after operation. For forty-eight hours before death, no diacetic acid or acetone was present in the urine, but acetone was present in the breath.

Beesly has gone so carefully into this subject of acetonuria following anaesthesia, that the observations of other workers need not be detailed.

By employing only qualitative tests for acetone, different observers have found that the number of urines which give a positive reaction to the test vary. Becker(6) found 66% of his cases after anaesthesia developed acetonuria; Hill Abram(78) 64%; Dr Blue, in the Roosevelt Hospital, at the instance of Brewer(45), found that in only seven cases, out of thirty-three urines tested, was acetone present in a pathological amount. From my own experience I do not place much reliance on these qualitative tests, and unless one has considerable practice, these tests are apt to give an erroneous impression.

It has been suggested that the varying results of different observers may be due to the employment of different tests. This may be so, but I am inclined to think that those who have most experience with the various tests obtain the more reliable results.

The presence of acetone in the urine gives us a fairly good index to the degree of acid intoxication. The presence of acetonuria, however, is an unsafe guide, as is apparent when we consider the power which the body possesses of neutralising acids

before their excretion. There is another substance, however, which may also give us an idea as to the amount of pathological acid in the urine, viz. Ammonia.

Ammonia is a normal constituent of the urine. In health, less than 5% of the total nitrogen excreted by the urine exists as ammonia. In severe cases of diabetes, eight to ten grammes of ammonia may be excreted in twenty-four hours, which means the neutralisation of over fifty grammes of B-oxybutyric acid. Thus the amount of ammonia in the urine in delayed chloroform poisoning will give us a rough index to the amount of acid intoxication present. The amount of ammonia, however, is by no means a reliable guide, as it has been shown that a considerable fall in the excretion of oxybutyric acid was not accompanied by so rapid a fall of ammonia. This discrepancy is due to the fact that the fixed bases of the blood and tissues are also called upon to neutralise acids produced in the body; especially is this so in diabetes, where the amount of potassium, sodium, calcium and magnesium in the urine is considerably in excess of the normal.

An extremely interesting observation is made by Rachford & Crane[116]. It is to this effect, that while the alkalies of the blood are not seriously

drawn upon for the neutralisation of acids until all the available supply of ammonia is exhausted, the salts of sodium and potassium, when introduced into the body as medicines, are seized upon, in preference to the ammonia, by the acids. They explain the non appearance of toxic symptoms, due to ammonia, in cases of acid intoxication, to the fact that the ammonium ion when combined with an organic acid largely loses its toxicity.

In a few of the cases of delayed chloroform poisoning, where the symptoms have been said to closely resemble those of acute yellow atrophy of the liver, leucine and tyrosine have been found in the urine. Such a case is reported by Bandler(33).

I will now proceed to give the results of my examination of the urines of thirty cases before and after anaesthesia. All the cases are those of children from three to twelve years of age, who were patients in the Queen's Hospital for Children, London, between the beginning of July and the end of November 1909.

The last specimen of urine passed prior to operation was examined in every instance. The urine passed during the twenty-four hours following the operation was also examined.

In fifteen cases (which I will now term series one), that is, one half the total number examined, a specimen of the urine, not a twenty-four hours' specimen, was examined each day for three days.

I did not examine any of the urines of this series for longer than three days, as in no case was any gross departure from the normal found on the third day after operation.

In series one, I paid particular attention to the following points:

1. The duration of the anaesthetic.
2. The presence of acetone in the urine, by qualitative tests only.
3. The power to reduce the Pavy Fehling solution.
4. The presence of albumen.
5. The presence of bile.
6. The microscopic appearances.

In eleven cases (series two), after operation, I had collected the twenty-four hours' specimen of the urine for a period of three days.

In this series I specially noted:

1. The duration of anaesthesia.
2. The nature of the operation.
3. The presence or absence of acetone, by qualitative tests only.

4. The presence or absence of diacetic acid.

5. The presence of albumen.

I omitted here the microscopic examination, as I considered the results obtained in series one were sufficient for my purpose.

In two cases (series three), I again had collected the twenty-four hours' specimen of the urine for a period of three days.

In this series I worked on the lines of Beesly. I confined my examination to acetone alone. I compared the value of the nitro-prusside test with the quantitative estimation.

Finally, I examined, for acetone and diacetic acid, the urines of the two cases whose symptoms I have already described.

I will now treat in detail each of the above series.

SERIES I. - consisting of fifteen cases, being one half of the total number examined.

The presence of acetone in the urine, as indicated by the nitroprusside and iodoform tests.

The urine before anaesthesia.

In no case was acetone found in the urine prior

to operation. The tests were performed carefully, and each urine was tested twice separately.

The urine after anaesthesia.

1. and 2. - Tested for acetone at the end of twenty-four hours, when its excretion is as a rule at its height.

Of my fifteen cases, in only five, or one third of them, was acetone present. Below I give each case whose urine was found to contain acetone. I also give the duration of the anaesthetic.

(1) R.S., male, aet.5½: chloroform anaesthesia 20 minutes.

In this case the nitroprusside test was positive as evidenced by the violet red colouration which appeared on the addition of ammonia to the urine, to which a few drops of a freshly prepared solution of sodium nitroprusside had been added.

The iodoform test for acetone was also positive. This test consists of the addition to the urine of a few drops of a solution of iodine in potassium iodide, then carefully adding a solution of caustic soda till the brown colour disappears; warm gently, and on cooling, iodoform separates out in small golden plates. On examining the deposit with the micro-

scope, iodoform crystals were present in large numbers.

(2) C.H., female, aet.9: chloroform anaesthesia 20 minutes.

A positive reaction both to the nitroprusside and iodoform tests was obtained.

(3) E.H., female, aet.7: chloroform anaesthesia 30 minutes.

The reaction in this case was positive to the nitroprusside test, though not so definite as the previous two cases. Fewer crystals of iodoform were also present than in the previous cases.

(4) L.W., female, aet.10: chloroform anaesthesia 40 minutes.

Both tests in this case were positive.

(5) A.W., female, aet.9: chloroform anaesthesia 45 minutes.

Here also the nitroprusside and iodoform tests were positive.

The duration of the anaesthesia in these five cases was from twenty minutes to forty-five minutes.

Of the ten cases in this series whose urines gave no positive reaction to acetone, the duration

of the anaesthesia was from twenty minutes to forty-five minutes also, thus :-

20	minutes	-	2	Cases
22	"	-	2	"
25	"	-	1	"
30	"	-	2	"
33	"	-	1	"
40	"	-	1	"
45	"	-	1	"

From these periods I cannot agree with some observers, chiefly the earlier workers, that the greater length of the anaesthesia, the greater the likelihood of acetonuria.

My figures as regards the number of patients whose urine I found to contain acetone fall considerably short of those of previous workers on this subject. I cannot definitely say why this should be, but I will show later that the nitroprusside test especially is not as delicate a one as is perhaps thought.

In only one case was the presence of acetone detected in the urine at the end of forty-eight hours. This was the case of L.W., female, aet.10, where chloroform anaesthesia had lasted forty minutes. No acetone was found in this patient's urine at the end of seventy-two hours.

3. - The power to reduce the Pavy Fehling Solution.

Perhaps this is the most remarkable observation in this series. In every case after anaesthesia the Pavy Fehling solution was reduced. This reduction occurred at once with urine collected at the end of twenty-four hours after anaesthesia. At the end of forty-eight hours, this reduction was still produced in every case, though in some only after standing for some minutes. At the end of seventy-two hours, none of the urines reduced the solution. Where acetonuria was indicated by the qualitative tests, the above reduction occurred more quickly and decidedly than in those where acetone was absent. I am quite at a loss as to the nature of these reducing substances. This reducing power of the urine has been recognised for some time, but I have found no definite statement as to what these bodies are. They are generally referred to as 'other reducing substances'.

4. - The presence of albumen after anaesthesia.

In only one case was there a trace of albumen after anaesthesia, and that patient had albuminuria, prior to operation. The amount of albumen was not increased by the administration of the anaesthetic.

In my opinion it is only when larger amounts of the anaesthetic are required than those with which I am dealing that we may possibly get albuminuria produced. In such cases, should the pre-existing amount of albumen be large, the anaesthetic will exaggerate the condition for a shorter or longer period, otherwise the presence of albumen, with one or two exceptions, need not be a deterrent to the giving of an anaesthetic.

5. - The presence of bile in the urine after anaesthesia.

In none of my cases did the naked eye appearance of the urine suggest the presence of bile. In no case did the nitric acid test reveal its presence. I am of opinion that a profound degree of toxaemia must exist before bile is detected in the urine. In those cases of biliurin, the post-mortem examination has revealed extensive central necrosis of the liver cells. In such a case, jaundice is a marked symptom, but the fact that jaundice is present does not necessarily mean that bile will be found in the urine.

6. - The microscopic appearances.

The most constant feature found in the examination, microscopically, at the end of twenty-four hours was the presence of epithelial cells. These cells were found in fourteen cases of the fifteen examined, but, except in two cases, they were not present in large quantities. In each of these fourteen cases bladder epithelial cells were seen; and these constituted, in eleven of the cases, practically the whole of the epithelial cells. In three cases, besides the presence of bladder epithelium, renal epithelial cells were also manifest, and in one case - that of C.H., female, aet.9 - these were in a comparatively large amount. At the end of forty-eight hours, the number of bladder epithelial cells had decreased greatly. In only one of the three cases where cells from the kidney were found, was any of these cells present, and then only very few. At the end of seventy-two hours, the microscope showed only a few cells from the bladder wall, and no renal epithelium was seen.

Ranking next to epithelial cells in point of frequency must be mentioned casts.

In seven cases casts were present. Hyaline and granular casts alone were found. These were few in number, thin and short. The granular casts per-

sisted for a longer time after operation than did the hyaline casts. The latter were absent at the end of forty-eight hours. I attribute no special significance to these casts.

Next in importance come red blood corpuscles. These were seen in four of my cases, on the first examination after anaesthesia. In all but one case they were very few in number. In this latter case, ten red blood corpuscles were made out in a single field of the high power. In each case these red blood corpuscles were absent at the end of forty-eight hours after operation.

Coming now to crystals, I found oxalate, phosphate and uric acid crystals present in several cases, thus:-

Oxalates in large numbers in three cases.

Phosphates in small numbers in three cases.

Uric acid crystals in comparatively large numbers in three cases,

making nine cases whose urines contained crystals. No phosphatic crystals were seen at the end of forty-eight hours. A few oxalates were seen at the end of forty-eight hours, but none at the end of seventy-two hours. Uric acid crystals persisted for forty-eight hours, none being seen after that time.

The above remarks record everything I found on microscopic examination of the urine; from them I conclude :- that chloroform is an irritant to the kidneys, but its effects, in comparatively small doses by inhalation, last no longer than forty-eight hours.

SERIES II. - (11 cases)

Included two cases where a septic element was present and nine cases in which no such element was found. I mention this because it has been already proved that septic cases are more liable to acetonuria after anaesthesia.

The septic focus in the above two cases took the form of an appendix abscess and a mastoid abscess respectively. In both these cases acetone was found to be present in the urine at the end of twenty four hours after operation. In addition to acetone, diacetic acid, as detected by the ferric chloride test, was also present. At the end of forty-eight hours both cases showed acetonuria, but the diacetic acid had disappeared. At the end of seventy-two hours, no acetone or diacetic acid was found in either urine.

In my clean cases, which included herniae (four

cases), excision of tuberculous knee (1 case), congenital hip (1 case), tonsils and adenoids (1 case), and glands in the neck (2 cases), four gave the acetone reaction to both the nitroprusside and iodoform tests at the end of twenty-four hours. I detected diacetic acid in only two of these cases, viz., in one case of inguinal hernia and in one case of glands in the neck. These two cases showed acetonuria at the end of forty-eight hours, but diacetic acid was absent. Acetone was not present in the other two cases, where it was found, at the end of forty-eight hours.

The remaining five cases had no acetonuria as far as I was able to find.

I again add that the duration of the anaesthesia seemed to have no special action on the production of more or less acetone in the urine.

Cases which are septic are more prone of acetonuria after an anaesthetic than are 'clean' cases, and therefore more liable to suffer from the after toxic effects produced by it.

SERIES III. - (2 Cases)

In these two cases, I examined the urine by the nitroprusside qualitative test, and also determined

the amount of acetone present by quantitative estimation.

The quantitative estimation was performed by Hoppe-Seyler's method, and is as follows :-

1. Collect first of all a twenty-four hours' specimen of the urine.

2. Take 50 c.c. of this, and if alkaline, acidify by a drop or two of acetic acid.

3. Distil over slowly, taking two hours to do this, until you have obtained 45 c.c.; collect this in a graduated vessel. To this distillate add a pinch of calcium carbonate, and 30 c.c. of cold water.

4. Distil again for half-an-hour, and add a few drops of a 1 in 7 solution of sulphuric acid.

5. Again distil, and collect the distillate in a graduated vessel. This is now ready for estimation.

(a) Now run in from a burette, a known quantity of a decinormal iodine solution, until a brown colour is obtained.

(b) To this, add sufficient nitric acid free caustic soda to at once discharge the brown colour.

(c) Shake up the resulting mixture for half-a-minute, and let it stand then for five minutes.

(d) Add now enough strong hydrochloric acid to make the solution distinctly acid and till the brown colour just reappears.

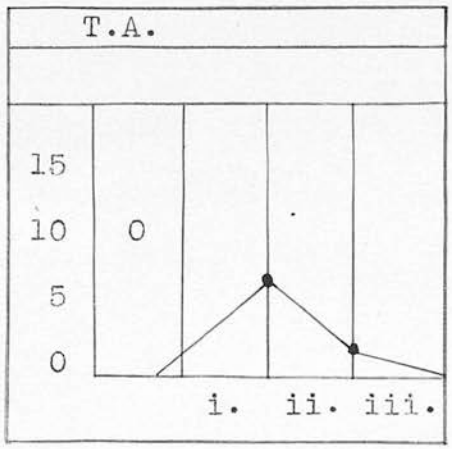
(e) Run in now a decinormal solution of sodium thiosulphate, along with a solution of starch to indicate when all the iodine has been neutralised. The amount of sodium thiosulphate used will correspond to the amount of superfluous iodine which has not united with the acetone to form iodoform. It is thus easy to estimate how much iodine has united with the acetone present. One cubic centimetre of decinormal iodine solution = 0·967 milligrams of acetone.

Results:

Case 1. T.A., aet.6, glands in neck: chloroform anaesthesia 33 minutes.

Prior to operation I failed to detect acetone by the nitroprusside test, and also on quantitative estimation, in 50 c.c. of the twenty-four hours' specimen. The urine was collected as before for the twenty-four hours immediately following the operation.

The quantitative estimation is graphically represented below. I have followed Beesly's diagramatic method of illustration.



The numbers at the side represent in milligrams the amount of acetone in every 50 c.c. of urine. The Roman numerals refer to the days after operation. O represents operation.

Thus eight milligrams of acetone were present in each 50 c.c. of urine passed during the twenty-four hours immediately following the operation.

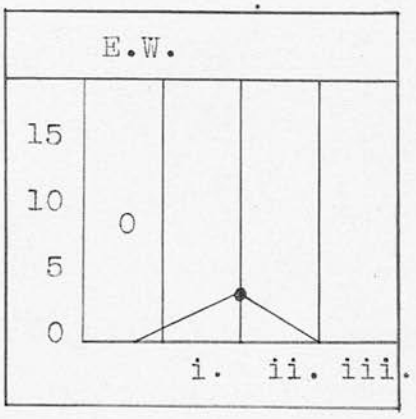
The nitroprusside test gave a positive reaction to acetone.

During the second period of twenty-four hours after operation, two milligrams of acetone were excreted per 50 c.c. of urine. The nitroprusside test failed to detect this amount, no reaction being obtained.

During the third period of twenty-four hours, acetone was found both by qualitative test and quantitative estimation to be absent.

Case II. E.W., aet.5, inguinal hernia: chloroform anaesthesia 22 minutes.

Prior to operation, acetonuria was absent. The subsequent amount of acetone found on quantitative estimation is given below :



In this case the acme of acetone excretion only reached 3·8 milligrams in every 50 c.c. of urine during the first twenty-four hours following the operation, and on estimation of the urine of the second period of twenty-four hours, no acetone was found. The nitroprusside test was positive in the first instance, but negative on the second occasion.

From these cases I conclude :-

1. Every case after general anaesthesia exhibits acetonuria, and that this can only be accurately demonstrated by means of a quantitative estimation.

2. The nitroprusside test for acetone fails to detect that substance if in smaller amount than two milligrams per 50 c.c. of urine.

I will now give the results of my examinations of the urines in the two cases where symptoms of poisoning were exhibited. These symptoms have been fully described on pages 91 and 96.

Case 1. Ethel J., aet.5½.

As I was interested in the subject of this thesis at the time the patient was admitted to hospital, I had her urine tested, prior to operation, for acetone. I failed to find any acetone.

I obtained the urine, which was the first passed after operation, at 6 p.m. the following day. The nitroprusside and iodoform tests gave the positive reaction indicating acetone. The ferric chloride test for diacetic acid was also positive.

I again tested the urine next day and again found acetone. Diacetic acid, however, was absent.

On the third day after operation, both acetone and diacetic acid were absent.

Case 2. Martha M., aet.8.

The urine in this case was not examined for acetone prior to operation.

The patient passed urine during the night after the operation. This was carefully tested for both acetone and diacetic acid, but neither of these were found. At 10 a.m. the following morning, six ounces of urine were withdrawn for examination. On this occasion both acetone and diacetic acid were present.

No further specimen was obtainable for examination prior to death, which occurred as described on

p. 99, forty-eight hours after the operation.

From the above sketch it will be seen that the urine in delayed chloroform poisoning is, as a rule, acid. The specific gravity is not noted. The colour may sometimes indicate the presence of blood, though this is rare. Albumen and casts are frequently found. Leucine and tyrosine have been found in one or two isolated cases. The output of ammonia in the urine is greatly increased. The presence of acetone and diacetic acid are really the only characteristic bodies found in the urine in delayed chloroform poisoning. The latter is by no means invariably present; but in every case, sooner or later, acetone appears in the urine. The prognosis in delayed chloroform poisoning does not depend on the amount of acetone present so much as the time and rate of its excretion. The prognosis is rendered the more grave if acetone is found to be present in the urine prior to operation. Should patient be suffering from 'acute acetonuria' before chloroform anaesthesia is administered, the case is practically hopeless.

THE POSTMORTEM CHANGES

in

DELAYED CHLOROFORM POISONING.

POST-MORTEM FINDINGS.

I will now deal in detail with the post-mortem changes which are found in a fatal case of delayed chloroform poisoning.

Langenbeck(9), in 1850, was the first to note the characteristic post-mortem feature in these cases, viz., the fatty liver. In 1866, Nothnagel(11) by experiments on rabbits, corroborated this fatty change in the liver, and also found similar changes in heart and kidneys. Since then, numerous observers have found fatty changes of varying degree in post-mortems on fatal cases of delayed chloroform poisoning.

The body in some cases presents a distinct icteric tinge[34, 3(Case 3)]; but this is by no means present in all cases. There may also be present in rare cases(33) small cutaneous haemorrhages. Rigor mortis is general and post-mortem lividity distinct 8(Case 2).

We next notice the condition of the wound. In a typical case, not complicated by sepsis, the wound is perfectly healthy and, according to the date of death, shows the varying stages of a healing wound. In one case(74) there was a cherry red discolouration in the neighbourhood of the wound.

Microscopically, the neighbourhood of the wound shows diffuse haemorrhagic infiltration of the tissues, with some polymorphonuclear leucocytes among the red blood corpuscles, and on culture is sterile.

Thorax.

The pericardial and pleural sacs are healthy as a rule. In some cases petechial haemorrhages are found on the pleural surfaces[3(Case 2)]. Stuart M'Donald[(12)] remarks that these petechial haemorrhages are common on all serous surfaces. The thymus may[8(Case 2), 74] or may not[(53)] be enlarged. There is no enlargement of the mediastinal glands.

Heart.

The pericardium shows nothing abnormal, and the endocardium is smooth. The heart contains some blood, which is dark in colour. The right side of the heart is not specially distended, and the left side may be arrested in systole, thus being firmly contracted[1(Case 3) 8(Case 2)], or in diastole[1(Case 1)]. The valves are competent, and the cusps show nothing abnormal. The myocardium itself may appear normal 3(Case 2), but in many cases is pale[8(Case 2), 53, 75]. The myocardium is, as a rule, firm to the finger, but may be flabby[(74)]. Frequently there is distinct

evidence of fatty degeneration[2(Case 2)]: in the majority of cases, however, no mottling or other distinct evidence of such degeneration[8(Case 2)] is noted.

Lungs.

The lungs may be perfectly healthy,[75(Case 2)]. In many cases[3(Case 2) 8(Case 2)], scattered over the visceral pleura are many sub-pleural haemorrhages, and these may be more pronounced towards the roots of the lungs[8(Case 2)] or the smallest bronchioles 3(Case 3). There are sometimes found areas of lobular collapse[8(Case 2)], or even consolidation[75(Case 1)]. The roots of the lungs and the pulmonary vessels are healthy. The large bronchi are congested[8(Case 2)] and contain frothy mucus[8(Case 2), 53], and at places may be blood stained. In one case[54], it is noted that there was no bronchitis present. In another case[74], the lungs were a bright cherry red colour and hyperaemic. The colour in one case[1(Case 5)] is mentioned as purple.

On section, the lungs in the majority of cases are congested[2(Case 2), 53], and are often oedematous[1(Case 4) 75(Case 1)]. In one case the lungs were full of air[3(Case 3)]. The lungs, in another case, were said to be full of blood[2(Case 2)], and

in still another, numerous areas of haemorrhagic infiltration[8(Case 2)] were present.

In the majority of cases, however, the lungs do not pass the stage of congestion. Guthrie[(69)] and Rolleston[(107)] state that the lungs show no characteristic appearances.

Abdomen.

A typical case shows no abnormality in the peritoneal sac, beyond some subserous haemorrhages. There may be a larger amount of fat in the mesentery than is usually met with[2(Case 1)]. The pancreas, as a rule, shows nothing abnormal. In two cases 53 & 75(Case 1), the pancreas showed necrosis. The stomach may be empty or contain a larger or smaller quantity of 'coffee ground' material, and this may be adherent to the mucous membrane[(85)]. The gastric mucosa to the naked eye often shows pin-point haemorrhages, which may be generally over its surface or confined to the cardiac end[75(Case 1) 85(Case 2)]. There is no ulceration or erosion visible to the naked eye. The intestines, as a rule, are healthy 8(Case 2), 53, but may contain altered blood[75(Case 2)] and the Peyer's patches are sometimes congested or prominent, pale and oedematous[(74)]. The solitary glands at the lower end of the small intestine may

be more prominent than normal[8(Case 2)]. The mesenteric glands are frequently enlarged[8(Case 2), 74], soft and pale.

Liver.

The changes found post-mortem in delayed chloroform poisoning in the liver are extremely interesting. The liver is practically always enlarged, but may be normal(69) or reduced in size(53) (54): the surface is smooth. The colour is strikingly pale, and often intensely yellow, almost of a canary tint 8(Case 2), 53. Scattered on the surface are small red[8(Case 2)] or purple[1(Case 2) 3(Case 3)] spots and lines(69) representing distended vessels. Schenk & Ballin reported ten cases in which the post-mortem appearances were those of acute yellow atrophy.

Various terms have been applied to the colour of the liver, viz. 'pale fawn'[3(Case 3)], 'pale buff' (74), 'canary yellow'[8(Case 2)]. The liver is also greasy to the feel[1(Case 4) 85(Case 2)], and is usually firm[1(Case 4)].

The liver may extend two[3(Case 2)] or more inches below the costal margin, and may weigh twenty-six ounces[3(Case 3)].

On section: - An intense degree of fatty change uniformly distributed throughout the whole organ is

observed; but the liver may be markedly fatty only in places[3](Case 4). The substance is brittle, breaking with a granular fracture[1](Case 2). The condition affects the whole of the hepatic lobule, and at places the periphery of the lobule has a more intensely yellow tint. There is no infiltration in the portal tracts, and no indication of septic foci.

The gall bladder is not distended, and the main ducts not obstructed.

Kidneys.

The kidneys are often normal to the naked eye 3(Case 3). Capsules strip easily, leaving a smooth surface(53). They may be slightly enlarged[8](Case 2) softer and paler(53)(74) than normal. The stellate veins are not unduly prominent[8](Case 2), 53. On section, the most striking feature is the intense pallor of the cortex, superficial and deep[8](Case 2), with often a slight yellow tint(53). The pyramids may be normal, but appear prominent in contrast to the cortex.

The naked eye appearances suggest cloudy swelling rather than fatty change. The malpighian bodies are not prominent[8](Case 2), 53. There is no haemorrhage to be seen - naked eye - in the kidney section.

Suprarenals.

The suprarenals are usually quite normal[3(Case 1)] but may be enlarged and firm, and of a canary yellow colour which extends right through them(53).

Spleen.

The spleen is not enlarged, and is pale and firm(74). It may be congested[75(Case 1)]. In some cases the surface is studded with purple dots[5(Case 1)]. The malpighian bodies are often large and distinct(54).

The spleen may be the seat of fatty degeneration (114). No septic foci to be seen.

Bladder.

Usually the bladder is quite normal[8(Case 2)]; the mucosa may be studded with petechial haemorrhages (54). The bladder contains some urine, which may or may not contain acetone.

Brain.

To the naked eye, the brain and its membranes, in the majority of cases, show nothing[8(Case 2), 54]. In one case slight oedema of the pia arachnoid was noted[75(Case 2)]; in another, slight oedema of the brain[75(Case 1)].

Bone Marrow.

The bone marrow was examined in only one case(53) and was found to be pale.

From what I have said about the naked eye appearances post-mortem, we find that the organs to attract most attention are the liver, heart, kidneys and the stomach.

Though some authorities hold that nothing characteristic is found in the lungs, I will deal in detail with the microscopical appearances in this organ in order to show the amount of pathological change which does very frequently take place, even when, to the naked eye, the lungs appear healthy.

Before going on to the microscopic appearances in each organ, I wish to mention that Guthrie(69) states that in some cases the blood resembles watery 'prune-juice'. He is the only authority I can find who makes this statement.

I will now deal with the various organs microscopically. In so many cases the mode of preparation of the sections is not mentioned, that I will omit this item.

Heart.

The heart may shew no change, naked eye or

microscopically(54). In many places the muscle fibres show no abnormality. In many cases, striation of the fibres is distinct(53), in others not so distinct8(Case 2), and here and there may be somewhat granular8(Case 2). There is therely transverse segmentation. In many carefully examined sections, no fat was demonstrated8(Case 2), 53. In some other cases, fine fat droplets were noted in the muscle fibres98(Case 1) 75(Case 1). In one case, every cell was affected, none being healthy. The nuclei of the cells stain well8(Case 2). No excess of pigment is found in the interstitial tissue(53). There is no special hyperaemia, and no fat in the epithelium of the vessels.

Lungs.

In many cases the lungs are said to be 'normal'. In these cases I hardly think a very exhaustive examination has been made, as in those cases where such an examination is made, a considerable amount of interesting pathological change is to be noted.

There is often found a condition of capillary bronchitis; this change may be confined to the small bronchioles3(Case 3), but we also, in many cases, find evidence of bronchitis in the larger tubes 8(Case 2). The capillaries in the alveolar walls

are often dilated to a moderate degree[53], and these are more or less congested. The walls of the bronchi are also unduly hyperaemic, but nowhere is distinct evidence of inflammatory change found. Fat is found to be present in the form of minute droplets in the cells of the alveolar septa[53], free in the alveoli[8(Case 2)] and in some of the desquamated endothelial cells. Fat may also be demonstrated in the endothelium of the capillaries, and some of the capillaries of the alveolar walls have been seen to be blocked by short columns of oil[8(Case 2)], giving the staining reactions of oil. Some similar minute droplets may appear free, or lying inside the desquamated cells inside some of the bronchi[8(Case 2)]. From this it will be seen that any fat found in the lung is in far too small a quantity to give rise to fat embolism. Beattie & Carmichael[53] conclude that the fat found in the lung is of local production and due to the action of the chloroform.

I will now deal with the organ which is the most interesting, pathologically and chemically, in this condition of delayed chloroform poisoning, viz. The Liver.

Some thickening of Glisson's capsule, not amounting to an actual cirrhotic condition, has been demon-

strated(8). As a rule there is no cellular infiltration round the portal tract. In sections where the fat has been dissolved out, we find a pale network with rounded meshes(69). The liver cells swell irregularly, leading in many places to an almost complete closure of the capillaries between the rows of cells(53). The liver cells are vacuolated, the nuclei alone stain with logwood8(Case 2), 53, 69, and the cytoplasm, where not destroyed, is granular and forms bridges separating the vacuoles from one another(53). This vacuolation was most marked at the periphery of the lobules. Guthrie(69) states that sometimes the fat is most in evidence at the centre of the lobule. In many of the cases it is noted that the fat granules are smaller at the centre of the lobule and increase in size towards the periphery (53); and this is the typical condition. In some cases the nuclei only stain indistinctly3(Case 3), and in the case mentioned, some nuclei were entirely absent. All the cells are as a rule crowded with fat globules; some observers note that the small droplets of fat do not tend to coalesce8(Case 2), while others have found that the cells at the periphery of the lobule are filled completely by one large globule(53). In cases where, naked eye, there seems to be only a small amount of fatty change,

microscopically, the cells show the fat globules, especially in the periphery of the cells[53]. Many of the cells surrounding the central venule appear to be completely disorganised[8](Case 2).

Wells[82], as I have already mentioned, divides cases of delayed chloroform poisoning into two groups. In the first group he includes mild cases, and here he states the change in the liver consists of a fatty degeneration about the periphery of the lobules. In the second group is included all the severe cases of this condition, and especially where jaundice is a marked symptom. The changes he describes in the liver, in these cases, are an extreme degree of necrosis of the cells, beginning in the centre of the lobule, with more or less peripheral fatty degeneration.

Weill, Vignard & Mourignand[92] found a total cellular necrosis in the liver.

Sommerville[98], in two of his cases, found the centre of the liver lobule completely disorganised and advanced fatty degeneration at the periphery of the lobule.

Williams & Becker[96] report a case in which the liver cells were practically all necrotic. Occasionally a lobule showed less change at the periphery than at the centre.

The above condition of the liver lobule has been demonstrated by several workers experimentally.

Howlands & Richards(95) found that, in dogs, after chloroform anaesthesia lasting one and a half hours, fatty changes in the liver first appeared in the intermediary zone of the lobule. In cases where larger quantities of chloroform were used, or after repeated administration, necrosis of the lobule commenced at the centre and spread until the whole was necrotic.

Whipple & Sperry(97) found that in man chloroform anaesthesia for a period of thirty-five minutes may cause almost complete liver necrosis. In cases where the change was not so severe, the centre of the lobule was necrotic, while the periphery showed more or less fatty degeneration. They were able to demonstrate in dogs that when the hepatic artery was ligatured, prior to the administration of an anaesthetic, no change in the liver lobule occurred.

Whipple & Sperry also observed the mechanism of repair in chloroform necrosis of the liver, and found that repair was effected by solution of the necrotic cells and rapid multiplication of the peripheral cells. The liver was thus brought back to normal in from two to three weeks.

Goodhart(103) performed experiments on rabbits

on the lines of Whipple & Sperry. He found the centre of the lobules to be composed of cells of hyaline appearance. The cell wall is usually intact, the nucleus stains poorly and is frequently fragmented. Here and there were collections of debris, evidently the remains of disintegrated cells. External to these necrotic cells is a ring of empty looking cells consisting of a cell wall and a central, and often irregular, nucleus surrounded by a clear space, or a very little granular protoplasm. Around the periphery of the lobule are two or three layers of healthy-looking cells. Droplets of fat were scattered throughout the lobule, but were more densely packed in the ring of cells lying immediately internal to the healthy peripheral cells. Stiles & M'Donald(8) found that this central area of disorganised cells extended into the intermediate zone, but the peripheral zones presented a different appearance. Here and there the oil droplets had coalesced into large globules, which displaced the nuclei to the sides of the cells. The nuclei when seen always stained perfectly. In a well marked case, no part of the lobule is free from fatty change. Fat may be demonstrated in the cells lining the bile capillaries(53). The walls of the sub-lobular and hepatic veins may be somewhat thickened. In some

of the hepatic veins cells are found which contain fat. Beattie & Carmichael[53] consider these are undoubtedly liver cells. They were unable to demonstrate any free fat in these hepatic veins. Stiles & M'Donald[8(Case 2)], on the other hand, demonstrated quite a considerable amount of oil in the hepatic veins. Much of this oil appeared as free droplets. At places the droplets were grouped together, as if resulting from the disintegration of a cell. They also demonstrated distinct liver cells in the hepatic veins, which closely resembled the disintegrated cells lying around the central hepatic venule. No fat has been demonstrated in the branches of the hepatic artery. Bevan & Favill[54] in their case report that the central portions of the lobule were congested and the columnar arrangement of the liver cells thrown into disorder.

I now come to speak of the microscopical appearance of the Kidneys.

Sections show an intense degree of degenerative and fatty change in the renal parenchyma. The change is universally distributed throughout the organ, the convoluted tubules, loop tubules and collecting tubules all suffering. Cells in all of the tubules, secreting and collecting, contain granules.

There may be distinct cloudy swelling, with a tendency to separation of the cells from one another in the convoluted tubules[8(Case 2)]. In a well marked case there is very extensive fatty change in nearly every cell of the tubule. The fat is present as minute droplets, not tending to coalesce, and specially situated between the muscles and the base of the cell[8(Case 2) 53]. In very few of the tubules are there any desquamated epithelial cells. Here and there a few of the collecting tubules may be free from fat[(53)]. A few of the convoluted tubules show necrosis[75(Case 2)], and some degenerated cells are found lying in the lumen[98(Case 2)]. The nuclei stain well throughout the kidney. There is no pigmentary change in the cells. No cellular increase is apparent in the tufts of glomeruli, or at any other part. There is a certain amount of granular precipitate[8(Case 2)] or exudate[(53)] between the capillary tuft and Bowman's capsule. The malpighian bodies show nothing abnormal. No fat has been demonstrated in the vessels of the kidney[8(Case 2), 53].

Some observers[(54)] note large amounts of granular material in the cavities of the glomeruli, compressing many of the tufts.

Supra-Renal Capsules.

Beattie & Carmichael[(53)] found extensive fatty

degeneration of the whole capsule, most marked in the cells of the cortex, especially those near the surface, and also definite fatty change in the cells lining the capillaries. Other observers have not paid much attention to this organ, and no other microscopic details are published.

Spleen.

Hyaline degeneration of the splenic arterioles has been observed, and some proliferation of the epithelium lining the pulp sinuses[8(Case 2)]. Many observers report the spleen as normal[85(Case 1)].

Pancreas.

Most observers have found nothing in the pancreas worthy of note[3(Case 3) 8(Case 2) 85(Case 1)]. Some have found areas of necrosis[53, 75(Case 1)]. The nuclei have been observed to stain badly, and the protoplasm to be filled with fat globules[75(Case 1)].

Mesenteric Glands.

In those cases where the glands have been found to be enlarged[8(Case 2), 53, 75, 85(Case 2)], on microscopic examination many of the cells at the periphery of the lobules are seen to contain fat[(53)]. Beattie & Carmichael consider that the fat cells were migratory and had passed by the lymphatic

channels to the glands.

Stomach.

The muscular and sub-mucous coat show nothing abnormal. The secreting cells show marked changes. The cells, central and peripheral, have been found to be swollen, granular and vacuolated, but the nucleus stained perfectly. In sections stained for fat, the peripheral cells were filled with globules, whilst the central cells showed only a moderate degree of fatty degeneration(53). The lining cells of the capillaries of the gastric mucous membrane also suffer from this fatty change, and the walls of these vessels, being thus in a weakened condition, are less able to withstand much increased strain, such as retching, so rupture, and we thus have the 'coffee ground' vomit.

Bone Marrow.

Beattie & Carmichael(53) found the fat cells to be in greater amount than normal. If anything, there may be a diminution of leucoblastic elements. The case in which they observed this was a girl who suffered from Tuberculous Elbow. Dr Carnegie Dickson has observed the same changes in the bone marrow in other tuberculous conditions. A Blood Count

done post-mortem in the above case showed a leuco-penia.

I shall now deal briefly with the Bacteriology.

No organism has been cultivated from the blood (53)(54). Cultivations from the haemorrhagic areas in the lungs made on blood agar, in twenty-four hours developed small, clear, transparent colonies[8](Case 2). These colonies, on microscopic examination, proved to be those of the pneumococcus. Films made from the same haemorrhagic areas in the lungs showed no bacteria. In no case, uncomplicated by sepsis, has any organism been found, except those organisms normally present in the special organ, e.g. pneumo-coccus in the lungs.

A

CRITICISM OF THE CAUSES

which have been suggested as

PRODUCING THE SYMPTOMS

of

DELAYED CHLOROFORM POISONING.

SUGGESTED CAUSES OF THE SYMPTOMS FOLLOWING CHLOROFORM ANAESTHESIA.

Prior to the acquaintance of surgeons with delayed chloroform poisoning, many cases of this condition were doubtless attributed to other causes. Even when it was recognised that the administration of chloroform as an anaesthetic might be followed by toxic after effects, many varying factors were suggested as producing the symptoms in the different cases reported. To one unacquainted with delayed chloroform poisoning, this is not to be wondered at; and even in the present state of our knowledge it is not easy to say definitely in many cases that the cause of the symptoms is the anaesthetic chloroform. Indeed in a case which is acutely septic, no one can say how much is due to the sepsis and how much to the chloroform.

As to the primary cause of delayed chloroform poisoning, opinion still differs. Those who belong to the London School, headed by Guthrie, believe that a pre-existent fatty condition of the liver is necessary. Those of the Edinburgh School, of whom Stiles and M'Donald are the leaders, do not agree that a pre-existent fatty liver is necessary.

Various observers are of opinion that the fatal result is caused by 'fat embolism' in view of the fact that fat has been found lying free in the blood vessels of the liver and lungs. Others again could not understand why some patients should suffer from this condition while other patients do not. They accounted for this by considering the patient to have an idiosyncrasy for the poisonous after effects of chloroform. It is known that a previous administration of chloroform renders the patient more susceptible to the poisonous after effects of a subsequent anaesthesia, especially should the latter follow closely upon the first.

Many other causes have been suggested, and I will now deal in more detail with these.

The Chloroform. The majority of observers agree that the amount of chloroform administered and the length of time the patient is under the influence of the anaesthetic, has no material influence on the future course of the case. Fatal cases are reported after only seven minutes'(84) anaesthesia and the exhibition of only ʒj of chloroform(80). On the other hand, fatal cases are reported after long periods of anaesthesia, requiring much chloroform. The chloroform manufactured for the purpose of anaesthesia is made from ethyl alcohol, methyl alcohol,

or acetone. Bleaching powder is mixed with either of the above substances, and the chloroform is distilled off. Water is now introduced to hold the chloroform in suspension. This is distilled several times for the purpose of purification. The last distillate is now dried by means of calcium chloride and again redistilled. It is impossible, if the end product has been thoroughly purified during the process of manufacture, to tell whether the chloroform was made from ethyl or methyl alcohol, or acetone. In the event of methyl alcohol being used, there is a greater chance of impurities being present than if ethyl alcohol was the basis of manufacture. The same holds good, and even more so, in the case of the chloroform being manufactured from acetone. The manufacturers say that it is more by the experience of surgeons than by chemical analysis that chloroform made from ethyl alcohol has been found to cause less trouble during and after anaesthesia. Again, the manufacturers maintain that the chloroform put upon the market, made from whatever source, passes all the purity tests of the British and other pharmacopoeias.

Chloroform, if exposed to light, quickly deteriorates in the presence of air. A poisonous substance, phosphene gas, is formed. Chloroform

should be kept in amber bottles.

From these notes which I have obtained from the three largest manufacturers of chloroform, it is difficult to see how one variety of chloroform can produce toxic symptoms and another not.

The Administration. It has been asserted by a French writer, quoted by Campbell[70], that symptoms of poisoning are always the result of using chloroform in a too highly concentrated state. He states that a two per cent. mixture of chloroform with air is the limit of safety. One observer[70] states that in his fatal cases he believes that too concentrated a vapour of chloroform was used.

Against the concentration of the chloroform as being a cause of the symptoms, is the fact that similar effects follow the use of other anaesthetics. Should too highly a concentrated vapour of chloroform be the cause, a great many more cases of delayed chloroform poisoning would have been reported. Guthrie[80] states that none of his cases showed symptoms of an over dosage of chloroform during anaesthesia.

The Age of the patient. Guthrie in 1894 pointed out that children were more susceptible than adults to the poisonous after effects of chloroform.

The earliest cases reported were those of adults, but sepsis, which is now known to greatly aggravate the toxic effects of chloroform, was present in the large majority of those.

Hubbard(59) found that acetonuria after operation was most common between the ages of 1 and 10 years: he reports five cases within these ages. Between the ages of 10 and 20 years, four cases are reported, three cases between 20 and 30 years, one case between the ages of 30 and 40, and two cases between the ages of 50 and 60. I have made a similar investigation, but have subdivided the ages more minutely. From among practically all the reported cases of delayed chloroform poisoning, I find the following:- between the ages of 2 and 5 years, 33% of the fatal cases occurred; between the ages of 5 and 12 years, 30%. Thus we find that between the ages of 2 years and 12 years, considerably over half, viz. 63%, of the deaths from delayed chloroform poisoning have been reported. Two per cent. of deaths are reported below 1 year of age, and 12% between the ages of 1 and 2 years. We therefore find 77% of deaths occurred in the first twelve years of life.

In view of these facts, one is fully justified in asserting that children, up to the age of 12, are more susceptible to the after effects of chloroform

than are persons at any other age.

It is well known to experimental physiologists that herbivorous animals take chloroform badly. Children, of the working class especially, between the ages of 2 and 5 years get less proteid in their diet than at any other age. They mainly exist on bread and jam, potatoes and gravy, and are therefore what we might term herbivorous. On the other hand, infants who are fed on milk take chloroform exceedingly well.

The nature of the operation. There has been a suggestion by various observers that after certain operations the patients are more liable to suffer from the toxic after effects of chloroform, than they are after others. On looking over the nature of the operation in the cases I have collected, I was attracted by the number of abdominal operations mentioned. On analysing the different operations, I find that in forty per cent. of the operations, the abdomen was opened into. In these I include herniae. This fact is all the more remarkable, because in children abdominal operations are not so frequent. I am of opinion that children, after an abdominal operation, where chloroform is the anaesthetic used, are peculiarly susceptible to the toxic

after effects of that drug.

From what Beesly has taught us, one is not surprised to find sepsis increasing the liability to the toxic after effects of the anaesthetic. Of my cases, ten per cent. were septic. In septic cases, very often there is not time prior to operation in which to apply prophylactic measures; if chloroform is to be the anaesthetic used in these cases, one must not be surprised to find cases of delayed chloroform poisoning occurring amongst them.

I might mention in passing that Bevan & Favill[54] believe that a patient is predisposed to the poisonous after effects of chloroform if there happens to be a gangrenous mass in the abdomen.

I strongly advocate ether as the anaesthetic in all septic cases.

Besides abdominal operations, two other conditions are deserving of mention because of the supposed susceptibility to toxic after effects of the anaesthetic. I have dealt (pp.27 & 50) with both these conditions already, therefore I will only mention them now. Bracket, Stone & Lowe[48] warned surgeons in operating upon cases of Infantile Paralysis. I may say their cases are almost the only examples in which the toxic after effects followed the anaesthetic in this infantile condition.

Telford (personal communication) is most emphatic in his belief that children suffering from rickets are more liable to suffer from delayed chloroform poisoning than any others.

With these three exceptions, fatal cases of delayed chloroform poisoning have been reported after a wide range of different operations, e.g. webbed fingers, naevi, tuberculous disease, etc. Each observer lays stress upon the nature of the cases which, in his experience, have been followed by toxic effects.

The Condition of the Patient, except where the case has been an acute infective condition, has, in the large majority of instances, been good. Frequently has it been noted that the patient seemed to be in the best of health. Again, many very weakly cases have been seen to take the anaesthetic extremely well, and to be followed by the minimum of discomfort afterwards.

I do not think that any conclusion as to the patient's susceptibility can be drawn from his condition prior to operation.

Carbolic Poisoning. It is well known that death may result from the absorption of carbolic acid by the skin. Stiles & M'Donald[8] report a

fatal case in a healthy boy of three months. A carbolic poultice was applied for ten hours prior to operation in two periods of six and four hours respectively. Four hours after the second application, the patient exhibited symptoms very much akin to those of delayed chloroform poisoning, and death occurred fifteen and a half hours after the onset of symptoms, the patient being in a comatosed state. The urine was almost black in colour. At the post-mortem examination the liver showed well marked furrows and grooves, but on section, appeared quite normal. Microscopically, the kidneys showed cloudy swelling and some necrosis of the cells of the tubules.

It has been shown(8) that in the case of children, 41·3 per cent. of the total amount of phenol which enters the system is absorbed in the first two hours. This fact, and the greater vulnerability of the child's nervous system, is quite enough to account for the number of cases of carbolic intoxication which have been recorded in children. The chief symptoms are collapse, weak running pulse, shallow respiration, sweating, repeated vomiting and lethargy, passing into coma. These symptoms closely resemble those of delayed chloroform poisoning.

Several cases(53) have been published where no

carbolic acid was used, as an antiseptic, with symptoms characteristic of delayed chloroform poisoning, and where carboluria was not present, that one is fully justified in excluding carbolic acid poisoning as a cause of these symptoms.

In the same way, Chemical agents as a whole, may be excluded. In the case(53) reported by Beattie & Carmichael, no chemical agent whatsoever was used, either before, at, or after the operation.

Fat Embolism has been suggested as a cause of the symptoms in delayed chloroform poisoning. I have already pointed out (p.148) in the case(8) reported by Stiles & M'Donald, that only a very small quantity of fat was found lying free in the blood vessels in the lungs. From their careful examination, no one could possibly be justified in attributing death to fat embolism. Beattie & Carmichael(53) state that the clinical manifestations of fat embolism are very similar to those of delayed chloroform poisoning, but that fat embolism rarely proves fatal. Stiles & M'Donald, in their case(8), report that during the operation, which was an osteotomy, about a teaspoonful of yellow fluid fat was seen to exude from the bone. Mr Stiles has since observed this in many similar cases, with no untoward result. In the above case, no fat was demonstrated

in a single vessel on the aortic side of the circulation. The presence of a considerable quantity of oil in some of the large hepatic veins is sufficient to explain the amount of fat found in the lungs. Stiles & M'Donald are of the opinion that the presence of fat in the lungs must be regarded as only an incident in the case, and in no way contributed to the fatal result. I entirely agree with these observers.

Sepsis, especially in the earlier reported cases, was an extremely probable cause of the symptoms following an operation, where an anaesthetic had been employed. Even now, if any septic element is present in the case, it is very difficult to say how much is due to that element and how much to the chloroform.

We have seen that in acute infective conditions, acidosis is present. On the other hand, in the large majority, viz. ninety per cent., of the reported cases of delayed chloroform poisoning, any septic element has been absolutely excluded. In these cases the progress of the symptoms is exactly similar to those in which there is undoubtedly a septic element present. Sepsis is, however, a predisposing cause; it also intensifies the symptoms and renders

the prognosis more grave when once toxic symptoms have manifested themselves.

With regard to the post-mortem appearances in the liver in delayed chloroform poisoning, these cannot be definitely separated from the morbid changes produced by sepsis(53). Subserous haemorrhages are found in severe septicaemia as well as in delayed chloroform poisoning. Stiles & M'Donald(8) report a fatal case which had all the symptoms of delayed chloroform poisoning. This patient suffered from recurrent perityphlitis. The post-mortem changes were exactly similar to those found in the former condition.

From the above facts we learn that symptoms and morbid changes similar to those of delayed chloroform poisoning may be produced by sepsis, whether an anaesthetic be administered or not. On the other hand, in clean cases, similar symptoms and pathological changes occur, where the only common feature is the administration of chloroform for the purpose of anaesthesia. In these cases, sepsis can be excluded as the cause of the symptoms.

Idiosyncrasy. I do not agree with Guthrie when he says that idiosyncrasy cannot play any part in the production of delayed chloroform poisoning. Guthrie states that idiosyncrasy, with regard to the

specific action of chloroform, is negatived by the fact that similar signs and symptoms are seen after other anaesthetics. Is it not more probable that certain persons suffer from an idiosyncrasy to narcotics as a whole? I know one lady now, who completely collapsed after one sixth of a grain of morphia.

Take two cases, both apparently in the best of health: both are anaesthetised with chloroform: one succumbs to the toxic after effects of the chloroform, the other shows not the slightest symptom of that condition. It is extremely probable that the one patient was more susceptible to the anaesthetic than the other.

Stiles & M'Donald, Beesly, Bevan & Favill, all admit that idiosyncrasy plays a part in many cases. This is naturally very difficult to explain.

A Pre-existent fatty condition of the liver is held by some, especially by Guthrie, to be absolutely necessary to the production of delayed chloroform poisoning. Stiles & M'Donald[8] have shewn experimentally that a piece of liver excised at the beginning of the anaesthesia contained a minimum degree of fat, and very much less fat than they were able to demonstrate to be present in the same liver after death. Telford[104] has proved the same to be

true in the human subject. In view of such evidence, I regard Guthrie's position as untenable.

Shock. Stiles[8] maintains that children suffer much less from shock after operations than is generally recognised. In cases proving fatal from shock, the marked pathological changes found in delayed chloroform poisoning are absent. Guthrie is of opinion that the condition of shock, after operation, cannot be altogether ignored in the causation of death. In his cases only one suffered from profound shock, and this case was the only one to recover.

Home Sickness. Against this theory is the fact that many of the patients had been in hospital before. Some had been in hospital for some time previous to operation, and were quite at home in the wards. The condition in many cases developed some hours after operation regardless of how long the patient had been in hospital. I do not consider this suggestion as a serious one.

Fright. Fright has been known to produce acetonuria in dogs. Many of the patients from Bracket, Stone & Lowe's hospital records had had previous operations, and knew what to expect.

Upon the first occasion no untoward symptoms developed, yet toxic symptoms developed on a subsequent occasion after anaesthesia.

It is difficult to even imagine that fright could produce such widespread pathological changes as occur in delayed chloroform poisoning.

Starvation. Acidosis due to starvation can at once be arrested by small quantities of carbohydrates. How is it, then, that in those cases where the patient has so far recovered from the immediate effects of the anaesthetic that he is again on light nutritious diet, that symptoms only begin to show themselves on the third or fourth day? Rarely are cases about to be operated upon subjected to long fasts. In cases of intestinal obstruction where the patient has been vomiting his food for days, if starvation was the cause of the condition, one would expect them all to be necessarily fatal. This is not so.

Loss of Blood. Many of the fatal cases of delayed chloroform poisoning lost practically no blood at the operation. One case(8) is reported where a knee joint was only moved, and no incision was made at all. This theory lacks any convincing support.

Meningitis. In delayed chloroform poisoning there is usually no headache, no intolerance of light or sound. There is no prodromal period; the symptoms begin suddenly. It is impossible to conceive of meningitis of such virulence with practically no temperature.

Ptomaine Poisoning. The symptoms here are due to the general effect of toxic substances which are generated in the gastro-intestinal tract by various fermentative and putrefactive processes. The symptoms are similar to those produced by some powerful and poisonous alkaloid. There is acute prostration, with rapid feeble pulse, cold perspiration and subnormal temperature, accompanied often by severe vomiting and purging. The symptoms appear suddenly, the progress of the disease is rapid, and in fatal cases death takes place in a few hours. In delayed chloroform poisoning there is an absence of such profound prostration early in the case, and certainly no signs of intestinal irritation. The diet is that which all the cases before operation have.

Uraemia. Uraemia can be excluded by the absence of any evidence of previous disease of the kidneys and by the fact that up to within a few

hours of death, the patient passes a usual amount of urine, containing a normal output of solids.

THE CHEMISTRY OF THE

ACETONE BODIES.

THE CHEMISTRY OF THE ACETONE BODIES.

It has been clearly demonstrated, chiefly by Geelmuyden and Waldvogel amongst others, that acetone is derived from fat. It is unnecessary here to detail their experiments by which they arrived at this conclusion. Suffice it to say that physiologists are agreed that acetone is so derived. In view of this, I shall first of all give a brief sketch of the physiology of fat metabolism.

The neutral fats absorbed with the chyle remain in the blood, until they are selected for combustion and storage in the subcutaneous tissues, para-peritoneal spaces and the liver. During fasting, the fat pours from these depots back into the blood to all the organs requiring it. A condition of 'lipaemia' of the blood is therefore a constant condition. This becomes manifest in phosphorus poisoning, alcoholic intoxication, and in diabetic coma, conditions of more or less inanition. Certain ferments have been found in the blood capable of splitting the fat and rendering it soluble. Ferments of this nature have also been found in the liver. In the above conditions, Rosenfeld[79] showed that an enormous passage of fat takes place from the fat

deposits of the skin and abdomen into the liver; and the latter becomes loaded with an enormous quantity of fat. Both in 'fatty infiltration' and 'fatty degeneration' the fat is deposited in the liver cells, and whether it takes the form of fine granules or large globules depends on the functional activity of the cell at the time the fat is taken up. This storage of fat only takes place if the glycogen has disappeared from the liver. Large quantities of fat may be found along with excessive storage of glycogen in the liver, e.g. in the livers of Strassburg geese (Magnus Levy). The storage of fat in the liver may be explained in two ways: (1) The liver must transform the fat molecule in some way before it can be consumed by the cells (Nasse): (2) The storage of fat in the liver is a reserve readily available to meet any sudden call made upon it, e.g. violent movements. The liver is centrally placed and is very vascular, and can supply fat to any one organ at a sudden call more promptly than any other organ could do(79).

The exact nature of the error or errors of metabolism which result in the appearance of acetone in the urine is one of the most complex problems in medicine. There is only one form of acid which is known to occur in the body in sufficient quantity

to be dangerous, as acid. This is now known to be B-oxybutyric acid. It is also known that the substances diacetic acid and acetone, which were recognised long before the B-oxybutyric acid itself, are oxidation products of the latter. Diacetic acid is not directly toxic, and occurs in too small a quantity to be of very noteworthy importance as an acid. Acetone probably occurs in only very small amounts in the organism, and being of only very slight toxicity, it may be considered to have but a small direct share in any severe toxaemia that may occur. Acetone may complicate matters, however, by damaging the kidneys and thus add a renal insufficiency to the pre-existing toxaemia. Wilbur(49) has shewn experimentally that the infusion of B-oxybutyric acid can cause all the symptoms of acid intoxication, including typical coma. We may therefore say without question that B-oxybutyric acid has a large share in producing the condition of acid intoxication. B-oxybutyric acid, CH_3-CHOH-CH_2-COOH, is then the mother substance which, in the acidosis caused by the acetone bodies, gives rise, by oxidation, to diacetic acid CH_3-Co-CH_2-COOH, and also to acetone CH_3-CO-CH_3, from the diacetic acid losing carbonic acid. In a normal individual, on a normal diet, a certain amount of B-oxybutyric acid, when taken by

the mouth, is completely oxidised in the body without the appearance of diacetic acid or acetone in the urine. In cases such as diabetes, or persons fed exclusively on fats, diacetic acid and acetone, after the ingestion of a small quantity of B-oxybutyric acid, appear in the urine. This incomplete combustion must therefore be due to a failure of some particular oxidative process. Spriggs(94) states that since the acid can be dealt with by the healthy organism, and since the beta oxidation by which it is formed is one that can take place in the body, it is possible that it may be a normal intermediate product and one of the usual links in the metabolic chain of transformations, along which the food materials pass to their final excretory products. The loss of carbonic acid which results in the diacetic acid being converted into acetone probably takes place in the bladder(81). The appearance of diacetic acid and acetone in the urine in abnormal quantity, therefore, proves an excess of B-oxybutyric acid in the organism.

I will try, briefly, to explain the prevalent theory as to the production, in excess, of B-oxybutyric acid in delayed chloroform poisoning.

This fatty acid, as I have said, is the mother substance from which diacetic acid and acetone are

derived. Chloroform narcosis is believed to cause a deficiency of glycogen in the liver. It is now known that a liver deficient in glycogen craves for fat, and therefore a transference of fat takes place, from subcutaneous tissues, and the para-peritoneal spaces, where it is stored, to the liver. We now have a great excess of fat in the liver, either in the form of a fatty degeneration or infiltration, which, as I have said, depends upon the activity of the cell at the time. These fats now undergo combustion, requiring in the process a great deal of oxygen, until the ultimate product is carbonic acid and water. During this process the fat is probably broken up into smaller molecules. Leathes'[81] view is that the smaller molecule would naturally be oxidised to carbon dioxide and water through the stages of diacetic and acetic acid, but that if, through some alteration of the normal process, as might be brought about by an excessive demand for the oxidation of fat, acetone is formed instead of acetic acid, then the occurrence of this abnormal step in the chain might result in the accumulation in the body of the preceding stages, viz. those of diacetic acid and B-oxybutyric acid. Halliburton[117] is of the same opinion, viz., that butyric and B-oxybutyric acids are normal intermediary products in fat rata-

bolism, but that in certain conditions, e.g. diabetes (and also now in delayed chloroform poisoning) the metabolism breaks down at this point, oxidation fails, and we get an excess of B-oxybutyric acid formed. Leathes(81) goes on further to say that all fatty acids in undergoing B-oxidation must give rise to butyric acid; each molecule of stearic or palmitic acid to one molecule of butyric acid. He quotes Geelmuyden as having found that of the fatty acids it is the lower members of the series, and especially butyric acid, that are most active. Spriggs(94) also agrees with Leathes. Hunter(79) regards the symptoms of delayed chloroform poisoning to be due to disturbances of the proteolytic and antitoxic functions of the liver. He is not so definite as Professor Leathes as to how the above changes are produced. Langmead(109) considers that the failure in the oxidation of fats is due to the excessive quantity of fat which is brought to the liver for oxidation, rather than the diminution of the normal amount of oxidising power of the tissues. Wells(82) thinks it probable that it is the oxidising enzymes that are particularly at fault in delayed chloroform poisoning.

OTHER CONDITIONS IN WHICH ACETONAEMIA OCCURS;

INCLUDING SOME GENERAL ANAESTHETICS

OTHER THAN CHLOROFORM.

In my introduction to the subject of this thesis I have indicated on pages 4, 5 and 6 several conditions, other than delayed chloroform poisoning, in which the symptoms associated with acetonuria are frequently exhibited.

I mention in the first place Diabetes Mellitus, because this is the one disease in which the presence of acid poisoning can be regarded as definitely proved. In severe cases all three acetone bodies are commonly present in the urine. In diabetes mellitus the alkalinity of the blood has been found depressed, the amount of carbon dioxide in the venous blood also much lower than normal, and the ammonia in the urine increased, both absolutely and relatively to the total nitrogen. These are all signs of severe acidosis. These signs may exist for a long period, while the body becomes more and more depleted of its bases, until acid intoxication supervenes. When acetonaemia does occur in diabetes mellitus, we would look for the same symptom complex as is exhibited in delayed chloroform poisoning. The symptoms we do find are, rapid pulse, deep respiration, 'bilious attacks', and restlessness giving place to drowsiness and coma. These symptoms can be produced in animals by giving acids, and they appear when the amount of organic acids in the

urine is greatest. It has been found that B-oxybutyric acid is an active poison apart from its acid properties, but the favourable result obtained by the exhibition of alkalies proves that its main poisonous effects are due to the acid properties of the B-oxybutyric acid.

It should be noted that the whole train of symptoms consequent upon the large quantities of organic acids in the body in diabetes mellitus hinge upon the failure of the patient to use carbohydrates. Even in health, the deprivation of carbohydrates may cause the appearance of organic acids in the urine. In contradistinction to the healthy person, the diabetic does not possess the power of using the sugar produced in the body from protein or from fat, therefore the prime condition in the production of the organic acids is much more complete in the diabetic than in the healthy man. The healthy man dies most probably from starvation rather than acid poisoning, while the diabetic succumbs to the latter condition.

The idea that severe diabetes is a condition of acid intoxication is strengthened by the beneficial effects of the ingestion of alkalies. The alkalies help to discharge the acid bodies in the urine, and may even ward off a threatening attack of coma.

In diabetes mellitus, the deficiency of carbohydrates probably causes an excessive metabolism of fat, and hence the production of the organic acids of the acetone series.

The next condition I will consider is known as Recurrent or Cyclic Vomiting. This disease is practically confined to children, as are the majority of the cases of delayed chloroform poisoning. In 1882 Dr Gee[118] called attention to cases of fitful or recurrent vomiting of unknown causation in children. Later observers noted acetone in the breath, urine and vomit in these cases. Much has been written on this disease since Dr Gee's paper was published.

Batty, Shaw & Tribe[119], in 1905, gave a very complete bibliography of this recurrent vomiting in children. In their paper they gave an analysis of fifty-five cases. The cases were found to occur in children usually between the ages of 3 and 4 years. The frequency of the attacks was variable, the common interval being three months. There may be a prodromal stage, in which dyspnoea, sighing respirations, offensive breath, choreic movements and general restlessness have been noted. The tongue may either be coated or clean. Then vomiting begins,

without nausea, and usually without gastric pain, all food is rejected, and, towards the end of the attack, bile appears and even blood. Constipation is common. The attack may last only a few hours, but the average duration is five to six days. It is the rule for fever to occur during the attacks of vomiting. Wasting is often a very marked symptom. These attacks tend to disappear when puberty is reached. Three of the 55 cases collected by Batty Shaw & Tribe were fatal.

As in delayed chloroform poisoning, the symptoms of Recurrent or Cyclic Vomiting may be readily mistaken for those of intestinal obstruction(121), and among all the various conditions from which delayed chloroform poisoning has to be distinguished, a differential diagnosis may be called for between them and recurrent vomiting.

In my opinion it is most probable that a mild degree of this condition is met with quite commonly in children who suffer from 'biliousness', in the same way as we have mild cases of toxic poisoning after chloroform.

Recurrent or cyclic vomiting is a rare condition. I have had the good fortune of seeing one case. The patient was a boy about 9 years of age. He was brought to hospital at the end of his attack

which had lasted three days. He was emaciated, pale, and his eyes were sunken and black underneath. He looked exactly like a patient suffering from delayed chloroform poisoning, and seemed as if he had been extremely ill.

Several observers, among them Edsall, have found B-oxybutyric acid, diacetic acid, and acetone in the urine; also acetone in the vomited matter.

In determining the cause of this condition it is important to know that acetonuria has been found to be absent prior to the occurrence of vomiting, and only appeared after the vomiting had persisted for some time(120). Spriggs(94) believes that the vomiting increases the acetonuria. This is the basis of a suggestion of the treatment by Tincture of Iodine, as this drug is known to have a beneficial effect upon most forms of sickness.

The primary cause of the attacks in the recurrent vomiting in children has been attributed to an auto-intoxication from incompetence of the liver. This is a purely hypothetical condition of which little is known.

Dr Theodore Fischer(121) suggests that some infection may be the original cause of the disturbance of metabolism. Langmead(109) records two cases and gives the post-mortem changes. The kidneys and

suprarenals showed cloudy swelling in each case. The spleen in each case was congested. The heart in one case is not mentioned: in the other, many lines of fine fat droplets were visible within the muscle fibres. The liver in each case showed fatty change. In the one case the change is described as an infiltration and there was also present cloudy swelling, but no necrosis. In the other case, there was intense fatty change throughout the liver, but less marked at the outer thirds of the lobules. At the junction of the outer and middle thirds, there were zones of necrosis.

The treatment of recurrent or cyclic vomiting is exactly the same as that of delayed chloroform poisoning.

In the Pernicious Vomiting of Pregnancy.

It is now recognised that, though the pernicious vomiting of pregnancy may be due in some cases to mechanical causes, such as displacement of the uterus, and in others to neurotic causes, there remains a more serious group in which a toxaemia is responsible. In these toxaemic cases the symptom complex almost exactly resembles that found in delayed chloroform poisoning.

Williams(122) in an interesting paper on the 'Vomiting of Pregnancy' pays special attention to

the toxaemic cases. The symptoms are described, which, as I have just said, are extremely similar to those of delayed chloroform poisoning. He divides the course of this toxaemic vomiting of pregnancy into three stages :

1st Stage - The urine is scanty and high coloured. The pulse is rapid and emaciation is evident.

2nd Stage - The emaciation is more marked. The breath has an acid foetid odour, and the pulse increases in frequency.

3rd Stage - There may now be an apparent amelioration of the symptoms for a short time; then the patient becomes delirious, torpid, may have convulsions, and finally lapses into a state of coma.

Williams found a striking increase in the percentage of nitrogen, eliminated as ammonia, which, compared with the total nitrogen of the urine, amounted to 16 to 32 or 46%, instead of the normal 3 to 5%. Ewing & Wolf(123) found that the percentage of nitrogen in the form of ammonia was as high as 38 and 43%.

Williams is of the opinion that the increase of the ammonia output is a sign that excessive acid material is being set free in the circulation, and whose neutralisation is absolutely essential to life.

He found gross hepatic lesions, and has collected, from the literature, other seventeen cases with similar pathological changes in the liver. These hepatic changes, Williams states, are the same as those found in eclampsia and similar to those in acute yellow atrophy. The entire central portion of the lobule was found to have undergone complete necrosis, while the peripheral portions showed signs of fatty degeneration.

Langdon Brown(67) quotes Dr Helen Baldwin as having found acetone and diacetic acid in the urine of such a case.

The treatment for this toxaemic vomiting of pregnancy is also exactly the same as for delayed chloroform poisoning. In addition, however, the pregnancy may have to be terminated.

In puerperal eclampsia acidosis appears to be a less constant feature. During the convulsive stage especially, we get acetonuria. Lactic acid is present in the blood and urine, but this is not likely to be very dangerous.

Longridge(124), in a paper which he read before the Obstetrical Society of London, states that in eclampsia there is a diminution in the alkalinity of the blood. He describes the symptoms, headaches, vomiting, diarrhoea, fits, jaundice, labial herpes

and itching. These, as I have shown, are typical of an acid intoxication.

The origin of this symptom complex is most probably the liver. Tarnier, quoted by Williams(122), states that a fatty degeneration of the liver is the usual concomitant of pregnancy.

The post-mortem changes found in the liver in eclampsia are very similar to those found in cases which succumb to the toxaemic vomiting of pregnancy. The central portion of the hepatic lobule is completely necrosed, whilst beyond this the lobule shows an intense degree of fatty degeneration.

Longridge, in his paper, does not mention the fact of acetone and diacetic acid being found in the urine, but he suggests the exhibition of citrates to bring the alkalinity of the blood up to normal. Sugar was also given to replace the glycogen in the liver. In addition, venesection is extremely useful, along with the infusion subcutaneously of saline solution, as well as per rectum.

Acute Yellow Atrophy of the Liver is accompanied by the signs of acidosis in the urine. The urine contains, besides the acetone bodies, other organic acids, such as lactic, acetic, butyric and succinic acids, and a large number of the amino-bodies of which the most important are leucine and tyrosine.

The latter two bodies, as I have already pointed out, have been found in the urine of cases of delayed chloroform poisoning, especially those which resemble closely the signs and progress of acute yellow atrophy. This is a severe toxic process, the progress of which is commonly so inevitable that no important part can be ascribed to the acidosis which accompanies it.

In the acetonaemia following or occurring side by side with starvation, the exact errors of metabolism are not more definitely known than in the case of delayed chloroform poisoning, with which I have already dealt.

The administration of carbohydrates quickly causes the acetonuria to disappear.

Symptoms of an acid intoxication may follow some gastro-intestinal conditions.

Langdon Brown(67) mentions the case of a lady, aged 24, who suffered from rapid wasting, constipation and occasional vomiting. She only weighed 5 stone 6 lbs., and all the ordinary causes of wasting were excluded. Diacetic acid was found in the urine, but no sugar or albumen. Then membranous casts were found in the stools. There was very little nourishment in the diet she was taking, and an enormous amount of stimulating substances. The

treatment given was a plain liberal diet, with alkalies before meals, and 20 grains of citrate of potassium three times a day. The diacetic acid soon disappeared, and the patient put on one stone in weight in six weeks. Langdon Brown's view is that the membranous colitis had caused both the emaciation and the acid intoxication. He believes the case to be one of gastro-intestinal acetonuria.

Eustace Smith(125) describes a condition which he calls 'Food Fever in Children', with symptoms exactly similar to the recurrent vomiting in children and also similar tc the case just quoted above. He does not mention that the urine was examined for acetone, an observation which, in the light of our present knowledge, is much to be regretted. The patients were feverish, vomited, and were constipated. The attack usually lasted five to six days. Emaciation was rapid, and the child soon looked to be seriously ill.

I am of opinion that 'Food fever in children' was an acetonaemic condition.

I have already mentioned Beesly(5) as having found that acute acetonuria was produced in <u>acute infective conditions</u>. To that I have nothing to add.

In phosphorus poisoning, there is a diminished oxidation going on in the liver, with the usual results of acid intoxication.

Oxygen Starvation. Dr Garrod(126) associates the symptoms of drowsiness, torpor and vomiting in broncho-pneumonia with the presence of acetone and diacetic acid in the urine. These symptoms are certainly compatible with those of an acid intoxication, and in view of the findings in the urine, most probably are due to such a condition.

Acid Intoxication Sui Generis. Edsall(128) reports a remarkable case of coma which he attributes to acid intoxication sui generis. The case is that of a milkman, aet.63. He evidently had had one acute attack of Bright's disease: recently he suffered from indigestion and nausea. He was habitually constipated. On the day before admission, he had been in his usual condition. On the morning of admission he felt weak and nauseated on getting up at 6 a.m. He was unable to eat, but drank one ounce of whiskey. While rolling milk cans to his waggon, he became conscious that he was seriously ill. He became giddy. He sank to the ground, but was quite conscious, though somewhat confused. On his way to hospital he became unconscious, and re-

membered nothing for twelve hours thereafter. On admission to hospital he exhibited marked cyanosis. Respirations, 18 to 20 to the minute, were full and deep: pulse full and strong, 90 to the minute. The arteries were sclerosed. The temperature was low. Eyes deviated to the right: pupils of moderate size and responded to light. No odour of acetone in the breath. There was a marked reaction to acetone in the urine. This lasted several days. The day after admission, the smell of acetone was very distinct in the breath. He was treated with alkalies and gradually recovered.

Edsall saw him on two occasions after his discharge from hospital and found his urine to be normal in every way: and the patient seemed in good health.

Dreschfeld & Moore(129) report several cases very similar to the above. They describe symptoms which are exactly similar to delayed chloroform poisoning. These are remarkable cases, and seem to me to resemble closely the acid intoxication of delayed chloroform poisoning.

I have, so far, confined my remarks upon the toxic effects following anaesthesia, to the anaesthetic, chloroform. Chloroform, however, is not the only anaesthetic which may be followed by symptoms of toxic poisoning.

Telford & Falconer[2] investigated the urines of 38 patients after chloroform anaesthesia and found acetone to be present in 35 of those cases, and diacetic acid in 24. They also made similar observations on 53 cases in which the anaesthesia was introduced by Ethyl Chloride, and thencontinued with chloroform. In these 53 cases, 47 were found to have acetonuria; while in the urine of 43 of the patients, diacetic acid was found. The acetone and diacetic acid remained in the urine of these patients who had had the ethyl chloride chloroform sequence of anaesthesia for as long a period after operation as did these bodies where chloroform alone was administered.

These observations do not tell us much, because chloroform was administered in all the cases, and we know that chloroform anaesthesia is followed by acetonuria.

Prior to the publication of Bracket, Stone & Lowe's[48] paper in 1904, it was thought chloroform alone could be followed by toxic poisoning.

Toxic Poisoning after Ether Anaesthesia.

These observers, however, reported seven cases having symptoms of poisoning similar to those which occur after chloroform anaesthesia, and also having similar pathological changes, after the administration of ether.

Previous to the publication of the above paper, deaths following ether anaesthesia were attributed to various causes other than the after toxic effects of the anaesthetic.

It is unnecessary here to treat in such detail of the symptoms, the findings in the urine, or the pathological changes, as these are practically the same as are found after chloroform anaesthesia. I will simply enumerate the symptoms as found by Bracket, Stone & Lowe in these cases.

The features which they found to be common to patients who suffered from the after toxic effects of ether anaesthesia were, vomiting, associated with collapse, weak, rapid pulse, absence of fever just before death, cyanosis in fatal cases, causing extreme dyspnoea, apathy and stupor, alternating with periods of restlessness, followed by coma and death. From what I have already said, it will be seen that these symptoms are typical of an acid intoxication. Acetone was found to be present in the breath of

these patients. The urine also was found to contain acetone.

Telford & Falconer[2] investigated the urines of nine cases after ether anaesthesia. Acetone was found to be present in eight of these, and in seven cases diacetic acid was found. After ether anaesthesia, however, the acetone and diacetic acid disappeared from the urine much more quickly than did these substances after chloroform anaesthesia.

Beesly[5] found that acetonuria was present in every case after ether anaesthesia, on quantitative estimation, but that it persisted for a much shorter period than the acetonuria after chloroform anaesthesia. He also found that the amount of acetone after ether was greater than after chloroform anaesthesia, but, as I say, it was excreted much more rapidly.

The pathological changes found in these cases were, a fatty liver and kidneys, and also an excessive amount of fat in the muscles of the legs. It is well to note here that the majority of Bracket, Stone & Lowe's cases suffered from Infantile Paralysis, and in these patients there is already an increase of fat present in the paralysed muscles. The authors state that they can make no sharp distinction between fatty degeneration and fatty infil-

tration. This remark is interesting in view of Professor Walker's remarks on a case of Guthrie's 3(Case 3). Walker reports that it is by no means always possible to differentiate between fatty infiltration and fatty degeneration microscopically. Small globules of fat point to a degeneration in contradistinction to the large fat globules of fatty infiltration. These two changes may occur together, and cannot be confidently separated in many cases. Fatty degeneration is generally distributed pretty evenly throughout the lobule; while fatty infiltration is confined to the outer zone. This is, however, only a matter of degree. A centrally placed healthy nucleus is against degeneration, but in the earlier stages it does occur. In the case in point, Walker is of opinion that the change was a degeneration.

We thus find that the features common to cases suffering from toxic poisoning after ether anaesthesia are the same as those in patients after chloroform anaesthesia. Bracket, Stone & Lowe recommend treatment by alkalies in these cases, on the same lines as those laid down for the same condition after chloroform anaesthesia.

Toxic Poisoning after Ethyl Chloride anaesthesia.

Since it was recognised that ether anaesthesia may be followed by after toxic effects, it was suspected that other anaesthetics might be followed by similar results. Cunningham(83) has recorded such a case.

The patient, a girl of 6 years, suffered from adenoids. She was prepared in the usual manner for such cases, and ethyl chloride was administered. The operation, including the administration of the anaesthetic, lasted about a minute. This short time is noteworthy.

Symptoms: Towards evening the patient vomited twice, but slept well during the night. Next day she complained of severe headache and nausea. She retched a good deal, and vomited a few minutes after taking food. The next night she slept fairly well, but vomited once. Two days after operation she complained of severe frontal headache, and vomited immediately after taking anything by the mouth. Towards evening the pulse became rapid and small, and the child felt cold. During the night she again slept fairly well, but vomited twice after taking milk. On the third day after operation, the whole aspect of the child had changed. She now lay in bed with her knees drawn up, taking no notice of any-

thing, but answering when spoken to and complaining of severe frontal headache and of pain in the abdomen; her eyes were sunken and her face somewhat pale, worn looking and drawn. The child was cold, her tongue coated and dry, and her pulse feeble, rapid and irregular. She retained no food.

Alkali treatment was now begun, and next day, i.e. the fourth after operation, the patient was distinctly better; the worn aspect had vanished and the eyes did not appear so sunken. She looked brighter and did not complain of pain in the abdomen; the pulse was still rapid, but regular and better in quality. On the fifth day after operation there was no vomiting, the child looked brighter, and did not complain of pain. The pulse was slower and steadier, and improving in quality; the tongue was becoming cleaner. The sixth day saw rapid improvement, no vomiting, and pulse normal. The patient made an uneventful recovery. The temperature during the illness never rose above 99·8° F., nor fell below normal.

Urine. In the above case diacetic acid was found in the urine on the third day after operation, and was found to be absent on the sixth.

Telford & Falconer(2) investigated the urines in eighteen cases after the administration of ethyl

chloride alone. They found acetone present in fifteen of these and diacetic acid in twelve. The acetone and diacetic acid disappeared from the urine as a rule in two days.

We thus find that ethyl chloride anaesthesia is usually followed by an acetonuria, but the acetonuria in such cases is excreted much more rapidly than it is after ether anaesthesia.

There is still another general anaesthetic which may be followed by toxic after effects, accompanied by acetone and diacetic acid in the urine, that is, Nitrous oxide gas.

Toxic poisoning after Nitrous Oxide Gas.

Langmead(109) has recorded such a case. The patient, a girl of 15 years, suffered from adenoids and middle ear disease: she had been subject to bilious attacks. The patient had the roof of one auditory meatus curretted under nitrous oxide. She was operated upon as an out-patient, and returned home apparently quite well. Two hours later vomiting started and became very frequent. Next day she was greatly prostrated and began to get drowsy. On the third day after operation the girl's doctor thought she was suffering from intestinal obstruction and she was sent to hospital for operation. She

was very restless, tossing about and sighing frequently. Since the operation the patient had wasted from plumpness to emaciation. The eyes were sunken, the abdominal wall collapsed, so that the vertebral column appeared as an abdominal tumour. The breath smelt strongly of acetone, and the urine contained a large quantity of both acetone and diacetic acid. The bowels were opened by enemata. Three days later the vomiting had ceased, and the acetone series had disappeared from the urine. Ten days later she regained her normal nutrition.

Hence we find symptoms similar to those found in delayed chloroform poisoning occurring after Ether, Ethyl Chloride and Nitrous Oxide Gas anaesthesia. The only factor common to all these different anaesthetics is that they all produce narcosis.

A

REVIEW OF THE TREATMENT

of

DELAYED CHLOROFORM POISONING

with a suggestion.

TREATMENT.

Since Guthrie[1], in 1894, first drew the attention of surgeons in this country to the condition of delayed chloroform poisoning, various forms of treatment have been recommended and tried for its cure. On looking over the reported cases of delayed chloroform poisoning, one is struck by the evident uselessness of all recommended treatment in these cases.

In 1906, when Beesly[5] showed the benefit to be derived from Alkalies given prior to operation, really nothing in the way of prophylactic treatment had been tried.

Since Beesly's paper, the most valuable contribution to our knowledge of prophylactic treatment in delayed chloroform poisoning is that by Wallace & Gillespie[87]. They confined themselves to qualitative tests for acetone and showed that cases treated with a definite amount of glucose prior to operation showed much less acetonuria after operation than did those patients who had been similarly treated with an alkali.

The above mentioned paper is the latest important work on this subject that I can find.

With regard to the actual treatment of delayed chloroform poisoning, when symptoms have manifested themselves, the results of such treatment are more disappointing than those of treatment instituted before the operation. Here again, alkalies have been very largely employed, the results being anything but satisfactory. In fact, two of the foremost authorities on the subject, Guthrie[80] and Telford[85], frankly state that they have seen no relief from such treatment.

In my own fatal case, the exhibition of large quantities of alkalies seemed in no way to alter the progress of the condition.

As in other conditions, e.g. Bacilluria, where the urine is highly acid, it is our endeavour to bring the reaction back to normal, if possible. This I think is common sense. It would be much more satisfactory, however, if we could prevent the excess of acid being formed. As I have already indicated, this has been partially successful in prophylactic treatment by means of sugar; but when sugar is not exhibited until late in the disease, it seems to have little effect on the condition.

A useful test as to the acidity of the urine is the giving of 3ij of Soda Bicarbonate in water or milk. The urine in a healthy person will become

alkaline and remain so for twenty-four hours. In a patient who is producing an excess of acid, the sodium will combine with the acid radicles and be eliminated as neutral salts: the urine therefore is not alkaline.

It has been found that when the liver contains a large amount of glycogen, there is only a small quantity of fat present. If the liver contains only a small amount of glycogen, then fat is transported, and is stored up as fine granules in the liver cells. It is well known that in starvation, or when carbohydrates are excluded from the diet, we get acetonuria. If sugar is given to these cases, the acetonuria rapidly disappears. By giving sugar we desire to increase the quantity of glycogen in the liver and diminish the amount of fat. From Wallace & Gillespie's observations this is fairly satisfactorily accomplished when the liver has not already been deranged by an anaesthetic, but once the metabolic processes of the liver have been deranged, it seems altogether a different matter; and the exhibition of sugar in these cases is of little or no avail.

I will now deal in more detail with the Prophylactic Treatment.

Whenever possible, it is advisable to have the

patient under one's own observation for some time previous to operation. Guthrie[3], in 1903, urged that the practice of admitting a patient to hospital one day and operating upon him the next should be discontinued.

The urine of each case admitted to hospital for operation should be tested for acetone as soon as possible. Unfortunately in those cases where we get acute acetonuria, e.g. acute infective conditions, as shown by Beesly[5], we have, as a rule, no time to wait. In those cases one would be wise, as Beesly showed, to use ether as the anaesthetic and not chloroform.

Having received the patient into hospital, are there any special conditions which are more liable to the after toxic effects of chloroform than others? I have already mentioned (p. 27) Infantile Paralysis; and Telford[85] emphasises the fact that children suffering from rickets should have special care.

In those cases which showed acetonuria on admission, prophylactic treatment should be resorted to at once, if chloroform is to be the anaesthetic used.

Diet. Hunter[79] believes the symptoms of delayed chloroform poisoning could be completely prevented if, instead of withholding food, the patient had a nutritious and easily digestible diet, well

sweetened; the last meal to be given only two or three hours before the operation. Guthrie(52) agrees with this suggestion.

With regard to Protein food, Hunter(107) says the ammonia which is absorbed from it and passes into the portal blood plays an important part in controlling the autolytic activities in the liver cell and in neutralising the fatty acids. He contends that as starvation and fright are both causes of acetonuria, a four hours' fast before an operation is too long. If over fattening is observed, Guthrie urges the delaying of the operation and administering purgatives and alkalies. Specially fattening foods are to be avoided. Telford thinks this to be one of the causes of fatalities in children who suffer from rickets.

Bowels. The bowels should be kept regularly open, and should not be allowed to become constipated. Beesly(5) and Kelly(58) have both shown that a certain amount of acetone is excreted by the bowel; therefore, if the bowels are freely open after the operation, the elimination of acetone is accelerated.

Guthrie(3 & 52) particularly emphasises the fact that the history of previous 'bilious attacks' should be carefully inquired into. He considers 'bilious attacks' as indicating a fatty liver.

I am strongly of the opinion that chloroform is a dangerous anaesthetic in those children who have been known to suffer from recurrent vomiting.

Urine. Besides what I have already said about the existence of acetone in a urine before operation, Guthrie(3) mentions in his second paper, in 1903, that carbolic acid may be used as a test to the susceptibility of chloroform. He states that if large quantities of alkaloidal substances are precipitated from the urine after the preparation of the patient by carbolic acid, the chloroform will be taken badly.

In the same paper(3) he mentions Poehl of St. Petersburg, who, having administered Phloridzin, found that glycosuria was produced from a healthy kidney, and contends that if the kidney is not healthy no glucosuria is produced. As the kidney is not the chief organ immediately concerned, I think this test might be omitted.

Preparation of Patient for Operation. If possible at all, carbolic acid should not be used in the preparation of the patient. We have already seen the effects of carbolic acid, with symptoms of poisoning so like those of delayed chloroform poisoning. As to when the patient should be prepared, I think that is immaterial.

In operating upon a patient, one must not forget what Achenk pointed out in 1889, that to follow one anaesthesia in a few days by another is courting disaster.

The Anaesthetic. Offergeld (quoted by Auburtin[115]) has found that the combination of oxygen with the chloroform renders the chloroform less liable to produce toxic symptoms. This observation has also been made by Lengeman[72]. Although the admixture of chloroform and oxygen is less toxic than the mixture of chloroform and air, Lengeman holds that it is still of sufficient toxicity to require caution in its use.

Drug Treatment.

This divides itself into the treatment by an alkali, e.g. soda bicarbonate, or by a sugar, e.g. glucose or dextrose.

Beesly[5], in 1906, states that Morse[127], in his paper on the acid intoxication of infancy, showed that attacks of indigestion could be aborted by giving sodium bicarbonate. This suggested to him the probable prevention or mitigation of the onset of chloroform poisoning by the same drug. He placed two cases of extensive tuberculous cervical

adenitis on 15 grains of sodium bicarbonate, three times a day, for eight days before operation. After operation he made a quantitative analysis of the urine for acetone.

Another case, suffering from the same condition, was not so treated, and he compares the results. In the cases treated by sodium bicarbonate, the apex of acetone excretion was reached the day after operation and did not exceed 5 milligrams in the 50 c.c. of urine. In the non-treated case, the apex of excretion was not reached until the second day after operation, and the urine contained 40 milligrams of acetone per 50 c.c. The cases treated with sodium bicarbonate vomited slightly on recovering from the anaesthetic, but at no time did they exhibit symptoms of poisoning. They took and retained food the same evening. The case not so treated with sodium bicarbonate showed uncontrollable vomiting on the morning after operation, and this later became haemorrhagic. There was a marked odour of acetone in the breath and the pupils were widely dilated. There were also present great excitement and thirst.

Beesly's results speak for themselves and show the great benefit to be derived from pre-operative treatment by an alkali.

I will now consider prophylactic treatment by means of the exhibition of glucose.

Wallace & Gillespie[87], in 1908, published the results of their investigations on 72 cases treated before operation with repeated doses of sodium bicarbonate, 100 cases treated in the same way with glucose, and 127 controls. The urine was examined before operation, i.e. the last urine passed; in females it was withdrawn by a catheter. The urine was examined again 18 hours after operation. The acetone was determined by Jackson Taylor's method and confirmed by Weyl's reaction.

In the first series of cases, i.e. 127 patients who received no treatment, they found the following, viz.: 25.2% showed acetone before operation, 60.4% after operation.

In the 72 cases treated with sodium bicarbonate (℥ss four hourly, in all ℥ss: last dose four hours before operation) 25.4% showed acetonuria before operation and 53.4%, that is 7% less than those patients not so treated, after operation.

In the 100 cases treated with glucose (℥ss every four hours before operation for six doses; last dose four hours before operation) 3% had acetonuria before operation, and 22%, or 31.4% fewer than those treated with sodium bicarbonate, after operation.

The results obtained by Wallace & Gillespie are as remarkable as those obtained by Beesly. They remark that none of their cases treated previously with glucose required any after treatment.

They recommend that emergency cases should be delayed a few hours if possible, to admit of treatment. The glucose may be introduced by transfusion in a 5% sterile isotonic solution.

Wallace & Gillespie recommend a routine treatment; for children, tablets of glucose grs.x. every four hours for twelve doses, and for adults, ℥i of glucose taken similarly.

If in the above investigations a quantitative estimation of the acetone had been made, I am certain a much larger percentage of the patients would have shewn a certain amount of acetonuria. The results obtained by Beesly and those obtained by Wallace & Gillespie are therefore not quite comparable, though each make out a strong case for their respective lines of treatment.

Wallace & Gillespie agree that for after treatment, sodium bicarbonate is the best treatment.

Wallace & Gillespie quote Ladd & Osgood[88] and Young & Williams[89], who show that ether given by the open drop method is followed by a lower percentage of acetonuria cases than when ether is given with

a cone. Beddard[77] has shewn by experiment that if dextrose be given to an animal the transport of fat is prohibited as it is no longer necessary, and that recovery from an anaesthetic is much more likely to take place than if the animal had been starved. He states that feeding with carbohydrates does not prevent the poison from damaging the cells, and has been found to be useless when the protoplasm has been severely damaged. But carbohydrates do provide the cells with the energy they can best utilise, and so prevent them dying from inanition and give them time to recover. Beddard, therefore, suggests giving dextrose by enemata, or continuous rectal infusion in 10% or 20% solution, or intravenously in 6% solution. He recommends this treatment in rickety and ill nourished children. Guthrie doubts the efficiency of dextrose.

Sippel[108] emphasises that every effort must be made not to allow the blood to become too concentrated before operation, but to rather dilute it, as this favours the ready elimination of the anaesthetic from the lungs. He concludes that the glycogen content of the liver must be kept at or above par, as glycogen is such an important factor in burning up fat.

The above includes all that has been recommended in the way of prophylactic treatment.

I now pass on to deal with treatment from a curative standpoint, when symptoms of delayed chloroform poisoning are present.

Curative Treatment.

Many of the symptoms, if not all, of delayed chloroform poisoning have to be treated symptomatically as they arise. In slight cases, no treatment is called for.

When symptoms of delayed chloroform poisoning do show themselves, and vomiting, as I have shown, is practically always the first grave symptom to arouse the surgeon's suspicion, it is well to wash the stomach out with sodium bicarbonate solution, leaving some of the solution behind.(87)

Kelly recommends no mouth feeding if there is any vomiting, and if the condition lasts several days, give nutrient enemata four to six hourly.

As Beesly very properly remarks, the excretions must be stimulated. There must be no hesitation; if any good at all is to come of the treatment, it must be employed at once. The patient must be wrapped in blankets and the skin made to act freely. Normal saline may be introduced by mouth, into the rectum, subcutaneously, or intravenously. The bowels must be opened and kept freely open. Diarrhoea

is not a symptom of delayed chloroform poisoning: it would be better for the patient that it were so. Sodium bicarbonate itself, in solution of ℥ss or ℥ij to the pint, may be introduced per rectum(70). One observer (quoted by Campbell) suggests lactate of soda as being more efficient, to be used in a similar solution.

Sodium salicylate along with sodium bicarbonate has been introduced subcutaneously. Sodium citrate and sodium bicarbonate[75](Case 2) have been combined and given in ʒj doses of each, four hourly, with 2 grains of calomel given frequently. The cases where these were given recovered.

Glucose and dextrose(98) have also been given in ʒj doses; but the results of all these varying methods of treatment are most disappointing. I myself, in two cases, have given sodium bicarbonate by mouth and rectum, normal saline subcutaneously; dextrose in 20 grain doses every two hours for four doses; stimulated the patients when on the verge of collapse with strychnine and oxygen. I have got the skin to act freely and the bowels to move: one case recovered and the other did not. I am very dubious as to how much my treatment contributed to the recovery of the one patient.

Langdon Brown mentions that sodium should not

be given alone, but in combination with half as much potassium and one twentieth as much of calcium and magnesium.

We have already seen what a prominent part is played in this condition by cardiac failure and collapse. This symptom above all others calls for immediate attention.

Hunter[79] notes that the heart's action must be maintained. At the first signs of collapse, Beesly[5] states that free stimulation of the patient must be commenced. Kelly, Guthrie, and all other observers are at one on this point. The most common remedies are brandy, champagne[98], strychnine, camphor and caffeine. One writer[76] suggests adrenalin in the conjunctival sac. Kelly[58], with whom Beesly thoroughly agrees, states that the best stimulant is adrenalin chloride, given subcutaneously every 8 or 12 hours. In children, Kelly gives 200 c.c. of a 1 in 50,000 solution of adrenalin chloride in normal saline, and for adults, 500 c.c. of the same solution. Kelly states that the effect of this is an increased tension and slowing of the pulse. The cyanosis, if present, is replaced by a rather ruddy appearance, apathy is less, and the general condition is markedly improved. This effect is only temporary, and lasts from three to four hours.

For thirst, enemata of salt solution may be given every six hours, alternating with nutrient enemata.

Kelly remarks that it is impossible to say if any treatment has any direct effect.

Oxygen[76] has been employed for collapse.

One writer[69] mentions the employment of venesection in the treatment of delayed chloroform poisoning. Venesection is performed in allied conditions, e.g. uraemia and eclampsia, and possibly some benefit might be derived from this mode of treatment.

Loss of blood has been suggested as a cause of the symptoms, but we have seen how that theory is untenable.

Wallace & Gillespie[87] conclude that the secondary vomiting is in direct proportion to the amount of acetone produced, that anaesthetics should be given by the open method.

I strongly urge that in future cases, as soon as there is a suspicion of toxic symptoms arising, that the patient should have his stomach washed out with sodium bicarbonate, ʒi to the pint, and that some of the solution be left behind in that organ. The patient to be then infused with large quantities of normal saline, and at the same time several ounces of blood, depending on the age of the patient, be

removed from an easily accessible vein. Dextrose or glucose, in doses of 20 grains or 3ℙ might be given four hourly, and the skin and bowels made to act, the latter by a strong solution of magnesium sulphate.

For collapse, I would suggest adrenalin solution, as recommended by Kelly.

From the above remarks upon the treatment of delayed chloroform poisoning, one must conclude that the employment of Prophylactic measures must be our sheet anchor in attempting to eliminate from surgical wards this grave and distressing condition.

SUMMARY.

5. The great predisposing cause which favours the appearance of the toxic after-effects of chloroform is the age of the patient. Ninety per cent. of the reported cases are of children below the age of 12 years.

6. Next in importance, as a predisposing cause, is the development of an acute infective condition shortly prior to the administration of the chloroform.

7. A pre-existent fatty condition of the liver, as indicated by previous 'bilious' attacks, the presence of active rickets in young children, infantile paralysis in older children, and the fact of a gangrenous mass in the abdomen, have been put forward as important predisposing causes by different observers.

8. The symptom complex of delayed chloroform poisoning makes its appearance from 10 to 150 hours, or even longer, after anaesthesia.

9. This symptom-complex consists of vomiting, restlessness, jaundice of varying degree, thirst, fright, delirium, convulsions, drowsiness, coma, 'Cheyne-stokes' respiration, 'air-hunger' and cyanosis.

10. The patient may be flushed or pale; the pulse increases in rapidity, is often irregular, and becomes progressively more feeble. The temperature rises as the fatal termination is approached.

11. Persistent vomiting is generally the first symptom to suggest the presence of delayed chloroform poisoning. This sooner or later reverts to the characteristic 'beef-tea' or 'coffee-ground' type.

12. Restlessness is preceded by an inability to sleep, and is quickly followed by delirium; the patient becomes wildly excited, utters wild screams, tosses himself about the bed, tears off his dressing, grinds his teeth and requires constant attention.

13. The delirium is followed by a drowsy apathetic state, and this gradually deepens into coma.

14. Jaundice, though not present in every case, is very characteristic of this disease. In some cases it is accompanied by haemorrhagic spots in the skin, especially over the abdomen.

15. As the case progresses the respirations become more rapid; in some cases more shallow; in others, deeper than normal. They may also be irregular in rhythm. Towards the end, the respirations frequently take on either the 'Cheyne-Stokes' or 'air-hunger' type.

16. A smell of acetone generally appears in the breath during the progress of the case, but may be absent altogether.

17. A fatal case of delayed chloroform poisoning terminates in one of three ways, viz., by sudden collapse, by increasing cardiac weakness, or by coma.

18. Acetone, in varying amounts, is always found in the urine after chloroform anaesthesia.

19. The acme of acetone excretion occurs during the first twenty-four hours after the anaesthesia.

20. The excretion of acetone may be delayed, and in such a case the prognosis is rendered more grave.

21. The excretion of ammonia in the urine is greatly increased. Leucine and tyrosine have also been found in the urine.

22. Various observers have noted albuminuria, haematuria; also the presence of casts and bile in the urine.

23. Acetone is also excreted in the vomit and foeces.

24. The nitro-prusside test does not detect the presence of acetone in quantities less than two milligrams per 50 cubic centimetres of urine.

25. Postmortem reveals fatty degeneration of the liver, fatty degeneration, cloudy swelling and a mild degree of inflammation of the kidneys, and in the severer cases of delayed chloroform poisoning, fatty degeneration of the heart and other muscles are seen.

26. Other pathological changes which have been noted are, fatty degeneration of the supra-renals and of the capillaries of the gastric mucosa. Hyperplasia of the lymphoid tissue, and a cherry-red appearance of the lungs have also been reported.

27. No definite pathological lesion has been found in the brain or its membranes.

28. The liver is generally larger than normal, and is of a 'pale-buff' or 'canary yellow' colour;

and on section is intensely yellow.

29. Microscopically the liver lobule shows an extreme degree of cellular necrosis around the central venule. The cells in the peripheral part of the lobule are occupied by larger or smaller fat globules, indicating a condition of fatty degeneration and fatty infiltration.

30. The fatty change in the kidney is universally distributed throughout the organ, the convoluted tubules, loop tubules and collecting tubules all suffering.

31. The fatty condition of the capillaries of the gastric mucosa, by causing their rupture, most probably accounts for the 'beef-tea' appearance of the vomit.

32. After anaesthesia, if symptoms of delayed chloroform poisoning make their appearance, the diagnosis is confirmed on finding acetone in the urine, or the smell of acetone in the breath. The diagnosis, however, may have to be made on the presence of the symptoms alone.

32a. A differential diagnosis between delayed chloroform poisoning, meningitis, uraemia and intestinal obstruction may be called for.

33. The prognosis, in seemingly mild cases even, is grave.

34. The prognosis is very bad should the patient be suffering from acute acetonuria at the time of the operation. Chronic acetonuria does not increase the usual risks of anaesthesia. Delayed acetone excretion renders the prognosis much less favourable.

35. Acetone (CH_3-CO-CH_3) is derived from diacetic acid (CH_3-CO-CH_2-COOH) by the loss by the latter of carbon dioxide. This change probably takes place in the bladder.

36. Diacetic acid (CH_3-CO-CH_2-COOH) is derived from B-oxybutyric acid (CH_3-CHOH-CH_2-COOH) by oxidation of the latter. This change takes place in the tissues.

37. The latest theory in regard to the formation of B-oxybutyric acid is that it is probably a normal product formed during the combustion of fats into carbon dioxide and water.

38. B-oxybutyric acid is formed in pathological quantities when the oxidation process, necessary for the complete combustion of the fats to

carbon dioxide and water, is not fully carried out. In consequence of this diminished oxidation, acetone is formed instead of acetic acid, and this may result in the accumulation in the body of the preceding stages, namely, diacetic acid and B-oxybutyric acid.

39. B-oxybutyric acid, when given to a healthy man, is completely oxidised, by way of acetic acid.

40. The oxidation of fats may fail either because the fat is in too large a quantity for the organism to metabolise, or because there is too little oxygen available.

41. Chloroform is a protoplasmic poison, and causes a deficiency of glycogen in the liver, hence the liver receives an excessive supply of fat from the storage depots of the body. At the same time the increased amount of oxygen necessary for the combustion of the excessive quantities of fat is not available.

42. Acetonuria is developed in many other conditions besides delayed chloroform poisoning. Chief among these are Diabetes Mellitus, Recurrent or Cyclical Vomiting in children, Acute Infective conditions, the toxaemic vomiting of

pregnancy, and eclampsia.

43. Anaesthetics other than chloroform may be followed by similar toxic after effects, with diacetic acid and acetone in the urine. Ether anaesthesia generally gives rise to an acute acetonuria, and fatal cases of poisoning have been reported after its use. Ethyl chloride and nitrous oxide are also followed by acetonuria, and symptoms of acid intoxication may be severe.

44. The most effective treatment of delayed chloroform poisoning is to forestall the appearance of symptoms by prophylactic measures. The best results have been obtained by the exhibition of glucose, grains 10 every four hours for children, and one drachm every four hours for adults, for twelve doses, prior to operation.

45. When symptoms of poisoning have appeared, the best treatment is that by alkalies. Soda bicarbonate, by mouth or rectum, alone, or combined with soda citrate, may be good. Normal saline solution subcutaneously or by rectum, dextrose and glucose by mouth or rectum have also been advocated.

46. Adrenalin chloride has also been recommended - 200 c.cs. of a 1 in 50,000 solution for children, and 500 c.cs. of a similar solution for adults.

47. The general experience, however, has been that, once the symptoms of delayed chloroform poisoning appear, no form of treatment has much curative effect.

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