

METHANOL POISONING

ITS CLINICAL COURSE,
PATHOGENESIS AND TREATMENT

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BY

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CHAPTER I.

The History of Methanol Poisoning.

Methanol (CH_3OH), also known as methyl alcohol or wood spirits, is a colourless liquid whose specific weight is 0.81 at 4°C , and whose boiling point is 64.7°C . On oxidation, it forms formaldehyde (HCHO) and formic acid (HCOOH).

Methanol is much used as an anti-freezing liquid for motor cars and as motor fuel. It is an excellent solvent and is much used in the preparation of lacquer and polish. In chemical industry it is used among other things in the production of aniline dyes and formaldehyde.

Poisoning with methanol occurs primarily when access to ordinary alcohol is much limited or prohibited as in time of war. But it may also occur in normal times. Methanol is very cheap in comparison with ethyl alcohol, and the superficial similarity of the two promotes the employment of methanol for the adulteration of beverages.

According to WOOD (1912) poisoning with methanol was practically unknown in America before about 1890 at which period a cheap method of producing fairly pure methanol was discovered. Formerly the wood spirits obtained by the dry distillation of wood had such a disgusting smell and taste that hardly anyone could be tempted to drink it.

A large-scale publicity which emphasized the harmless character of this new preparation and presented it as an excellent substitute for ethyl alcohol was in part responsible for the occurrence of several hundred cases of methanol poisoning at the end of the last and the beginning of the present century. As early as 1904, WOOD and BULLER gave an account of 153 cases of blindness and 122

deaths due to the consumption of methanol or the inhalation of its vapour.

In the same year, STRÖHMBERG reported 16 cases of poisoning in Russia. When the monopolies were closed during the mobilization against Japan, some soldiers, for want of vodka, drank the so-called »Kuntzenbalsam«, consisting of a solution of vegetable oils in methanol.

In 1909, several cases of poisoning occurred in Hungary also. On this occasion GRÜNING expressed the opinion that the prevention of these poisonings belonged to the most important tasks of the medical profession, hygienists and social economists.

As early as 1899 in Germany, KUHNT reported a couple of cases, but otherwise there were no such cases before the Christmas week of 1911 when there were 163 cases of poisoning, with 72 deaths, in Berlin. The persons poisoned had been lodged in a shelter for the homeless, and had drunk spirits in a neighbouring tavern. Subsequent enquiries showed that the spirits had been mixed with considerable quantities of methanol.

During and immediately after the World War, cases of poisoning occurred again in Germany (UHTHOFF 1915) and in Poland (GOLDFLAM 1920). The same was the case in America under prohibition (1919—1933).

During the last war, poisoning on a large scale would seem to have been confined to Finland and Norway. A few cases have also been recorded in peacetime in Norway (HARBOE, GULDBERG, BERNER, USTVEDT and MOHN).

Ever since the close of the last century and up to the present time, the toxicity of methanol has been much debated. There has been a quite general opinion that the poisoning is due to impurities and not to methanol as such. On the other hand, certain authors have at an early stage challenged this belief. KUHNT (1899) maintained that the substances which might occur in small quantities as impurities, i.e. acetone, acetaldehyde, as well as traces of allyl alcohol and higher alcohols, could not account for the characteristic manifestations of poisoning, in particular not the long latent period associated, as a rule, with this form of poisoning.

The fact that various investigators failed to demonstrate any great differences in the toxicity of methanol given to experimental

animals was, in the opinion of REID HUNT (1902), contradictory of the theory that impurities played a part in the poisoning. It was not very likely that the same impurities were present in the same concentrations in samples of methanol obtained at various times and places. He considered as most deplorable the great ignorance of the toxicity of methanol in the medical profession.

WOOD and BULLER (1904) were also of the opinion that methanol itself was responsible for the poisoning, the manifestations of which were the same whatever the combinations in which the methanol was consumed.

The mass poisoning in Berlin already referred to led to a lively discussion in the Medical Society of Berlin on January 10, 1912. Several doctors participating in this discussion expressed their doubts as to the toxicity of pure methanol. FRITZ MENDEL maintained that GEHEIMRAT VON WASSERMANN had said that methanol was not toxic. WOLFF-EISNER was of the same opinion. He had given large doses of methanol to rabbits by subcutaneous injection — the dosage corresponding to about 300 ml. for an adult male — without signs of poisoning.

The report ARONSON could present pointed very strongly to the lack of toxicity of methanol. He had been informed from a most reliable source that in a factory in which large quantities of methanol were produced, six Russian workers had drunk four litres of a 40 per cent. solution. They had become drunk and had vomited somewhat, as after the consumption of large quantities of ordinary alcohol, but they had not suffered from any disturbances of vision.

The study of the toxicity of methanol in experimental animals has yielded somewhat varying results. BIRCH-HIRSCHFELD (1901) claimed to have demonstrated changes in ganglion cells of the retina in rabbits and fowls after poisoning with pure methanol. IGERSHEIMER and VERZAR (1913) gave considerable quantities of methanol over a long period to fowls, but could demonstrate neither diminution of vision nor changes in ganglion cells. They concluded from these experiments that pure methanol is not toxic, and that cases of poisoning in human beings must depend on impurities.

It shows how little was known of the toxicity of methanol that EHRLICH at one time used it as a solvent for salvarsan (PENZOLDT and STINTZING 1914).

Definite proof of the toxicity of pure methanol for human beings was not forthcoming till 1922 when many dock workers in Hamburg were poisoned by methanol which had been imported from New York and was destined for use in chemistry. REIF (1923) found that this methanol was fairly pure, his analysis showing 98.5 per cent. methanol, 1.4 per cent. water, 0.0075 per cent. aldehyde and acetone, 0.008 per cent. acids (calculated as formic acid) and 0.0150 per cent. esters. Ethyl alcohol, allyl alcohol, hydrocyanic acid, alkaloids and compounds of arsenic were not demonstrable.

There can be no doubt that REIF's investigation can serve as evidence that methanol is toxic for human beings. It would be unnatural to assume that the other substances, demonstrated in minute quantities, could have provoked signs of poisoning.

One would have thought that all doubts as to the toxicity of methanol would have vanished after the publication of the above-mentioned investigations. But this has not been the case. HÄMÄ-LÄINEN and TERÄSKELI (1928) put the blame for the poisoning on allyl alcohol. In recent text-books on ophthalmology one may still read that fusel oil is probably the substance responsible for the poisoning. (BERENS 1936 p. 803, ENROTH 1936 p. 460).

The constantly recurring doubt as to the toxicity of methanol must in the main be due to the fact that the consumption of methanol has frequently not been followed by signs of poisoning. But this observation can in no wise support the hypothesis that the poisoning is due to impurities which may be present. The fact that several persons drinking methanol tapped from one and the same cask react very differently is established and is equally difficult to explain whatever may be considered as the toxic substance.

All who have had occasion to observe several cases of poisoning have noted how great are the differences of reaction. UHTHOFF (1915) has related how out of 200 persons all drinking practically the same quantity of methanol, 50 fell ill, and 12 of them died. GOLDFLAM (1920) noticed that many of the persons who had drunk large quantities continued to be well, whereas others, who had drunk much less, developed amblyopia.

ARONSON's communication to the Medical Society of Berlin, already referred to, shows that some persons can tolerate large quantities of methanol. Each of the workers he referred to had drunk

260 ml. of methanol without showing signs of poisoning. On the other hand, reports of blindness following very small doses appeared quite early, witness the communication by WOOD and BULLER (1904 p. 1214):

There are many well-authenticated instances in which the drinking of a couple of teaspoonfuls of wood spirits was followed by blindness.

No wonder that the assumption of the existence of hypersensitiveness to methanol in several human beings gained general credence. On the other hand, the persons who did not fall ill after drinking large quantities of methanol were regarded as particularly resistant. To quote WOOD and BULLER again (p. 1215):

The varying effects of methylated fluid on individuals is largely due to idiosyncrasy, exactly as in the case of ethyl alcohol and other poisons . . . That about 50 per cent. of those exposed to the poisonous influences of wood spirits escape permanent damage is now a recognized fact, and this immunity is mostly due to a peculiar resistance inherent in the nervous and digestive apparatus.

This commonly accepted explanation why poisoning runs a most varied course does not seem very convincing. Some authors have, however, confined themselves to the statement that the variable course of the poisoning is inexplicable (BRÜCKNER, FOERSTER, GOLDFLAM). FOERSTER has pointed out that certain observers have presumed that methanol was particularly toxic when consumed together with ordinary alcohol. Even in the newest text-books on toxicology it is stated that individual predisposition is responsible for the variations in the course of the poisoning (FÜHNER 1943).

If, as it would seem, the toxicity of methanol varies greatly, it must be very difficult to determine the quantity needed to cause blindness or death. According to ZIEGLER (1921) an ounce, or 28.5 g, may prove fatal, whereas others put the fatal dose somewhat higher, i.e. from 50 g upwards (POULSSON, GOLDFLAM). But, as already pointed out, there are cases in which several hundred g of methanol have been tolerated.

Great variations in the duration of the *latent period* have also been observed. It is usual for an interval of about 24 hours to occur between poisoning and the appearance of severe manifestations. Not infrequently this interval may last two or three days. It can be

considerably shortened, lasting only some hours, up to 12, when exceptionally large quantities of methanol have been consumed. GOLDFLAM has stated that death may follow very rapidly after the consumption of several hundred ml. Some of the cases recorded by WOOD and BULLER ended fatally in 6 to 12 hours (cases 34 and 35 p. 1121). In the first case some 500 ml. »bay rum» were consumed, and in the other case the same quantity of »wood spirits».

It is not surprising that the latent period is, as a rule, shortest when the cases are most severe. It is, however, well to note that this is not always the case. Some patients with a much longer latent period than others have developed more severe signs of poisoning although all the patients concerned became poisoned at the same time.

STADELMANN and LEVY (1912 p. 196) have given an account of a young man who, suspected of being poisoned, was admitted to hospital together with others from a refuge for the homeless. He was symptom-free, and he wanted to be discharged at once. But he was persuaded to remain. During the following night and day he was symptom-free. On the evening of the second day he had lain down to sleep when he sat up in bed in a state of anxiety, complaining of air hunger. A moment later his pupils became dilated and failed to react to light, and he was blind. He died an hour after the onset of his symptoms.

This case shows how exceedingly capricious such poisoning can be, and many other observers have had a similar experience. It seems difficult to explain the behaviour of such a case by invoking the hypothesis of individual predisposition.

A good account was given quite early of the symptoms by WOOD and BULLER who classified them in three groups according to the severity of the poisoning. In the first group with slight poisoning, the patient is listless and suffers from headache and slight gastro-intestinal disturbances. There is complete recovery in a few days, but now and then there is more or less serious injury to vision. The cases of moderately severe poisoning in the second group are characterized by more prominent symptoms, vomiting often being violent. Severe disturbances of vision, often increasing to amaurosis, are characteristic of poisoning in this group.

Lastly, these authors put in the third group the cases in which the poisoning is soon followed by coma and death.

X Other authors have described such manifestations as giddiness and an unsteady gait, intense abdominal pain localized to the epigastrium in particular, great thirst and drowsiness. STADELMANN and LEVY as well as FELIX PINCUS (1912) insisted that severe dyspnoea is an ever-present manifestation in the serious cases. PINCUS remarked that cyanosis was usually present in such cases. Among the psychic manifestations, amnesia was very common, and there might be attacks of incoherence and excitement now and then. Motor paralyses were not observed, and the tendon reflexes were retained, being often livelier than normal. Constipation was the general rule. Proteins were not infrequently found in the urine, but never any casts. The proteinuria disappeared rapidly as the patient improved.

Opinions seem to differ as to how far *diminution of vision* bears any definite relationship to the other manifestations. STADELMANN and LEVY, as well as GOLDFLAM, maintained that amblyopia might be the only manifestation, and the first-named authors grouped in the lightest form of poisoning those cases in which the only manifestation was diminution of vision. On the other hand, LEWIN (1912) and RÖNNE (1932) maintain that the ocular manifestations usually occur simultaneously with or after the severe signs of poisoning.

In all the cases running a fatal course, the patients were blind some time before death, the pupils being dilated and not reacting to light (MENDEL, FELIX PINCUS, STADELMANN and LEVY, GOLDFLAM, MENNE). WOOD and BULLER maintained that in some of these cases a history of previous blindness was lacking. Unlike the other authors, they had not themselves examined the patients, and there were no data concerning the reactions of the pupils in these cases. In all the cases of severe amblyopia in which the reaction of the pupils to light was tested, it was found to be sluggish or absent.

X With regard to other ocular manifestations, many investigators have demonstrated pain on movements of the eyes and slight tenderness on pressure on the eyeballs. In most cases the ophthalmoscope shows slight blurring of the borders of the optic discs which are somewhat injected. In other cases there is an exudate on and

around the optic discs whose borders are ill-defined. According to WOOD and BULLER, anaemia of the fundus oculi has been observed, and they concluded from this that methanol might act in the same way as quinine. In several cases an examination of the fundus oculi has revealed no pathological change. In the acute stage, the appearance of the blood vessels has nearly always been normal, except perhaps for slight dilatation of the veins. In cases of permanent amblyopia, atrophy of the blood vessels sets in after some weeks. FUCHS (1919) has described variations in the calibre of the blood vessels in the retina.

The course of the disease is characterized by more or less improvement of vision during the first weeks after which there is almost invariably a gradual deterioration which may lead to complete blindness. GOLDFLAM maintained that this might happen even in the cases in which vision had become normal.

On the other hand, the opinion has been expressed that some of the patients suffering from amblyopia preserve the vision they have regained (ZIEGLER 1921, RÖNNE 1932).

According to WOOD and BULLER the boundaries of the field of vision are as a rule contracted, and the central scotoma is seldom lacking. RÖNNE (1932) also believes that the central scotoma is usually demonstrable, and that in severe cases it can extend right out towards the periphery, so that there are only peripheral remnants left of the field of vision. In other cases there is peripheral limitation of the boundaries.

It is remarkable that some experiments on animals have failed to demonstrate pupils not reacting to light or signs of reduced vision (KROHL 1913, IGERSEIMER and VERZÁR 1913).

It would seem that investigations of the *morphological condition of the blood* have been carried out only on experimental animals. TYSON and SCHOENBERG (1914) found some increase in the number of the erythrocytes and the polymorpho-nucleated leucocytes and in the amount of the haemoglobin in dogs, whereas the number of the lymphocytes was below normal. MIURA (1913) found anaemia in some but not all the rabbits he examined. He also found a rise in the number of leucocytes and lymphopenia.

There has also been no complete *chemical* examination of the blood in cases of methanol poisoning. After SCHMIEDEBERG had

demonstrated an increased excretion of ammonia in the urine in cases of methanol poisoning, and KROHL (1913) had found the same in dogs, interest was taken in the possibility that methanol poisoning may provoke acidosis.

After HARROP and BENEDICT (1920) had demonstrated acidosis in a case of methanol poisoning and had obtained good results with the administration of sodium bicarbonate, investigations were made on experimental animals. HASKELL and his fellow-workers (1921) experimented on dogs and demonstrated a moderate degree of acidosis in some but not in all of them. They concluded that the acidosis had no influence of importance on the course of the poisoning, for some of the dogs with acidosis recovered, whereas among those which died there were some with a normal alkali reserve.

Experimenting on two rabbits and a dog, LOEWY and MÜNZER (1923) found no appreciable reduction in the capacity of the blood to bind carbonic acid although large doses of methanol had been given for several days in succession.

LEO (1925) gave sodium bicarbonate to mice, rats and rabbits poisoned with methanol, and he failed to demonstrate any good effect from this treatment. Accordingly he concluded that acidosis was of no importance in this connection. He does not seem to have ascertained whether the animals suffered from acidosis or not before he treated them with bicarbonate.

Several authors have shown that *human beings*, poisoned with methanol, suffered from acidosis which was often very severe (RABINOWITCH 1922, USTVEDT and MOHN 1932). But certain authors (UNDERHILL, LUND 1944) are sceptical as to the degree of the acidosis playing any part of importance in the course of the poisoning.

It must be considered of the greatest importance to solve the problem of acidosis, and I shall come back to it in the discussion of my own investigations.

Concerning other biochemical investigations, reference should be made in the first place to RABINOWITCH (1922) who found an increase of uric acid (9.3 mg per cent.), creatinin (4.5 mg per cent.), urea (144 mg per cent.), phosphorus (11.2 mg per cent.) and blood sugar (228 mg per cent.).

This author had occasion to carry out several investigations of

the concentration of the above-mentioned substances in the course of two to three days in a patient who died of methanol poisoning and who had, apparently, received no treatment. At the first examination the figures for all the substances analysed were normal, and they rose gradually to the above-mentioned concentrations.

In the case recorded by USTVEDT and MOHN, some increase of the blood sugar (120 mg per cent.) was found, and they also found an increase of the non-protein nitrogen (70 mg per cent.). USTVEDT (1936) demonstrated a difference between the total base and the total acid in the blood of 31.15 milliequivalents per litre, and this was indicative of large quantities of organic acids in the blood.

It is also of considerable interest that HARROP and BENEDICT (1920) found large quantities of lactic acid in the urine in a case of methanol poisoning.

The *pathological-anatomical* findings in human beings have been described by several authors (PICK and BIELSCHOWSKY, FRAENCKEL, STRASSMANN, GETTLER and GEORGE, GULDBERG, MENNE).

Marked rigor mortis is always present. The cadaveric ecchymoses are reddish or reddish blue, and may be reminiscent of the colour of carbon monoxide poisoning (FRAENCKEL, STRASSMANN, GULDBERG).

The meninges are hyperaemic and oedemic, and in some cases definite cortical and subcortical oedema has been described (PICK and BIELSCHOWSKY, MENNE). A microscopic examination of the brain by these authors showed chromatolysis in the ganglion cells, but these changes were much less marked than in the retina. PICK and BIELSCHOWSKY believed that the microscopic findings justified the assumption that there would have been no permanent changes in the central nervous system had it been possible to tide the patient over the acute stage of the poisoning. MENNE also (1938) found that the changes in the cells were not marked.

PICK and BIELSCHOWSKY as well as GETTLER and GEORGE have mentioned the presence of a large quantity of cerebro-spinal fluid which may be blood-stained.

The mucous membrane of the trachea is injected, presenting small haemorrhages here and there. The lungs are much congested with blood and oedematous. The heart is firmly contracted. Small

and scattered haemorrhages, subpleural as well as subpericardial, are to be seen.

The mucous membrane of the stomach and duodenum shows injection and small haemorrhages. In the mucous membrane of the small intestine, MENNE found superficial necroses surrounded by cell infiltrations consisting mainly of plasma cells, eosinophils and monocytes. FRAENCKEL and STRASSMANN have described marked contraction of the intestines, more frequently observed in the large than in the small intestine.

There are no great changes to be found in the liver, spleen or kidneys. Most authors have described slight parenchymatous degeneration of the liver, whereas MENNE found fatty degeneration in 19 out of 22 cases. In these cases the patients were chronic toppers.

The above-mentioned authors found the renal tissues well preserved. Only in a few cases was moderate parenchymatous degeneration of the epithelium of the tubuli contorti found.

The histological changes in the eyes are most interesting. PICK and BIELSCHOWSKY (1912) were probably the first to investigate these changes in human beings. They found considerable changes in the ganglion cells, particularly the large cells. The most significant changes were those demonstrated in the nuclei of cells which stained more deeply than normal and contained many granules packed closely together. The nuclear bodies were for the most part collected in the periphery of the nucleus which always lay in the periphery of the cell body. This position of the nucleus may be normal in small cells, but it is never so constant a phenomenon as in such cases.

In the cytoplasm there were only scant remains of Nissl's bodies, and these were displaced to the periphery of the cells. The fibrillary substance, which normally forms a fine network, was converted into a finely granular mass. Many of the ganglion cells were bullet-shaped, and no dendrites could be seen even in silver-impregnated preparations in which they usually appear quite plainly.

Compared with the changes in the layer of ganglion cells, the other layers of the retina were but little affected. There was hyperchromasia of the inner nuclear layer, with clumping of the chromatic substance.

In two of the three cases examined, the changes in the retina were equally marked throughout, whereas in the third case some normal ganglion cells were seen in the periphery.

The changes in the optic nerve were small in comparison with those demonstrated in the retina. In certain myelin sheaths, spread over a transverse section of the nerve, finely granular decomposition of these sheaths was noticed. On fibrillary staining, distension of the axis cylinders could be seen in a few places. No pathological changes were demonstrated in the optic tract, the external geniculate body, or in the calcarine fissure.

In recent times, histological investigations have been carried out by MENNE (1938) who demonstrated irregular staining of the ganglion cells of the retina, with eccentric localization of the nuclei, irregular and jagged outer limits of the cytoplasm, vacuolization and autolysis. The changes were most prominent in the neighbourhood of the optic disc. There was some hyperaemia and a little oedema of the optic nerve, but this did not lead to any appreciable dislocation of the nerve fibres.

If we now take note of the pathological-anatomical changes demonstrated in animals, it will be remarked that they do not coincide completely with the changes found in man. Thus McCORD has in some instances observed necrosis of the liver, and this has never been described in man.

Some investigators, but not all, have found pathological changes in the retina. BIRCH-HIRSCHFELD (1901) found changes in the ganglion cells of fowls and rabbits. The changes were for the most part observed in the tigroid substance, whereas there was little change in the nuclei. But, as already mentioned, PICK and BIELSCHOWSKY found, in the case of human beings, the greatest changes in the nuclei of the cells.

BIRCH-HIRSCHFELD gave experimental animals very large doses of methanol, and IGERSHEIMER and VERZÁR (1913) pointed out that the changes he had found might have been due to the prolonged death agony. To avoid severe intoxication in their experimental animals (fowls), they gave moderate doses of methanol over a long period. Further, in forming an opinion of the action of methanol, they found it desirable not only to undertake pathological-anatomical examinations, but also to investigate the vision of

their experimental animals. The moderate reduction of vision observed during the tests could, in their opinion, be easily explained as the outcome of the state of intoxication of the animals. Shortly after the completion of these tests, vision was apparently normal. These investigators failed to demonstrate any pathological changes in the ganglion cells.

ADLER and his fellow-workers (1938) investigated the action of methanol on rats and rabbits. The ganglion cells showed small changes after poisoning with methanol »Merck». On the other hand, they believed they had observed certain cells in a more pathological state in animals poisoned with synthetic methanol. The ophthalmoscopic findings were normal.

There should be no difficulty over the *diagnosis* when the clinical picture presented by methanol poisoning is fully developed. Quite early, WOOD and BULLER pointed out that poisoning with methanol gives rise to manifestations differing from those of every other form of poisoning. The clinical picture is so unique, characteristic and plain that there can be no difficulty in arriving at the right diagnosis if only the examiner's attention has been drawn to the manifestations of this form of poisoning. When acute abdominal symptoms and bilateral amblyopia or amaurosis occur after a drinking bout, methanol poisoning is more than likely.

Yet, mistakes in diagnosis have been very common because most doctors are ignorant of the clinical picture. The diagnoses of cholera and botulism were discussed on the occasion of the mass poisoning in Berlin before methanol was thought of.

While it should not be difficult to make the right diagnosis when the poisoning has developed fully, it seems to be almost impossible to do so before the onset of severe general and ocular manifestations. How easily fatal diagnostic mistakes can be made in these cases is evident from the statement made by FELIX PINCUS in connection with the poisonings in Berlin (p. 43):

Die Leichtkranken als krank zu erkennen, hatten wir an diesem ersten Abend noch nicht die nötige Übung. Sie wurden, ich glaube fünf an Zahl, wieder zurückgeschickt. Alle kamen nach 2 bis 3 Stunden mit schweren Symptomen wieder zur Untersuchung.

The *pathogenesis* has given occasion for much discussion. The tendency of older authors to regard formic acid as the peccant sub-

stance may perhaps be traced to the demonstration by POHL that there is a connection between the time at which the maximum excretion of formic acid occurs and the severest manifestations of poisoning. Yet, among these same authors there were to some extent diametrically opposed views as to the mode of action of formic acid. While HARNACK (1912) maintained that the toxic effect was due to the formiate ion, SCHMIEDEBERG regarded it as non-toxic. He was of the opinion that the real cause of the toxic effect was the acid poisoning due to formic acid.

In opposition to this latter view, several authors have pointed out that the quantity of formic acid demonstrated is too small to provoke acidosis of any great degree. EGG (1927) has noted that formic acid is a weaker acid than malic acid and tartaric acid, and the quantity of formic acid produced by 8 ml. of methanol corresponds to the quantity of free malic acid and tartaric acid present in 400 ml. of the juice of ripe grapes. He did not think that methanol poisoning was characteristic of acid poisoning, and he was sceptical as to the life-saving action of treatment with alkalis. Experiments on animals were, in his opinion, opposed to the view that methanol is not poisonous until it has been oxidized.

EGG believed that methanol was toxic on its own account, and that its toxicity depended on a complex binding of the iron in the cells' granules leading to an inhibition of the processes of oxidation. In support of this hypothesis he pointed out that methanol inhibits several processes of oxidation which are katalyzed by iron (the guaiacol and benzidin reactions, the indigo oxidation and phenol reaction with hydrogen peroxide). However, these reactions are also inhibited by ethyl alcohol, the two last reactions more so than by methanol.

On the basis of these investigations, EGG came to the following conclusion:

Die Aehnlichkeit der beiden Alkohole in ihrer Reaktionsweise in vitro entspricht ihr aehnliches toxikologisches Verhalten, die grossere Giftigkeit der Methylverbindungen ist eine Folge von deren geringeren Zerstörbarkeit, der Methylalkohol kursiert im Organismus länger und in höheren Konzentrationen als der Aethylalkohol.

The author certainly seems to contradict himself when on the one hand he maintains that methanol poisoning does not resemble

an acid poisoning, and on the other hand he attempts to explain the symptoms as the consequence of inhibition of the processes of oxidation which must necessarily give rise to an acidosis.

It is also impossible to agree with the view that methanol is more toxic than ethyl alcohol because the former stays longer in the body. If this were the cause of the differences in the action of the two alcohols, ethyl alcohol could be made to provoke a similar clinical picture of poisoning by its administration several days in succession.

The view that formaldehyde is the substance responsible for the symptoms of methanol poisoning seems to have been almost unchallenged in recent years (FLURY and WIRTH 1936, ALDER and fellow-workers 1938, KEESER and VINCKE 1940).

The way in which formaldehyde is supposed to act is described by FLURY and WIRTH as follows (p. 223):

Das Hauptgewicht ist bei der Beurteilung der Methylalkoholwirkung auf die Formaldehydbildung zu legen, und zwar auf die Entstehung dieses hochwirksamen Giftes an Ort und Stelle, gewissermassen in Statu nascendi, innerhalb der Zellen. Formaldehyd ist überaus reaktionsfähig, es fällt Eiweiss und hemmt viele fermentative Vorgänge.

These authors explained the disturbances of vision, the nervous disturbances and coma by assuming that formaldehyde has a selective action on nerve tissue. *

In disagreement with HARNACK, they considered that the formiate ion is not toxic.

In the discussion of the manifestations of methanol poisoning, I have already pointed out that the part played by acidosis continues to be debated. LUND (1944) believes that acidosis is probably merely a phenomenon running parallel with the other symptoms, and does not by itself cause permanent injury.

It is hardly surprising that the ocular manifestations have been interpreted as the expression of an acute retrobulbar neuritis. The well-known manifestations of this condition are pain on movements of the eyeballs, the central scotoma, and absent or scanty pathological changes demonstrable by the ophthalmoscope.

When the ophthalmoscopic findings were normal, Wood and BULLER assumed that retrobulbar neuritis existed, and they interpreted oedema of the optic disc as an expression of papillitis.

KRÜDENER believed that in certain cases primary atrophy might develop, and in such cases there was no chance of recovery, whereas the prognosis was better for retrobulbar neuritis.

The pathological-anatomical findings in the retina and optic nerve already referred to have, however, shown that there is no inflammatory condition in either the optic nerve or the optic disc. Certain authors have pointed to disturbances of the circulation in the retina as a possible cause of the degeneration of the ganglion cells, partly as a result of increased viscosity of the blood (TYSON and SCHOENBERG), partly because of vaso-constriction (WOOD and BULLER). Lastly, oedema of the fundus oculi has also been regarded as a causative factor. ZIEGLER (1921) associated the first improvement in vision with diminution of the oedema, and HÄMÄLÄINEN and TERÄSKELI (1928) interpreted the favourable effect they observed from lumbar puncture as a sign that there was a causative relationship between the oedema and the degeneration of the ganglion cells.

In opposition to this view, NÜEL (cit. BIRCH-HIRSCHFELD) believed that the oedema was a secondary phenomenon resulting from the degeneration. The observation that the retina can for a long time tolerate stasis without any appreciable reduction of its functions is, in his opinion, opposed to the assumption that the oedema is the primary factor.

Since SCHANZ (1920) put forward the hypothesis that light has an injurious influence on the course of methanol amblyopia, several authors have studied this problem. In his experiments on rabbits and dogs, SCHWARZKOPF (1922) could find no difference between the illuminated and the non-illuminated eye.

GOLDSCHMIDT's (1922) demonstration of a much reduced cell respiration in the retina under the influence of methanol is of considerable interest. This effect was much more marked in the retina adapted to light than in the darkness-adapted retina.

There have been no clinical investigations of the possible effect of light on methanol amblyopia. SCHIECK (1922) observed a case in which there was a rapid diminution of vision after the patient had been dazzled by sunlight six weeks after the poisoning. It is conceivable that at this stage there would have been a diminution of vision even without the action of sunlight. As, however, the

diminution of vision followed immediately upon exposure to light, one cannot ignore its possible influence.

The main principles in the *treatment* of poisoning with methanol have consisted in eliminating it from the organism and in stimulating the patient with a view to preventing collapse.

Gastric lavage has been recommended by almost every author. PENZOLDT and STINTZING have pointed out that it is difficult to carry out, either because the patient is unconscious or because he is very restless. STADELMANN obtained no benefit from this treatment. Enemas, the administration of large quantities of fluid, measures to promote sweating, and the inhalation of oxygen have also been recommended.

Much use has been made of various cardiac stimulants among which WOOD and BULLER include ethyl alcohol. In this connection they refer (p. 1220) to a colleague, Dr. R., who had seen treatment with whisky have a good effect on a patient. This doctor believed that ethyl alcohol helps to prevent collapse. Furthermore, he was of the opinion that what had primarily saved the patient was the removal of methanol from the stomach and intestine.

Treatment with alkalis was proposed about 1920 (ISAACS, HARROP and BENEDICT, ZIEGLER). RÖNNE (1932) maintained that even if the reports of this treatment were most promising, further investigation was required in order to establish its value. On the assumption that acidosis is a phenomenon which does not decisively influence the course of the poisoning, doubts have been expressed also in recent times as to the value of treatment with bicarbonate (UNDERHILL).

The treatment of amblyopia has not been very promising. Pilocarpine, potassium iodide and injections of strychnine have been given, but in PENZOLDT's and STINTZING's toxicology their use is discouraged as their beneficial effect is very doubtful.

On the other hand, several authors have had high hopes for lumbar puncture as a treatment for the amblyopia (ZETHELIUS and WERSÉN, FRIEDRICH PINCUS, HESSE). SCHIECK, however, has seen no effect from this treatment. We must surely agree with RÖNNE that further investigations are necessary in order to determine the value, if any, of this treatment.

Lastly, it must be admitted that it is impossible to form a

prognosis. STADELMANN expresses his opinion on the prognosis in the following words (p. 196):

Diese ist sehr infaust und nicht zu stellen. Ich habe es schliesslich gar nicht mehr gewagt, bei den Kranken den Verlauf der Krankheit vorauszusagen. Leichte Fälle wurden schwer und schwere Fälle besserten sich, ohne dass wir dafür Anhaltspunkte hatten.

In particular this author was struck by the fact that several persons who had been admitted to hospital for observation, and who had been symptom-free at this stage, suddenly became ill and died 36 to 48 hours after admission.

Summary of Earlier Investigations.

It is most difficult to form an opinion as to the nature of methanol poisoning on the basis of the findings of the investigations available for scrutiny.

The records of investigations show that on the whole there is agreement over the clinical picture of methanol poisoning, with dyspnoea and disturbances of vision as the most prominent manifestations together with gastro-intestinal and nervous disturbances. But opinions differ widely over the pathogenesis of these phenomena.

It may be considered as proved that the poisoning is due to methanol itself and not to accidental impurities. But it has not yet been shown in what way methanol or the products of its combustion give rise to the clinical manifestations.

There is also no satisfactory explanation of the great variations in the reactions of different persons, for instance in the latent period preceding the onset of symptoms.

The elucidation of these problems requires further research. With a view to defining the lines such research should follow, some of the problems involved will be discussed more fully in the following chapter.

Table XXV.

Case nr.	Volat. red. s. in blood %	Alk. res. vols. %
6	0.075	22
7	0.024	24

The acute course run by case nr. 22, compared with that run by case nr. 23, may have depended on the great restlessness of the former before his admission to hospital.

On account of the factors mentioned which, apart from the consumption of ethyl alcohol, may influence the degree of acidosis and thereby the effects of the poisoning, it is natural to conclude that the smallest quantity of methanol required to cause blindness or death may vary somewhat from case to case. Case nr. 46 seems to show that a very small quantity can render the patient blind. This patient drank two very small drams of methanol which was probably mixed with sugar and water. He stated that the vessel out of which he drank was somewhat smaller than a measured medicine glass with a capacity of 15 ml. It is therefore probable that he did not drink more than about 20 ml of methanol. The 50 ml said to have been drunk by patient nr. 36 induced amblyopia, but he survived without bicarbonate treatment. Severe poisoning (nr. 3) may be caused by 70 to 80 ml which may undoubtedly prove fatal if no treatment is given.

The time taken before methanol is eliminated from the body depends on the amount taken. A very small amount will have disappeared within two days (nrs. 9 and 46). Patients who are not treated during the first days of the poisoning, and who drink moderate quantities (70—80 ml) may present symptoms up to 4. day (nr. 3).

When much methanol has been consumed, the time taken for its elimination can be reckoned only in those cases in which bicarbonate treatment is given or ethyl alcohol is drunk, for the other patients will quickly die, usually in one to two days. Recurrence of the acidosis may be observed on 4. day, as happened in several cases (nrs. 23, 24, 52, 78), but such recurrence has not been observed at a later date. Methanol could not be found in case nr. 67 which

ended fatally from pneumonia on 5. day. It is important to know that the patient must be kept under supervision until 4. day if we are to be sure to avoid a catastrophe.

As I have repeatedly pointed out, the poisoning runs a much more acute course when large quantities of methanol have been drunk than when its dosage has been moderate, always provided that no ethyl alcohol has also been drunk.

It is not always possible to show that the latent period is shortest when the dosage of methanol has been greatest, but, as already pointed out, it is often difficult to determine exactly the length of the latent period, particularly in the most severe cases when the patient cannot give an account of himself and of the onset of symptoms. What is certain is that patients who have drunk large quantities of methanol may die within a few hours after the onset of symptoms. On the other hand, when the poisoning is due to a moderate dose, the patient may present signs of severe acidosis for two to three days, and may survive even without treatment. The organism's ability to prevent a fatal fall of the alkali reserve under such conditions must in large part depend on the diminution of chlorine in the blood which sets free alkali.

The observation that ethyl alcohol, when drunk at the same time as methanol, seems to prolong the latent period by almost exactly the same interval as that required for the oxidation of ethyl alcohol, seems to warrant the conclusion that even a low concentration of ethyl alcohol in the organism is enough to prevent acidosis. The observation that ethyl alcohol, drunk on the day after the poisoning but before the onset of symptoms, can prolong the latent period by a *longer* interval than that required for its oxidation, shows that it can under such conditions evoke a rise of the alkali reserve. The fact that even severe symptoms quickly vanish after the consumption of ethyl alcohol late in the course of poisoning (see nr. 17) shows that ethyl alcohol not only arrests the further increase of acidosis, but also reduces it.

The course of the poisoning may be varied in many ways, for it not only depends on the quantity of ethyl alcohol consumed, but also on the time at which it is consumed, as well as on the quantity of methanol taken. Let us picture to ourselves a patient who drinks a large quantity of methanol, for example 200 to 300 ml. If

he drinks a large quantity of ethyl alcohol on 1. day, there will be a corresponding prolongation of the latent period. If he does not subsequently drink ethyl alcohol and receives no bicarbonate treatment, he will die. If on 2. day he drinks a quantity of ethyl alcohol which is not eliminated till 3. day, he may yet develop alarming signs of poisoning for, as we have seen, acidosis may recur on 4. day. If he drinks ethyl alcohol also on 3. day, it is probable that he will show no signs of poisoning.

When poisoning is due to a small quantity of methanol such as 50 ml for example, a single large dose of ethyl alcohol, which prolongs the latent period till about 2 days, may turn the scales, as during this interval so much methanol may be excreted that what remains of it can hardly provoke alarming symptoms. Approximately the same effect can be obtained by a smaller quantity of ethyl alcohol when it is consumed on the day after the poisoning.

Briefly it may be said that, when methanol only is consumed, the severity of the course of the poisoning has been found always to depend on the quantity consumed. There is thus no evidence to show that individual predisposition plays any part.

Ethyl alcohol has been shown to have a powerful antiloxic action which is undoubtedly the main reason why the behaviour of these cases, as repeatedly observed in mass outbreaks of poisoning, is so remarkably variable. In Chapter V I shall try to provide a theoretical explanation of the mode of action of ethyl alcohol.

C. Diagnosis.

The clinical picture of methanol poisoning is so characteristic in severe cases that it can hardly be confused with other ailments. Manifestations of severe acidosis, bilateral amblyopia or amaurosis with dilated pupils which react feebly or not at all, must be said together to be pathognomonic of this poisoning.

Even when these characteristic manifestations are lacking and only a slight or moderate degree of acidosis is demonstrable, this warning should always make one suspect methanol poisoning if no other cause of the acidosis can be found. Such patients enter hospital usually because they or the criminal police have learnt that some of their fellow-carousers have fallen ill. Reports on what has

happened should under these conditions be sufficient to prevent a mistaken diagnosis even if there is no acidosis at the moment when the patient is examined. This, as already pointed out, may be so because ethyl alcohol has been consumed. By measuring the alkali reserve repeatedly, acidosis will be revealed in time to save the patient's life.

At a time when methanol poisoning is of common occurrence, it is inevitable that many persons suspected of methanol poisoning will be admitted to hospital without definite evidence of the consumption of methanol. Such cases often concern persons found dead drunk, quite incapable of explaining themselves. In such cases the assumption that the patient is merely drunk may prove fatal to him. If in addition to ethyl alcohol he has drunk methanol, acidosis will as a rule be demonstrable a day or two after admission to hospital where he must of course be kept under supervision for some days before the existence or non-existence of methanol poisoning can be ascertained.

A test ensuring an earlier diagnosis is needed. It is by no means fitting that a person who is merely drunk should monopolize a hospital bed for several days. If the patient has drunk methanol, it can be demonstrated in the urine or the gastric contents. Such a demonstration requires only a few hours at a chemical laboratory.