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Clinical Investigations of Methyl Alcohol Poisoning with Special Reference to the Pathogenesis and Treatment of Amblyopia.

By

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I. Introduction.

During the five last decades, several investigators have studied methyl alcohol poisoning both clinically and experimentally. Yet there seem still to be widely divergent opinions as to the causes of the toxicity of methyl alcohol.

Apparently the reaction to the drinking of methyl alcohol varies greatly in different individuals. Uhthoff (50) found in a mass outbreak that only about one quarter of the drinkers fell ill, and yet their consumption of alcohol did not differ appreciably from that of the rest. Goldflam (13) noted that even if the severity of the poisoning was usually proportional to the amount of methyl alcohol consumed, some patients were dangerously ill even after small doses. Poulsson (38) states that alarming symptoms have been observed after 11.5 g, and according to Ziegler (57) one teaspoonful of pure methyl alcohol can provoke blindness.

These and several similar observations have led to the general assumption that individual predisposition to this poison varies greatly. In his discussion of the serious prognosis, Jackson (21) writes: »Idiosyncrasy plays a large part in the condition, and what might be an inocuous dose for one person might be fatal for another.»

This view does not, however, tally with Pohl's (37) statement: »Die biologische Bewertung der Alkohole hängt ganz ab von der Dosis in der sie aufgenommen werden.»

If this ruling is applicable to methyl alcohol, the general belief that its toxicity varies in different persons must be incorrect. In which case the most varied course of the poisoning must depend on other factors than the methyl alcohol itself.

Brückner (6) has, in opposition to other writers, evidently not been convinced as to the soundness of the theory that individual predisposition is of importance to the course of the poisoning, for he writes: »Disposition und Idiosynkrasie sind Umschreibungen die gegenüber so unterschiedlicher Wirkungsweise nichts erklären können.»

There are great differences of opinion as to the causes of the toxicity of methyl alcohol. While Pohl (35), Krohl (27) and Schmiedeberg (cit. Krohl) consider that its toxicity depends on formic acid, Brückner (6), Flury and Wirth (10) and Kazas (24) maintain that formaldehyde is the potent agent. Egg (9) considers that it is the methyl alcohol which is toxic. He assumes that it forms a complex compound with the iron in the granules of the cells resulting in inhibition of the processes of oxidation. He finds that formic acid is present in too small quantities to be injurious.

The divergent opinions of different writers as to the mode of

action of methyl alcohol betray many gaps in our knowledge of the processes of poisoning with this substance.

We do not yet know why methyl alcohol exerts a selective action on the retina.

II. The Object of the Investigations.

The long latent period is one of the characteristic features of this form of poisoning. This period usually lasts some 24 hours, and is not infrequently a matter of several days. During this period it is possible that other factors than the methyl alcohol itself influence the course of the poisoning.

It is primarily a solution to this problem which has been sought in the present study.

Many of the patients were chronic tipplers. Some of them would, as a rule, drink ordinary alcohol even before feeling unwell after the poisoning. Hence the need of an investigation of the action of ethyl alcohol on methyl alcohol poisoning.

Others among the patients did not usually drink much alcohol. They would, as a rule, go to their work on the day after the poisoning, whereas the chronic tipplers would, for the most part, always be out of work. Hence the call to investigate the influence, if any, of muscular action on the course of the poisoning.

It is blindness, and only this, which renders those who survive this poisoning invalids for life. This is why special interest attaches to the pathogenesis of this condition.

Is there, in the first place, any relationship between the severity of the general symptoms and the degree of the amblyopia? In the second place, are there other factors of importance in the development of amblyopia? This may well be so, for there are cases on record in which amblyopia occurred in the absence of other serious signs of poisoning. In this connexion the part light may play in the genesis of amblyopia will be discussed.

In the follow-up investigations, it has seemed advisable to elucidate the course of the amblyopia. This line of research does not hitherto seem to have been followed over a long period after the poisoning. Even though failing sight has often been observed in these cases after the first period of improvement, it is assumed that there are some patients who retain the vision they regain

(Rönne and others). Further knowledge on this score would greatly facilitate the prognosis.

Finally an attempt will be made to give a theoretical explanation of the selective action methyl alcohol exerts on the retina and the optic nerve.

III. The Methods Employed.

Great importance has been attached to obtaining as complete records as possible of cases. Hospital records, being often scanty, have been supplemented by information obtained from the patient after the acute stage of the poisoning. Many of these patients, however, suffer from marked amnesia, and the value of their evidence may therefore be called in doubt. The patients' relations and boon companions have, accordingly, been written to or interviewed whenever possible.

Special importance attaches to the information given by those boon companions who did not themselves fall ill. They have, as a rule, been able to state how much the patient drank, and how much they themselves drank of spirits containing methyl alcohol and ordinary alcohol. This information has been useful in seeking an explanation for the diversified manifestations of the poisoning.

Exact data have also been needed for timing the onset of visual disturbances in relation to the general symptoms — an important point in determining the part played by acidosis in the development of amblyopia. Without these data it would be impossible to form an opinion on this point in those cases in which the general manifestations had wholly or partly disappeared on the patient's admission to hospital.

The findings of the clinical examinations and blood tests have been obtained from hospital records. In a couple of cases, and at the author's request, the lactic acid content of the blood was determined.

The ophthalmological examinations have been carried out by myself on all the patients who survived the poisoning. Data concerning patients Nr. 1 and 2, who had been treated in other hospitals before admission to Ullevål, have been obtained from that source. Abstracts have been made from the records of two cases already published, by Harboe (16) in 1920, and Ustvedt and Mohn (32) in 1932.

After correction of refraction errors, vision was determined by Snellen's types, finger-counting, movements of the hand and light. By »normal vision» is meant 6/6 even though this is not, scientifically speaking, strictly identical with full acuity of vision.

The field of vision was examined according to Donders' method in the hospital wards. When, at a later date, it was examined at the Eye Department, the perimeter and Bjerrum's screen were used.

During their treatment at Ullevål, the eyes of nearly all the patients were protected against light, those who suffered from amblyopia wearing darkened spectacles also after discharge from hospital. For the examination of the acuity and field of vision, the patients were given about 10 minutes in which to adapt themselves to the illumination employed.

The perimeter was placed between two electric bulbs, each of 100 watt, to make its illumination as constant as possible. The distance from each of these bulbs to the perimeter was about one meter. The bulbs were raised or lowered a little when necessary to avoid a shadow being cast by one half of the perimeter arc on the other.

It soon became evident after the first examinations that the acuity of vision of the periphery of the retina was surprisingly high even when central vision was much reduced. Use was therefore made of a 10-millimeter object when the outer limits of the field of vision were investigated.

It was also found that, on testing with Bjerrum's screen, it was convenient to use the same object, as the limits for the scotomata, notably the relative scotomata, could be determined with greater precision than with larger objects.

When a scotoma is central and absolute, one cannot be sure that the fixation mark on Bjerrum's screen lies in the prolongation of the optic axis of the eye. It is therefore doubtful if the scotomata found are in reality in that part of the field of vision indicated on the charts. This possible source of error is to a certain degree corrected, after a preliminary determination of the approximate size of a scotoma, by drawing a white cross whose crucial point coincides with the fixation mark. This cross is drawn a little larger than the scotoma in question. The patient is then told to adjust his vision in such a way that he can just see the four ends of the cross.

When the amblyopia has lasted a considerable time, the acuity of vision is registered graphically from the date of admission to hospital in periods of two to three months. On these graphs, the starting point coincides with the day of the poisoning, the abscis with the time, and the ordinate with the acuity of vision.

IV. Case Records.

The material studied consists of 16 patients suffering from methyl alcohol poisoning. Cases Nr. 15 and 16 have already been published and are the only cases of methyl alcohol amblyopia hitherto on record in Norway.

The other 14 patients were treated at Ullevål Hospital between July 31, 1941 and April 14, 1942. Two of these patients (Nrs. 1 and 2) had been treated at other hospitals during the acute stage of the poisoning, whereas the other 12 were admitted direct to the medical wards of Ullevål Hospital.

In the discussion of the pathogenesis of the poisoning, brief reference will be made to two patients who were treated on the medical side of Drammen Hospital in November 1941.

Case 1.

Reference number 11883/41 — S. K. A man, unemployed, aged 56.

On May 4, 1941, he drank about 90 cm^3 of methylalcohol destined as a freezing solution for motor cars. He knew it was wood spirits he was drinking, and he said that he did not become intoxicated.

On the morning of May 5, he felt well and went down to the sea shore to attend to a boat. The sun was shining. After spending a couple of hours on the piers, he suddenly noticed that his vision became cloudy. After he had returned home at midday, he was seized by an attack of vomiting, severe thirst and breathlessness. He had the same symptoms on May 6 when, according to his wife, he was very drowsy. This he could not remember himself. On May 7, vision was much reduced, whereas the other symptoms showed improvement. It was not till May 8 that he was admitted to the Eye Department of the Rikshospital. He was now blind. He gave no information concerning his consumption of methyl alcohol

On May 8, an ophthalmological examination showed normal externa and clear media. The pupils were dilated, reactionless. The optic discs were injected, their limits blurred, with slight oedema around them. The size of the arteries was normal, but there were some small, punctiform haemorrhages scattered along the blood vessels. The veins were well filled. Vision = 0. o. u. (both eyes).

Blood pressure 135/90 Hg. Normal findings on clinical examination. A trace of albumin in the urine.

On May 16, a neurological examination showed left-sided hyposmia, right-sided deviation of the tongue and palatine raphe, as well as increased patellar and Achilles reflexes on the right side.

A radiological examination of the cranium showed nothing amiss, and the cerebro-spinal fluid was normal. Wassermann negative in blood and cerebro-spinal fluid. He was discharged on June 14. Vision o. s. (left eye): Finger-counting at 1 meter. o. d. (right eye): Finger-counting ½m.

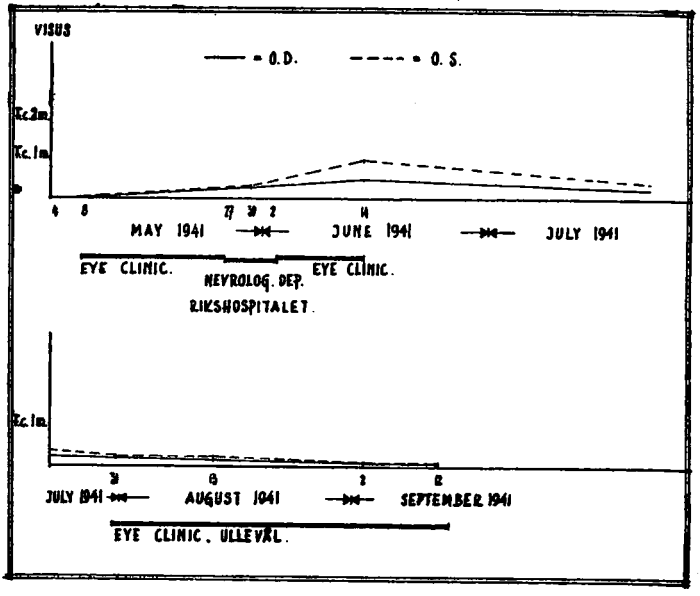

Fig. 1. Case 1 — S. K. F. c. = Finger-counting.

On his admission to the Eye Department of Ullevål on July 31, the pupils measured 5.5 mm. reacting feebly to light. The optic discs were sharply defined, fairly pale, the blood vessels thin and uneven in calibre. As the chart shows, vision declined after his stay in the Rikshospital, and it continued to do so during his stay at Ullevål Hospital.

He was treated with potassium iodide and sweat baths, and he was also given injections of vitamin B_1.

Analysis of the spirits revealed pure methyl alcohol. He was discharged on September 13, 1941.

The alkali reserve was not investigated in this case, but the symptoms indicated severe acidosis before his admission to hospital.

Some time later he was admitted to the Psychiatric Department for depression and insomnia. On re-examination on February 21, 1942, there was weak perception of light on both sides and projection of light upwards.

Case 2.

Reference number 16100/41. K. L. L. A workman pensioner, aged 61.

The patient, a chronic drunkard, was transferred from the Eye Hospital at Hamar. On August 25, he travelled from Oslo to Hamar on a visit to his daughter. Next day he slept much more than usual, and had to be awoken whenever he was served with food. On August 27, there was no change in his condition. On his admission to hospital on August 28, he denied having drunk methyl alcohol, but he admitted that, two days before his journey to Hamar, he had drunk a couple of bottles of beer and some »akevit» — potato spirits.

There was bilateral amaurosis, with injection of the optic discs whose limits were somewhat ill-defined. The fundus was in other respects normal. A slight degree of vision returned gradually, and on September 29,

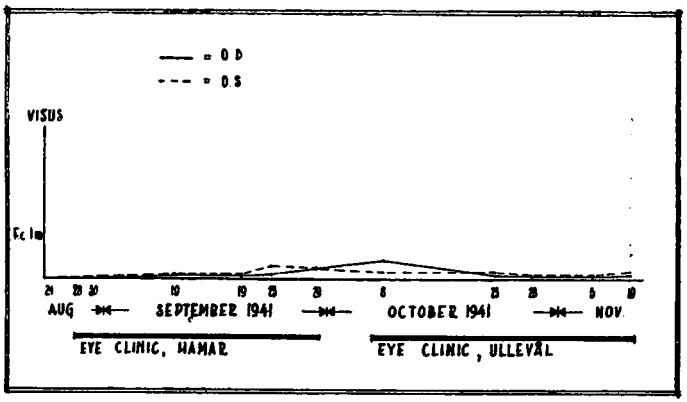

Fig. 2 Case 2, K. L. L. F. c. = Finger-counting.

he could count fingers at 30 cm with either eye. On the same date some limitation of the outer limits of the field of vision and an absolute central scotoma were demonstrable.

On coming to the Eye Department of Ullevål on October 7, the patient looked well. Pulse 48, regular. Temperature 36.5° C. Blood pressure 145/75 mm Hg.

The clinical findings, including the urine analysis, were normal. Apart from the eyes, the neurological examination proved negative. A skiagram of the cella turcica and sinuses was normal. In the blood and cerebrospinal fluid Wassermann was negative.

The ophthalmological examination showed normal externa, pupils about 4 mm, with sluggish reaction to light. The optic discs were pale and excavated, with atrophic blood vessels.

The chart shows the course of vision.

He was treated with preparations of vitamin B_1 and roborants.

This patient also showed signs of a severe poisoning. He was late in coming for treatment and is practically blind.

Case 3.

Reference number 16952/41 — G. H. A man, bookbinder, aged 32.

He had hitherto been well, and vision had been good. On the evening of October 18, 1941, he shared with three companions spirits brought in two beer bottles. He believed he drank two tumblersful of a mixture of spirits and lemonade, in the proportion of 1 to 2.

He did not become intoxicated, but he felt tired and went to bed at 23 o'clock. He slept till 14 o'clock next day when he suffered from headache and nausea, and saw black spots before his eyes. Having eaten a little, he fell asleep again. On October 20 he felt tired, could not go to work, and had misty vision.

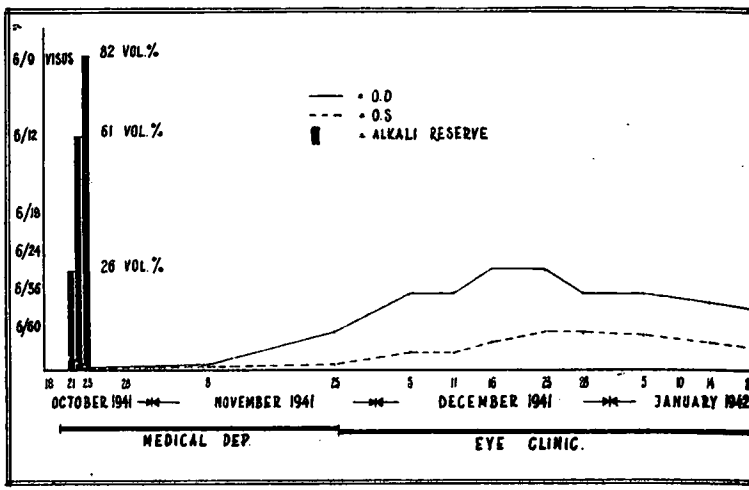

Fig. 3 Case 3. G. H.

On admission to hospital on the same day, he could give a clear account of himself though he felt tired and drowsy. Though vision was poor, he could read a newspaper. He complained of pressure over his eyes. Pulse 90 and regular. Temperature 37.7° C. Respiration not embarrassed (respiration rate not recorded). Blood pressure 150/100. Pupils equal and dilated, reacting to light and accommodation. The clinical findings, including the urine analysis, were normal.

Ophtalmological examination was not performed till October 21 at 14 o'clock. He was then very restless, throwing himself about in his bed. There was severe dyspnoea with markedly deep respiration.

The ophthalmological examination showed normal externa and clear media. The pupils were equal, 6 mm, reacting very sluggishly to light. The outlines of the injected optic discs were ill-defined. There was considerable oedema about the optic discs and in the central portion of the fundus. The appearance of the arteries was normal, the veins were slightly dilated.

Vision: Finger-counting 1.5 m for both eyes. The limits of the field of vision and the tension were normal.

The alkali reserve was not investigated till the morning of the day after admission when it was 26 volumes per cent. In the course of this morning his condition became rapidly worse and he was, as already stated,

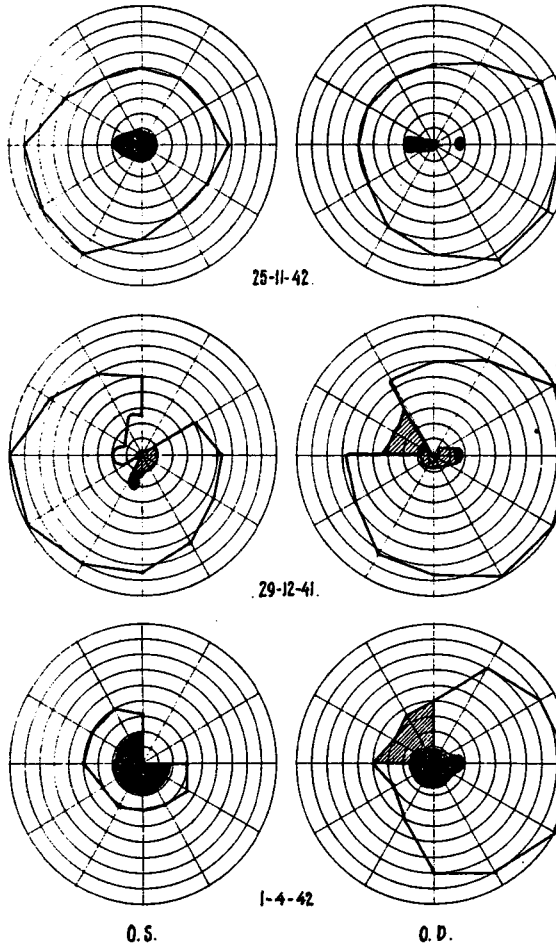

Fig. 4. Case 3. G. H. — Size of objects 10/330 and 20/1150. Red-green blind. Central scotoma for blue.

very exhausted and dyspnoeic at 14 o'clock. It is therefore probable that the alkali reserve was lower at this stage, but apparently further examinations were not carried out on this day.

On October 21, he was given $NaHCO_3$ 10 g × 4 by the mouth and 1000 cm³ of a 5 per cent. glucose solution by intravenous injection. On the two following days he was given $NaHCO_3$ 5 g × 3 by the mouth.

On November 25 he was transferred to the Eye Department. An ophthalmological examination showed normal blood vessels and no marked pallor of the optic discs. The course of his vision during his stay in hospital is indicated on the chart.

December 28: The optic discs are sharply defined, with considerable pallor, notably in the temporal region. The arteries are abnormally thin and their calibre is irregular. Both the inferior temporal arteries resemble wire-thread arteries. The left is obliterated, the right transmits little blood. The veins are well filled and show calibre variations, the course of the small veins being tortuous. The state of the visual field is seen in the following chart.

On re-examination on September 15, 1942, O. s.: Perception of light, o. d.: Finger-counting 1.5 m.

The patient stated that the three companions with whom he had caroused had between them drunk a bottle of »akevit» (potato spirits= 750 cm^3 42 vol. per cent. ethyl alcohol) just before they had joined him. Each of them had therefore consumed about 100 cm^3 of ethyl alcohol. The patient thought that these three had drunk about the same quantity of methyl alcohol, whereas he himself had drunk less. Two of his companions did not fall ill, but they told him later that they had both felt enervated on the day after the spree, and one of them had suffered from nausea and severe headache. Shortly afterwards, both these men went to work elsewhere, and it was not till September 1942 that they were traced. They confirmed the patient's statements, adding that on the day after the poisoning each of them had drunk two glasses of heady wine, one dram of »akevit» and half a litre of Pilsner beer at a restaurant. On the following day they had drunk two glasses of heady wine and half a litre of Pilsner beer. Neither of them had suffered from disturbances of vision.

The third companion, who had brought the spirits, was admitted to hospital on the same day as the patient, dying shortly after admission. After his death a beer bottle, which still contained some spirits, was found in his home. Analysis revealed 62 weight per cent. of methyl alcohol.

Case 4.

Reference number 20371/41 — B. D. Woman, aged 40.

The patient was admitted to hospital on December 9, 1941, in the company of her cousin who stated that she had been much out on the spree of late. She had not been at home for some days, and had returned one morning obviously exhausted. She lay down to sleep, and did not awake till the afternoon. She complained of feeling very ill, of abdominal pain and of laboured respiration.

On admission to hospital at 20.45 o'clock, she did not react to speech or pin-pricks. Her dilated pupils were reactionless. Her respiration was superficial and intermittent, and her lips and limbs were cyanosed. The alkali reserve in the blood in a double test was 9 volumes per cent. Formic acid in the blood 19 mg per cent.

She was at once given 5 cm³ of coramin by intravenous, and lobelin by subcutaneous injection. The pulse steadily became weaker, the cyanosis increased, and the respiration became more intermittent. Death occurred at 21.05 o'clock after a couple of attacks of general clonic convulsions of small degree.

Methyl alcohol was found in the stomach and urine. The necropsy showed cyanosis of the organs and purulent salpingitis.

Case 5.

Reference number 20322/41 — K. B. A workman pensioner, aged 69. Hitherto well. He admits habitual drinking, and frequent indulgence in denatured spirits.

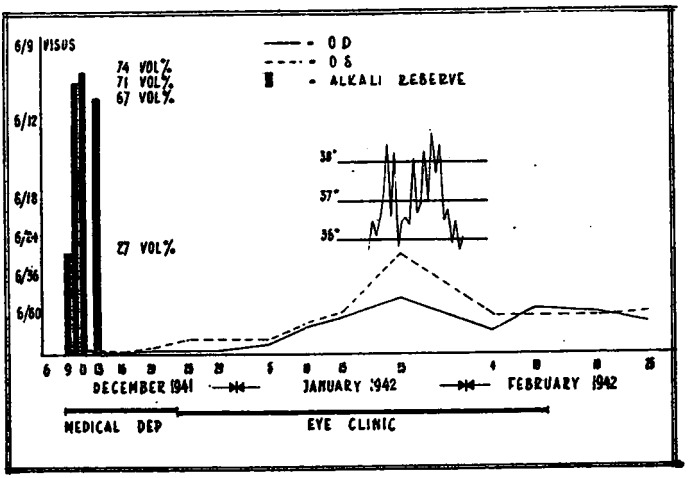

Fig. 5 — Case 5 — K. B. The development of a febrile sore throat coincided with a strikingly rapid diminution of vision.

On December 6, 1941, in the company of three strangers, he drank spirits mixed with coffee, the combination tasting of perfume. He did not become intoxicated. Next day he again drank the same mixture. On the night between December 7 and 8 he was awoken by nausea and vomiting, and he noticed that his vision was impaired. He slept almost the whole day of December 8.

On his admission to hospital on December 9, he had only slight perception of light. Accompanied by a friend, he walked into hospital, a man in fairly good condition, of a ruddy complexion. Pulse 80 and regular. Temperature 37° C. No embarrassment of the respiration whose frequency was not recorded. Blood pressure 130/80. The dilated pupils were reactionless. The clinical findings, including the urine analysis, were normal. The ophthalmological examination on December 10 showed normal externa and clear media. The right pupil 5 mm and reactionless;

the left 6 mm reacted feebly to light. The limits of the hyperaemic optic discs were blurred. The appearance of the blood vessels was normal. Vision O. s.: Finger-counting 30 cm. O. d.: Feeble perception of light. The field of vision O. s.: Normal (Donders) O. d.: Uncertain light projection. The tension felt somewhat reduced on both sides.

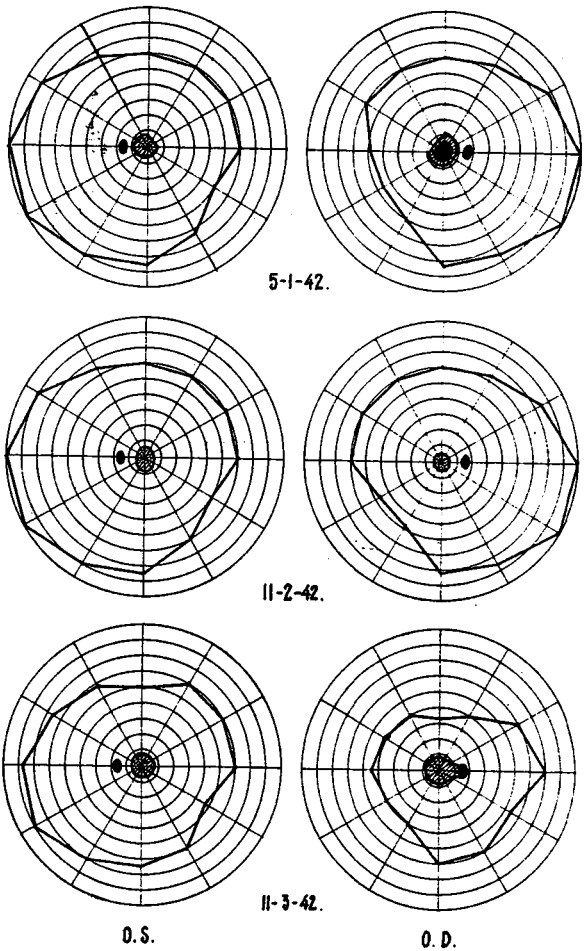

Fig. 6 — Size of objects 10/330 and 10/1150. Red-green blind. Febr. 11. Central scotoma for blue with almost normal outer limits.

He was treated with $NaHCO_3$ 10 g × 2 given by the mouth on the first two days, 10 g × 1 on the third day.

On December 24, he was transferred to the Eye Department. On January 5, the optic discs were possibly a little paler than normal, but there were no visible changes in the blood vessels. On February 10,

the optic discs were white and the blood vessels atrophic. The chart shows that the vision decreases after January 23.

The field of vision: See fig. 6.

He received 12 injections of vitamin B_1, each of 20 mg while in hospital.

Vision gradually diminished after his discharge. At the last examination on September 25, 1942, vision O. s.; F. c. 1 m O. d.: F. c. 1.5 m.

Case 6.

Reference number 20389/41 — H. D. A man, proprietor of a workshop, aged 59.

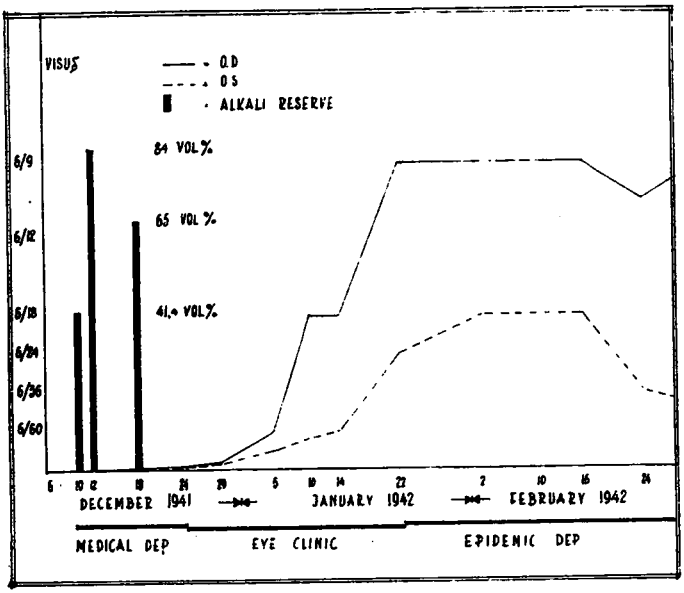

Fig. 7 — Case 6 — H. D.

He had hitherto enjoyed good health and vision. On December 6, 1941, a stranger entered his workshop and offered him spirits of which he drank about a tumblerful without becoming intoxicated. The spirits tasted of gin.

He was unwilling to part with his visitor who felt ill towards evening, and they both turned in to sleep at the workshop. He did not awake next day till 10 o'clock, and the visitor was then dead. Though he felt well, he was very depressed by this death, and he did no work on the following days, spending some time in bed and eating as usual.

On the afternoon of December 8, a man turned up and asked him to carry out an autogen welding. He went with him to the workshop, and as he was about to weld, his sight failed him so much that he could not continue his work. He wore the protective glasses which he generally employed.

On December 9, there was still further loss of vision, and he suffered from nausea, breathlessness and trembling of the legs. He applied to an emergency medical post where he was advised to seek admission to hospital. As he left this post, he felt as if he was falling. He drove to his home

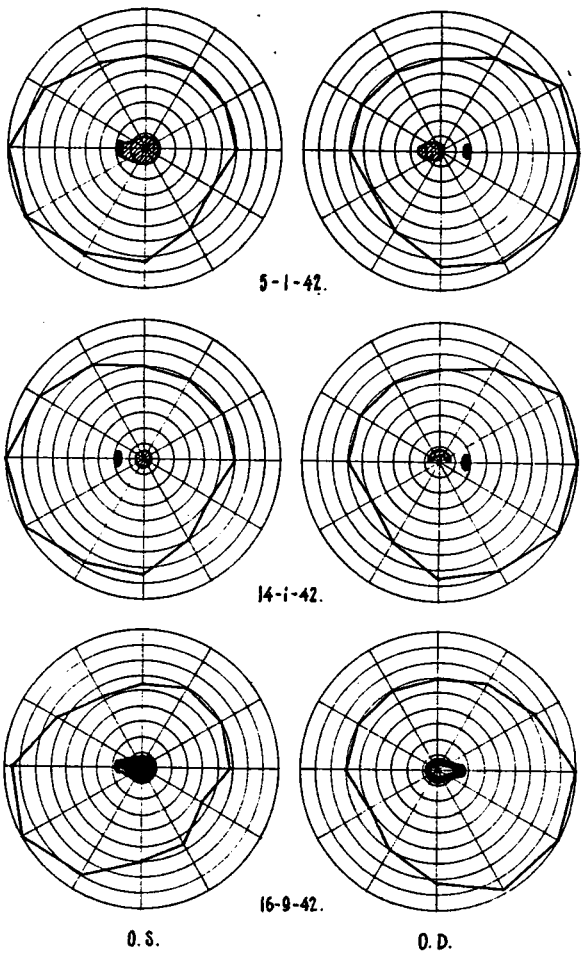

Fig. 8. — Case 6 — H. D. Size of objects 10/330 and 10/1150. Red-green blind.

and went to bed. Next day the general symptoms had vanished, but he was now blind. On coming to the Eye Department, he was at once recommended treatment in the Medical Department.

On December 10, he was admitted to hospital. He seemed to be fit and without general symptoms. The pulse was 100 and regular. The temperature was 37.8° C, and the blood pressure 160/110. The respiration

was not embarrassed, its rate not recorded. The clinical findings, including the urine analysis, were normal.

The ophthalmological examination showed normal externa and clear media. The round and dilated pupils were reactionless, and the limits of the injected optic discs were ill-defined. The appearance of the blood vessels was normal. Vision of both eyes: 0.

He was given an intravenous injection of 1000 cm³ of a 5 per cent. solution of glucose, and $NaHCO_3$ 5 g × 3 by the mouth from December 10 to 18.

He was transferred on December 24 to the Eye Department. For acuity of vision see chart. (Fig. 7).

On January 22, he was transferred to the Epidemic Department as diphtheria bacilli had been found in the fauces.

As the chart shows, the vision of the left eye improved gradually till February 16. From that date the vision of the right eye also diminished slightly, but it was again 6/9 on March 5. Since then vision has diminished, and at the last examination on September 16, 1942, O. s.: Finger-counting 1 m. O. d.: 6/18 ÷.

It was noted on March 5 that the colour of the right optic disc was quite good and the appearance of the blood vessels normal. The left optic disc was pale, and the thick-walled arteries showed calibre changes, notably near the optic disc.

The field of vision: See fig. 8.

He was treated at the Eye Department with injections of vitamin B_1 and a few sweat baths.

In this case it was remarkable that the patient noticed his failure of vision at the moment when he looked at the welding light, and that the other symptoms did not appear till more than 12 hours later.

Case 7.

Reference number 20/519/41 — A. K. A salesman, aged 44.

He suffered from syphilis in 1922, and had been subject of recent years to »chronic bronchitis.» He was a chronic alcoholist and had often drunk denatured spirits. On December 9, 1941, he wanted to buy a bottle (750 cm³) of denatured spirits at a colour-shop. But by a mistake of the shop he was sold methyl alcohol. On the same day he drank about 100 cm³ of it mixed with coffee. On the morning of December 10, he felt unwell and his vision was cloudy. On this day also he drank a considerable quantity of the spirits, and he admitted to the police that he had drunk a total of 250 cm³. He confessed later to having consumed at least 300 cm³.

Becoming steadily worse in the course of the day, he wondered if ordinary alcohol would not restore him to health. He drank five glasses of port wine at a neighbouring restaurant (about 300 cm³ 18 vol. per cent. of ethyl alcohol). During the night he was but partially conscious, walking about at times. He did not remember this. On the morning of December 11, he was still very ill and drank a tumblerful of gin (about 150 cm³ 45

vol. per cent. ethyl alcohol). A friend having called on him with some 96 per cent. spirits, he partook also of this beverage, he knew not how much. On the morning of the same day he was admitted to hospital.

On admission he was only partially conscious, and his face was very flushed. The pulse was 96, regular. The temperature was 36.4° C, and the blood pressure 125/100. The respiration was 32 and laboured. Apart from numerous adventitious sounds heard over the lungs, the clinical examination was negative.

A radiological examination showed bilateral infiltration of the apices and a cavity in the left lung. Tubercle bacilli were found in the sputum.

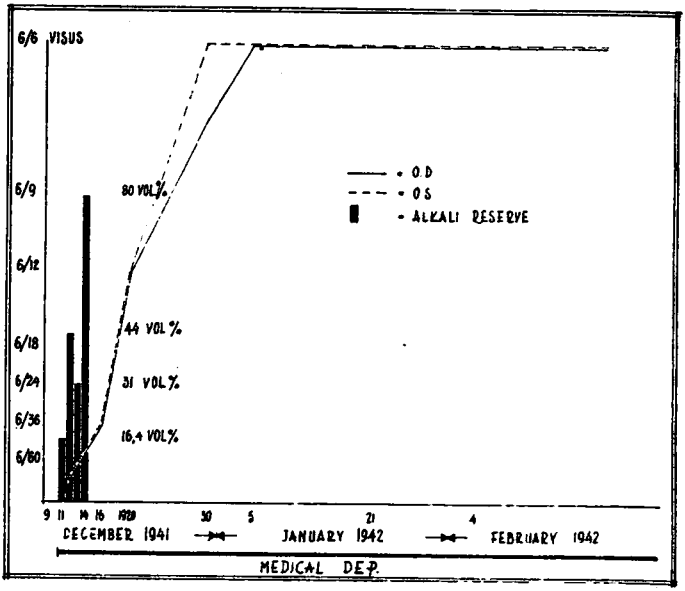

Fig. 9 — Case 7 — A. K.

On December 12, an ophthalmological examination showed normal externa apart from a marked vertical and rotatory nystagmus. The media were clear. The pupils were dilated, 7 mm, reacting feebly to light. The outlines of the injected optic discs were blurred. Finger-counting 3 m. O. u. The limits of the field of vision were normal (Donders). Tension on palpation satisfactory. The nystagmus disappeared after about a fortnight.

As the chart shows, there was a rapid improvement of the vision.

On December 11, $NaHCO_3$ 10 g × 4 was given by the mouth and 1000 cm^3 of a 5 per cent. solution of glucose by intravenous injection. On December 12, $NaHCO_3$ 5 g × 3. On December 13, $NaHCO_3$ 10 g × 4. On December 14, $NaHCO_3$ 10 g × 2.

On December 12, the methyl alcohol content of the blood was 0.14 per cent.

On re-examination on June 8, 1942, his vision was normal.

This patient presumably drank about three to four times the dose of methyl alcohol regarded as lethal. In addition, he drank large quantities of ethyl alcohol. It was amazing that a man who on admission to hospital was suffering from active pulmonary tuberculosis should have recovered from the poisoning completely.

Case 8.

Reference number 20665/41 — M. Th. J. A casual labourer, aged 34.

In the company of one of his friends, this patient had drunk »denatured spirits» bought in a colour shop. When admitted to hospital on December, 14, 1941, at 12.30 o'clock, he was unconscious, and his respiration was superficial and intermittent. He was much cyanosed, and there was scum about his mouth. His pulse was not palpable, and his dilated pupils were reactionless. The alkali reserve was 7.8 vol. per cent., and the blood contained 5.7 mg per cent. of formic acid. He died 40 minutes after admission to hospital. The necropsy showed subpleural ecchymoses, cyanosis of the organs and oedema of the lungs. Methyl alcohol was found in the stomach, blood and urine.

Case 9.

Reference number 2193/42 — L. M. H. A sausage-maker, aged 37.

Hitherto well, he shared on February 1, with two companions, a bottle of spirits (750 cm³) which one of them had bought at a very high price of a stranger. All three agreed that they had drunk the same amount of the spirits to which sugar and hot water had been added. On the following days the patient did not drink ethyl alcohol in any form.

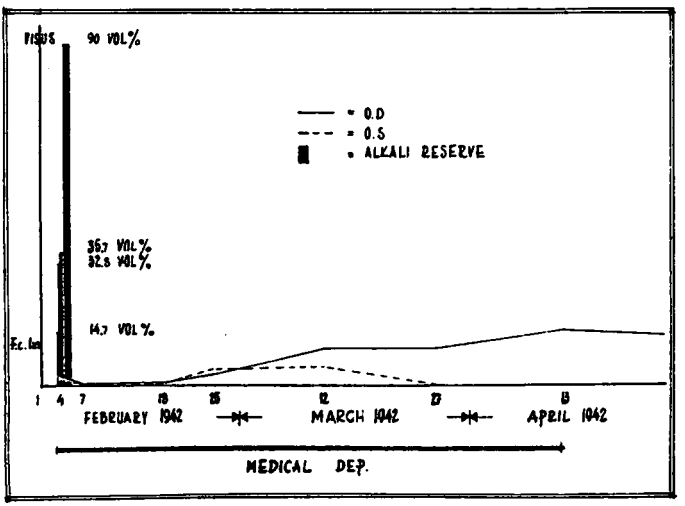

Fig. 10 — Case 9. — L. M. H.

He worked as usual on February 2, but at 8 o'clock on February 3 he became limp and giddy, and therefore went home. At 20 o'clock he developed an intense headache and severe dyspnoea, with nausea and repeated vomiting. He suffered from photopsia, and during the night his vision failed rapidly.

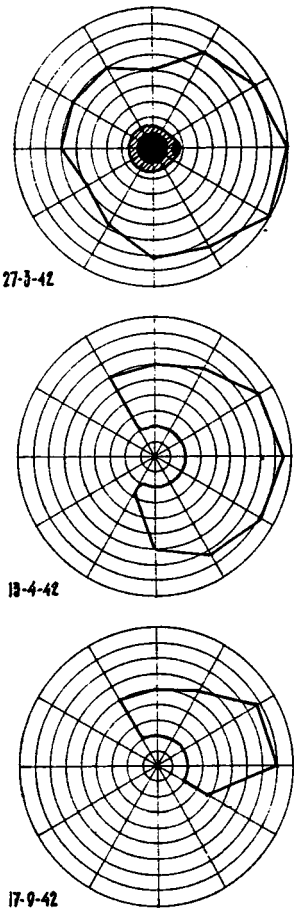

Fig. 11 — Case 9. — L. M. H. Size of objects 10/330 and 10/1150. No colour perception.

On admission to hospital on February 4, he was clear-headed, but loss of vision was almost complete. The pulse was 8, regular. The temperature was 37.1° C, and the blood pressure 160/95. Respiration very deep, frequency 18. A clinical and neurological examination showed nothing amiss apart from the eyes. A trace of albumin in the urine found at first was not demonstrable on the following days.

Case 16.

Reference number 12770/31 — O. K. A telegraph worker, aged 30.

This case has already been recorded by Ustvedt and Mohn (52). He was treated in 1927 at the Eye Department of the Rikshospital for an injury to his right eye whose vision had since been defective. In other respects he had been well.

On October 25, 1931, he drank some spirits which he had not bought himself but which, he was told, had been bought at the Wine Monopoly. Next day he felt well and continued at work till the evening. He drank

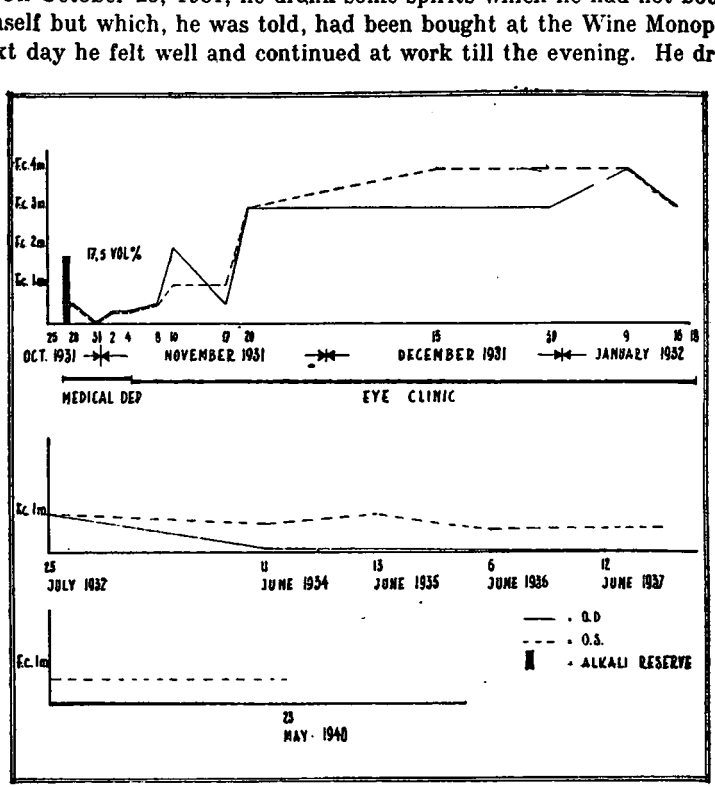

Fig. 13. — Case 16. O. K. The chart is drafted according to the account of Ustvedt and Mohn and notes from the hospital record.

some port wine in the afternoon. He vomited on the following night, and on the morning of October 27, his vision was cloudy when he went to work. Arrived at his destination, he vomited again and had to taxi home at 8.30 o'clock. His vision diminished rapidly in the course of the day. He was not fully conscious when he came to hospital.

On October 27, the brownish-yellow contents of the stomach, repeatedly vomited, were malodorous. His respiration was laboured, but his breath did not smell of acetone. He could see only movements of the hand. His pupils were dilated, reacting feebly to light. The right eye showed a

macula of the cornea and a coloboma of the iris. The clinical findings were normal.

Urine: Heller + Rothera ++ Gerhard ++ Schlesinger ++. A few granular casts, leucocytes and erythrocytes. Alkali reserve 17.5 vol per cent. Blood-sugar 120 mg per cent. Urea in total blood 70 mg per cent.

Five hours after admission, the patient was very drowsy, and his breath smelt faintly of acetone. An intravenous injection of 500 cm^3 of a 5 per cent. solution of glucose, and a drop-enema of 1 liter of a 3 per cent. solution of glucose were given. Methyl alcohol was found in the stomach and the blood.

On ophthalmological examination on October 28, the pupils were 6.5 mm, reactionsless. The optic discs were injected and their limits ill-defined. Movements of the hand ½ m on both sides.

The further course of the case is seen on the chart.

On his transfer on November 4 to the Eye Department, the limits of the field of vision were normal, but there was a large absolute central scotoma for white. Totally colour blind.

December 3: The optic discs, particularly the right, pale.

January 16: Both optic discs pale, the blood vessels atrophic.

For several years he came to the Eye Department to be re-examined and certified as unfit for work. As the chart shows, vision has diminished all the time, and his right eye is now blind.

It is obvious that, with so small a number of cases, the opportunities for drawing conclusions as to the pathogenesis and treatment of this form of poisoning are limited. It has, however, earlier been shown that clinical investigations, even of a single patient, have yielded valuable information as to the nature of the poisoning. There are thus grounds for recalling that the correctness of the findings of Harrop and Benedict (17) in a single case have been confirmed by later clinical experiences. It is, therefore, undoubtedly justifiable to seek in clinical investigations the key to the problem of methyl alcohol poisoning in man.

The conclusions drawn depend partly on observations on the cases just recorded, partly on the clinical observations and experimental findings of other workers.

V. The Relation between Acidosis and Amblyopia.

In looking for the factors determining amblyopia, it is natural first to ascertain if there is any relationship between it and the general symptoms, — limpness, nausea, headache, dyspnoea, vomiting, pain in the muscles, — precisely the manifestations of acidosis.

Alkali reserve at 9 o'clock 14.7 vol. per cent. At 12 o'clock 32.8 vol. per cent. At 15 o'clock 35.7 vol. per cent., and on February 5, 90 vol. per cent. Formic acid in the serum 7.2 mg per cent., in the urine 3.2 mg per cent.

On February 4, he was given an intravenous injection of 500 cm^3 of a 5 per cent. solution of $NaHCO_3$ in 1400 cm^3 of normal saline solution. $NaHCO_3$ 10 g × 4 by the mouth. On February, 5, $NaHCO_3$ 10 g × 4 by the mouth.

An ophthalmological examination showed normal externa and clear media. The pupils were round, 6 mm, reacting very feebly to light. The outlines of the injected optic discs were ill-defined, and there was some oedema at the centre of the fundus.

Vision O. s.: Movements of the hand 0.2 m. O. d.: Movements of the hand ½ m. Light projection uncertain on both sides, tension normal on both sides. The further course of the case is indicated on the chart.

Visual fields: See fig. 11.

On February 25, the colour of the optic discs and the appearance of the blood vessels were normal. On March 12, the right optic disc was a trifle pale in the temporal region, and the left was pale grey. The appearance of the blood vessels was normal.

On March 13, he was sent home, and on March 27, both optic discs were pale and the blood vessels atrophic. He was now blind on the left eye. On re-examination on September 17, vision of the right eye: Finger-counting ¾ m. The field of vision more limited.

In the following case, the poisoning ran a much milder course.

Case 10.

Reference number 2192/42 — O. G. An electrician, aged 37.

This patient participated on February 1 with the last-mentioned person in the same spree, the same quantity of methyl alcohol-containing spirits being drunk by the two.

On February 2, about 15 o'clock, he suffered from nausea and vomiting, and pain in the limbs, stomach and kidney regions.

On February 3, he also suffered from nausea and vomiting, and his vision seemed a little cloudy. A third companion, O. H., who had not fallen ill, visited him on this day. Together they drank a bottle of »akevit» (750 cm^3 of 42 vol. per cent. of ethyl alcohol) and three bottles of »landsöl» — light beer — (2250 cm^3 of 2 vol. per cent. of ethyl alcohol). That evening he felt better than earlier in the day.

On February 4, he felt on the whole better than on the previous day, and he was free from pain, but he felt limp and drowsy. Having heard that one of his companions (patient nr. 9) had been admitted to hospital in a much exhausted state, he also wished to receive in-patient treatment.

On admission to hospital he had no other symptom than feeling limp. His pulse was 100, regular. His temperature was 37.4° C, his respiration unembarrassed. Normal findings on clinical examination and urine ana-

lysis. Alkali reserve 27 vol. per cent. An ophthalmological examination showed normal externa and clear media. The pupils measured 4 mm, reacting well to light and accommodation. The ill-defined optic discs were injected and a trifle oedematous. Vision 6/9 O. u. Satisfactory accommodation and normal limits of fields of vision and normal tension.

Treatment on February 4, — $NaHCO_3$ 10 g × 4 by the mouth, and on February 5, $NaHCO_3$ 10 g × 1.

On re-examination on February 19 and March 15, conditions were normal. Vision 6/6 o. u.

The person, who drank methyl alcohol-containing spirits with the last two patients, and who also drank »akevit» and beer with the last patient on February 3, experienced no discomfort after the poisoning. On the day after it (February 2) he consumed, together with another companion, a bottle of gin (750 cm^3 of 45 vol. per cent. of ethyl alcohol) as well as an unknown quantity of beer. He thus consumed large quantities of ethyl alcohol on both February 2 and 3. Also on February 4, he was seen notably drunk.

Case 11.

Reference number 6641/42. — W. J. A storehouse clerk, aged 32.

Hitherto well. At 15 o'clock on April 12, a comrade appeared with half a bottle of spirits which was drunk by them and the patient's wife in the course of a few hours. He stated that he felt slightly tipsy. He slept well during the night, but felt limp next morning, suffering from nausea and unable to eat. At 10.30 o'clock he drank half a bottle of Pilsner beer, vomiting shortly afterwards. The vomiting did not recur, but the nausea persisted. About 13 o'clock he felt faint and drove home.

On admission to hospital on April 13, he seemed fit, but he complained of pressure over the eyes and feeling limp. His pulse was 80, regular. His temperature was 37.2° C, his blood pressure 105/65. Respiration unembarrassed. The pupils were equal, reacting well to light and accommodation. Normal findings on clinical examination and urine analysis. His stomach was washed out immediately after admission to hospital, and magnesia and charcoal were introduced through the stomach tube.

Alkali reserve on April 13 — 33.8 vol. per cent. Formic acid in the serum — 8.8 mg per cent., and in the urine 1.8 mg per cent. Alkali reserve on April 14 — 72 vol. per cent.

An ophthalmological examination showed normal externa. The pupils reacted well to light and accommodation. The limits of the optic discs were slightly blurred. Vision 6/6, the fields of vision normal. Tension X/12 (20 mm) on both sides.

He was given an intravenous injection of 300 cm^3 of a 5 per cent. solution of $NaHCO_3$ plus 700 cm^3 of normal saline solution. On the same day, $NaHCO_3$ 10 g × 3, and on April 14, $NaHCO_3$ 15 g × 3 by the mouth.

On April 16, all was normal and vision was 6/6 on both sides.

On re-examination on October 5, the ophthalmological findings and vision were normal.

Case 14.

Reference number 6682/42 — O. B. A printer, aged 40.

A friend stated that the patient had always drunk much alcohol, and had had access to methylated spirits at his place of work. Having started work on the morning of April 14, he walked out and fell down »blue in the face» and snoring. He was quite stiff, and he had, it was alleged, drunk an unknown liquor out of a bottle containing a white sediment.

On admission to hospital at 7.35 o'clock, he was comatose, and his stertorous respiration was of the Cheyne-Stokes type. His face was red-blue, and much mucus escaped from his mouth. There was general rigidity of the limbs with a few clonic contractions.

Pulse 100, regular. Blood pressure 130/60. Pupils dilated, about 6 mm, reacting very feebly to light. Clinical findings normal apart from albuminuria.

At 8 o'clock alkali reserve 19 vol. per cent. At 12 o'clock 86.2 vol. per cent. Lactic acid in the blood 170 mg per cent. Formic acid in the blood 3.5 mg per cent., and in the urine 5.2 mg per cent.

He was treated with 450 cm^3 of a 5 per cent. solution of sodium bicarbonate given by intravenous injection, supplemented by 30 g of the same drug introduced through a stomach tube.

An examination at 13 o'clock showed vertical nystagmus. The equal, 3.5 mm pupils reacted well to light and accommodation. The optic discs were injected, vision was 6/6 on both sides, accommodation was good, and the fields of vision were normal. On examination on April 23, the nystagmus had disappeared. Vision normal. The stomach contained methyl alcohol and pyridin.

In spite of his alarming state, the patient made a remarkably rapid recovery. The acidosis was quickly corrected by large quantities of sodium bicarbonate.

On re-examination on September 19, 1942, he stated that he had drunk of the same bottle on the evening before he fell ill. He had been very thirsty in the morning, and had taken another dose of methyl alcohol-containing spirits mixed with beer. The examination showed a normal ophthalmological picture and normal acuity of vision.

Case 15.

N. N. A postman, aged 24.

This patient, whose case has already been recorded by Dr J. F. Harboe (16) had hitherto been well, and his vision had been good. Said to be moderate in his consumption of tobacco and alcohol.

On August 5, 1919, he drank about one dessertspoonful of spirits mixed with four times as much water ostensibly for the cure of a cold. On the following day he went to work as usual, and at midday he suffered from headache, nausea and vomiting which did not, however, prevent his working till the end of the day.

On August 7, the above symptoms were supplemented by cloudiness of vision. On August 8, vision was considerably reduced, and the vomiting

Case 12.

Reference number 6642/42 — I. J. A housewife, aged 32.

Previously well, she drank on April 12 together with her husband (case 11) and his companion about the same quantity of methyl alcohol each of them had taken. She did not become noticeably intoxicated, but next morning she felt giddy and unwell, vomiting once and suffering from nausea. Since then she had continued to feel unwell and giddy. She complained of flimmering, but not of any definite diminution of vision.

When examined on April 13, she felt limp but looked well. The pulse was 74, regular. The temperature was 36.9° C, and the respiration was 18, unembarrassed. The blood pressure was 120/75. The pupils were equal, reacting well to light and accommodation. There were no demonstrable disturbances of vision, and the clinical examination was negative. The trace of albumin found in the urine was not demonstrable on the following days.

April 13, alkali reserve 26.2 vol. per cent. April 14, 47 vol. per cent. April 15, 71 vol. per cent. Formic acid in the serum on April 13, 4.6 mg per cent., in the urine, 2.2 mg per cent.

The ophthalmological examination showed normal externa. The pupils were 4 mm, equal, reacting well to light and accommodation. The outlines of the optic discs were blurred. Vision was 6/6 on both sides, and the limits of the field of vision were normal (Donders). Tension on palpation normal.

On April 13, 300 cm^3 of $NaHCO_3$ 5 per cent. plus 700 cm^3 of normal saline solution were given by intravenous injection, and $NaHCO_3$ 15 g × 3 by the mouth. On April 14, $NaHCO_3$ 5 g × 4 by the mouth.

April 17, normal ophthalmological findings. She felt well and was discharged. October 5, the fundi and vision were normal.

Case 13.

Reference number 6683/42. — J. K. An engineer, aged 54.

In 1931, he had been treated at the Psychiatric Department for alcoholism. It seemed that in November 1941, he had drunk some methyl alcohol, and his vision had been defective for some time after. On April 12, he drank methyl alcohol together with the two preceding patients, according to whom he had probably drunk some of this alcohol on April 11 also.

On April 13, he was pale and looked ill, but he went to work. At 5 o'clock on April 14, he awoke with severe epigastric pain and violent vomiting. He complained of failing vision.

On admission to hospital at 8.15 o'clock on the same day, he was unconscious and cyanosed, in a cold sweat. The pulse was 60, weak but regular. The respiration was stertorous and irregular, but not rapid. The pupils were dilated, about 6 mm, reactionless. The clinical findings were otherwise normal.

Alkali reserve 16 vol. per cent. Formic acid in the blood 17 mg per cent., lactic acid in the blood 180 mg. per cent.

Death occurred at 9.10 o'clock, and the necropsy showed cyanosis of the organs, subpleural ecchymoses and purulent bronchitis.

continued. During the following days there was gradual improvement in the general condition, and during the last few days preceding his admission to hospital. his vision improved somewhat. He was admitted to hospital on August 13 when the fundi were seen to be normal. Vision as indicated on the following chart.

O. s.: Remaining part of field of vision between 10° and 40° in the temporal region. The field of vision gradually extended, and on September 2 its limits were normal, with a small relative central scotoma. O. d.: On August 14, a sector-shaped defect in the upper nasal region, the limits in other respects normal. On September 2, the limits were normal, with a central scotoma for red and green.

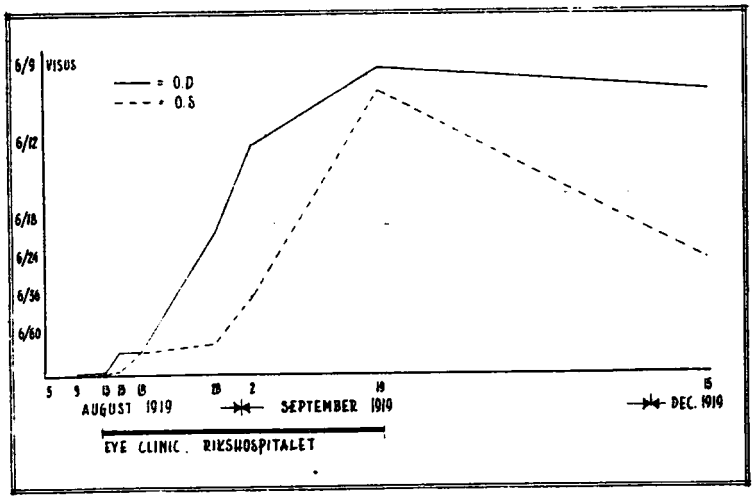

Fig. 12. — Case 15 — N. N. The chart is drafted according to Dr Harboe's description. After September 19, the scale of the abscis is only half what it was before this date in order to economize space.

On the patient's discharge from hospital on September 19, there were no definite changes in the fundi apart from some pallor of the left optic disc.

On re-examination on December 15, the pupils reacted a little more sluggishly than on discharge. The optic discs were now definitely paler than normal, particularly on the left side where the blood vessels were atrophic. He was red-green blind throughout the field of vision.

An analysis showed the spirits to be methyl alcohol.

Though this patient had, it would seem, drunk a very small quantity of methyl alcohol, the general symptoms were severe and vision was much reduced. His work was heavy, consisting of bicycling and walking up and down stairs all day as a postman.

Can we then establish any relationship between amblyopia and acidosis?

As many of the patients were admitted to hospital after their condition had improved, the determination of the bicarbonate content of the blood could not in these cases give any indication of the degree of the acidosis at the most acute stage of the poisoning. It is, therefore, of importance to recognize the clinical manifestations of acidosis in its various stages in order that the history of a given case may indicate the stage of acidosis at which disturbances of vision developed.

According to Kirk, (26) the clinical manifestations of the milder degrees of acidosis are, as a rule, lassitude, anorexia, nausea and headache. When the alkali reserve has fallen to the half of normal, the dyspnoea of acidosis develops and is at first regarded by the patient merely as functional dyspnoea. In the severe degree of acidosis, dyspnoea is more pronounced, and attacks of vomiting and pain in the muscles occur. In addition, sopor and coma often are present, but the development of the psychic disturbances depends not only on the degree of the acidosis, but also on other factors such as the degree of dehydration.

The alkali reserve was not determined in cases Nrs. 1 and 2. They were not admitted to medical wards on entering hospital as their consumption of methyl alcohol had not been admitted and they showed no general symptoms. One may, however, assume that both had suffered from severe acidosis before entering hospital, as the first had suffered from vomiting and dyspnoea, as well as being light-headed, and the second had been drowsy for two days. To judge by their clinical records, both these patients must have suffered from prolonged acidosis. They recovered but little of their sight and are now practically blind.

In case Nr. 5, the patient was admitted to hospital after the general symptoms had subsided. There was now a moderate degree of acidosis (27 vol. per cent.). Earlier he had shown signs of severe acidosis (vomiting and drowsiness) and they had lasted for at least a day and a half. On admission to hospital this patient's vision was almost nil, and afterwards he was blind for many days.

In case Nr. 15, the headache, nausea and vomiting lasted several days after the poisoning, and dimness of vision was observed after

they had lasted about 24 hours. Loss of vision was progressive during the following days, and there was only perception of light on the fourth day, after which vision improved. On and after the fourth day, there was a gradual improvement in the general symptoms.

In cases Nrs 4, 7, 8, 9, 13, 14 and 16, in which the patients were admitted to hospital during the most acute stage of the poisoning, the alkali reserve was respectively 9, 16.4, 7.8, 14.7, 16, 19, and 17.5 vol. per cent. In all these cases there were severe disturbances of vision as well as profound exhaustion. Cases Nrs 4, 8, and 13 ended in death. In the two first, the alkali reserve was remarkably low, 9 and 7.8 vol. per cent. respectively. It was 16 vol. per cent. in the third case which was, however, complicated by purulent bronchitis. This probably contributed to the fatal issue. In all three cases the pupils were dilated and reactionless.

In case Nr. 14, in which the patient was comatose on admission and the alkali reserve was 19 vol. per cent., the pupils were dilated, reacting feebly to light. There can be little doubt that the rapid correction of the acidosis saved this patient's life and sight.

In cases Nrs. 11 and 12, the general symptoms were slight and the degree of acidosis moderate, the alkali reserve being respectively 33.8 and 26.2 vol. per cent. The first patient had not noticed any disturbances of vision, whereas the second had noticed flimmering without any reduction of vision being demonstrable.

To judge by these cases, the degree of the amblyopia depended on the degree and duration of the acidosis. The disturbances of vision were not noted till such symptoms as nausea, vomiting and dyspnoea had lasted some time. It is, therefore, probable that failure of vision in these cases began when the degree of acidosis changed from moderate to severe. (About 23 vol. per cent.).

It might seem that case Nr. 3 was an exception, as there was severe amblyopia on the day on which the alkali reserve was found to be 26 vol. per cent. The blood test was, however, taken early in the morning. During this day, his condition became rapidly worse, and when his eyes were examined at 14 o'clock he suffered from very severe dyspnoea — typical Kussmaul's respiration — and such great restlessness that it was most difficult to examine him. At this stage he must, therefore, undoubtedly have been suffering from much more severe acidosis than earlier in the morning.

Cases Nrs. 1 and 6 are exceptions in so far as the disturbances of vision appeared before the general symptoms. The possible reasons for this will be discussed later.

Haskell and his associates (18), experimenting on dogs, have come to the conclusion that there is no causal relationship between the severity of the general symptoms and the degree of the acidosis. In their experiments large doses of methyl alcohol were given. Thus in their experiments Nrs. 16 and 23, the dosage of methyl alcohol per kilo body weight was 10 cm^3, the dogs also being given 1 cg of morphine per kilo body weight. The dogs became profoundly comatose, dying in a short time without a low alkali reserve in the blood being observed.

It is a general experience that smaller quantities of ethyl alcohol than of methyl alcohol are needed to kill an experimental animal rapidly. This evidently depends on the narcosis, for the narcotic action of ethyl alcohol is greater than that of methyl alcohol because of the former's greater capacity to reduce surface tension in aqueous solutions (Warburg's narcosis theory). When, however, small doses are given repeatedly, the action of methyl alcohol is more toxic, whereas ethyl alcohol can be tolerated for a long time.

Clinical observations do not tally with these workers' experimental findings, and we are not justified in applying them to the reaction of human beings to methyl alcohol. For they never take such large doses that any appreciable degree of narcosis is induced. Usually such patients say they did not become intoxicated on drinking methyl alcohol.

To judge by the clinical observations mentioned, the degree and duration of the acidosis would seem to determine the degree of the amblyopia. To throw further light on its pathogenesis, we must therefore find out how acidosis arises.

VI. The Mechanism of Acidosis.

Berens (2) says of the metabolism of the retina: »If, as seems likely, the retina and brain metabolism parallel each other, it could logically be stated that dextrose is the precursor of lactic acid which is probably the fuel of the living retina.» According to the same author, Adler found that the retina contains more carbohy-

drates and consumes them more rapidly than any other of the eye's tissues.

If we compare this with Goldschmidt's finding that methyl alcohol greatly reduces the tissue respiration of the retina, it seems natural to conclude that methyl alcohol induces inhibition of the processes of oxidation throughout the body, for glycolysis takes place in every cell.

Can the manifestations of the poisoning depend on the action of the methyl alcohol itself or on that of formaldehyde or on that of formic acid?

It is primarily Carlo Egg (9) who has maintained that methyl alcohol itself is responsible for the poisoning. He assumed that methyl alcohol forms a complex compound with the iron in the cells and thereby checks the processes of oxidation. In support of this view he pointed out that methyl alcohol checks in vitro many processes of oxidation, e. g. the guaiac and benzidin reactions, indigo oxidation, and the phenol reaction to H_2O_2. These reactions are also checked by ethyl alcohol, and the check to the last two reactions is greater than that effected by methyl alcohol.

If the check to the processes of oxidation in the body depends on the same processes in operation in vitro in the above mentioned reactions, it is impossible to explain away the fact that ethyl alcohol and methyl alcohol do not give rise to one and the same kind of poisoning. Egg's view can, therefore, hardly be correct.

In the opinion of many, formaldehyde is the active agent (Brückner, Flury and Wirth, Kazas).

The oxidation of methyl alcohol proceeds very slowly, and various investigations have shown that formaldehyde is present in the tissues only in very small quantities. Thus Pohl (35) could find it only in muscle, and here only in small quantities. Völtz and Dietrich (53) could not find it in the exhalation of dogs, although Keeser (cit. 20) found it in the distillation of animals.

Brückner (6) considers that formaldehyde acts by reacting with the protein molecules. A formol reaction, with the formation of methylenimin derivatives possessing acid properties, must be considered as a possibility. Only part of the formaldehyde can, however, be altered in this fashion, for this reaction is not quantitative till pH = 9 is reached. The resulting acid products can exist

only in very small quantities, and the acidosis cannot be explained as a result of them.

Pohl, who assumed that the specific toxic action of methyl alcohol depends on the formic acid produced, has shown experimentally that, as a rule, the peak of excretion was reached on the third and fourth day after the poisoning, and that at this stage the experimental animals suffered most. He found from 5.8 to 18 per cent. excreted when he gave the animals between 1 and 2 g of sodium formiate. Hence his conclusion that most of the formic acid is converted into carbon dioxide and water. Asser (1) found after a dose of 2 g of formiate, 15 to 20 per cent. excreted in the urine. Schmiedeberg considered that the acidosis demonstrated in the patients in the mass outbreak of methyl alcohol poisoning in Berlin in 1911—1912 depended on formic acid in the same way that the acidosis of diabetes depends on beta-oxy and beta-keto butyric acid. He evidently thought that formic acid was present in such large quantities that it could induce acidosis by binding alkalis.

This view would not seem to be correct. Because the oxidation of methyl alcohol is slow, and because most of the formic acid is converted into carbon dioxide and water, the quantity of this acid in the body cannot be great enough to account for the acidosis. In certain cases very small quantities of methyl alcohol induce severe acidosis.

In those cases of the present study in which the concentration of formic acid in the blood was investigated, the highest figure was 19 mg per cent., or 4.13 millimol (case Nr. 4). In this case the plasma bicarbonates were 3.91 millimol (9 vol. per cent.) as compared with the normal 26. This enormous reduction can, therefore, not have been due to formic acid alone.

Another possible effect of formic acid, hitherto apparently overlooked, may be mentioned here.

One of the qualitative tests for demonstrating formic acid is the colour reaction it gives rise to with iron chloride. According to Gmelin (12), when sodium formiate and iron chloride are mixed, a compound of iron and formic acid is formed. In this compound, the iron is bound in complex fashion both in the kat-ion and the an-ion. Another complex compound is sodium-ferri-formiate. $Na_3[Fe(COOH)_6]$.

According to the theory of Warburg (Langfeldt 28) concerning the oxygen activation in the cells, whatever reacts with iron may disturb the transmission of oxygen provided that the substance in question can penetrate into the cells, and that its affinity for iron is so great that it can dissolve its natural compounds. Even if one cannot without more ado assume that formic acid reacts as easily to the iron in the pyrrols in the respiratory enzyme as to ionized iron, the possibility may yet exist that formic acid may form a complex compound with iron also in the body. The formic acid would thereby come to act like prussic acid, with this difference only that the affinity of the latter for iron would seem to be much greater.

According to Poulsson (38) the minimum lethal dose of HCN is 0.06 g. As 0.10 g of HCOOH can bind as much iron as the quantity of HCN mentioned, it is difficult to accept the opinion of Egg (9) who maintained that the quantities of formic acid in the body are too small to hurt it.

It is also impossible to agree with Flury and Wirth (10) in their opinion that the formiate ion is harmless.

Discussing the oxidation of methyl alcohol in the body, Pohl has written: »Die geringere Oxydirbarkeit des Methylalkohols gegenüber dem ihm homologen Aethyl-alkohol kann nach obigem darin ihre vorläufige Erklärung finden, dass der Körper die bei letzterem intermediär gebildete Essigsäure selbst in grossen Mengen noch zu zersetzen vermag, während er für die Formiate nur ein bald erschöpftes Oxydationsvermögen besitzt.»

This observation is the more remarkable for the fact that formic acid is very easily oxidized in vitro, whereas the reverse is the case with acetic acid.

The gradually diminishing capacity of the organism to oxidize formic acid can, however, apparently be explained by the assumption that it forms a complex compound with the iron in the respiration enzyme (citochrom-oxydase). The processes of oxidation in the cells will thereby be gradually inhibited, and this reduced capacity for oxidation will also affect the oxidation of formic acid formed as long as methyl alcohol is present in the body. The concentration of formic acid in the tissues will then increase, and this in its turn will bind more iron.

According to this theory of the processes of acidosis, one would

expect to find an increase of organic acids, notably lactic acid, in the blood and urine. Several earlier investigations would seem to show that this is the case.

Krohl (27) found that the excretion of ammonia in the urine was very great in proportion to the excretion of formic acid. He did not ascertain which was the acid that had neutralized the bulk of the ammonia.

Harrop and Benedict (17) demonstrated large quantities of titratable organic acids, mainly lactic acid, in the urine.

In a case of methyl alcohol poisoning investigated by Ustvedt (51), the difference between the total base and the total acid was 30.15 mille-equivalents — an observation indicative of large quantities of organic acids in the blood. He indicated the possibility of an increased lactic acid concentration in the blood, but he did not demonstrate it.

This state was demonstrated in cases Nrs. 13 and 14, the lactic acid concentration in the blood being found to be respectively 180 and 170 mg per cent. (the normal is 10 to 20 mg per cent. when the patient is at rest both before and during the withdrawal of blood).

This proves that the reduction of the bicarbonates in the blood plasma depends in the main on lactic acid. *The factor primarily responsible for the acidosis would seem to be formic acid.*

VII. Factors Influencing the Degree of Acidosis.

A. *The Influence of Increased Metabolism on the Acidosis.*

If the processes of oxidation are checked, no unqualified parallelism can be expected between the dose of the poison and the degree of the acidosis.

In cases Nrs 13 and 14, the lactic acid in the blood was found, as already mentioned, to be respectively 180 and 170 mg per cent. In the first of these cases, 17 mg per cent. formic acid was found in the blood, and the alkali reserve was 16 vol. per cent. In case Nr. 14 the figures were respectively 3.5 mg per cent. and 19 vol. per cent.

In spite of the great difference in the concentration of formic acid in the blood of these two patients, the difference between the lactic acid concentration and the alkali reserve was small. The first patient fell suddenly ill at 5 o'clock when he was awoken by violent

vomiting and pain in the abdomen. The other lost consciousness and fell while at work.

Two patients were admitted to the Drammen hospital on November 18, 1941, having drunk methyl alcohol-containing spirits. The one — A. J. — who had drunk more methyl alcohol than the other, was not fit to work on the day after the spree, being able to eat, but suffering from nausea and giddiness. He was light-headed at intervals, but felt better after resting. On the morning of November 18, he felt quite well, but he again was light-headed after he had been up and about for some time. His vision was slightly cloudy, but he noticed no breathlessness.

On his admission to hospital on the evening of the same day the methyl alcohol content of the blood was 0.075 per cent., and the alkali reserve was 22.3 vol. per cent. On ophthalmological examination (H. Gjessing, M. D.) the fundi were found to be normal. Vision O. s.: 5/5, o. d.: 5/9. A relative central scotoma for colours.

The other patient — B. J. — did heavy work on November 17. In the evening he was tired and giddy, and he noticed slight cloudiness of vision and a little dyspnoea, but he could eat as usual. Next morning there were no symptoms, and he went to work again.

On his admission to hospital the methyl alcohol content of the blood was 0.024 per cent. and the alkali reserve was 24.1 vol. per cent. The ophthalmological examination (H. Gjessing, M. D.) showed normal fundi. Vision o. s.: 5/5, o. d.: 5/8.

Though the quantity of methyl alcohol in the blood of this patient was barely one-third that of the first patient, the alkali reserve was almost equally low in both. This may have been so because the second patient had been at work, whereas the first patient had kept at rest, spending part of his time in bed.

What is also remarkable is the severity of the symptoms in case Nr. 15 when compared with the smallness of the quantity of methyl alcohol he was supposed to have drunk. This patient also did heavy work on the day after the poisoning.

Lewis Ziegler (57) has recommended thyroid extract for methyl alcohol poisoning. This seems irrational as acidosis increases with the increase of metabolism.

Other things being equal, the acidosis must become more severe and the clinical picture correspondingly more alarming if great demands are made on oxidation.

B. *The Influence of Ethyl Alcohol on the Acidosis.*

As some patients drink ethyl alcohol just before, or on the days following, methyl alcohol poisoning, it would be interesting to learn how, if at all, its course is influenced thereby.

As a rule, the exact quantity of methyl alcohol consumed is not known, but in some cases it is stated that several persons in the same party had drunk the same amount of methyl alcohol-containing spirits. By comparing the course of the poisoning in those patients who had also drunk ethyl alcohol with that of the patients who had not done so, some clue as to the action of ethyl alcohol on methyl alcohol poisoning should be found.

In cases Nrs. 9 and 10, the two patients and a friend of theirs (O. H.) drank on February 1 equal quantities of methyl alcohol-containing spirits according to the statements of all three. The first patient came to hospital on February 4 with severe symptoms, an alkali reserve of 14.7 vol. per cent. and much reduced vision. He had not drunk ethyl alcohol.

The second patient, admitted to hospital on the same day, was much less seriously ill. The alkali reserve was 27 vol. per cent., and his slight disturbances of vision passed off rapidly. On the day before admission, i. e. February 3, he had shared with O. H. a bottle of »akevit» (750 cm^3 42 vol. per cent. of ethyl alcohol) and 3 bottles of light beer (2250 cm^3 2 per cent. of ethyl alcohol) in the course of the afternoon. Each of these two had therefore consumed about 180 cm^3 of pure ethyl alcohol on this day.

O. H., who had been used to drinking alcohol almost daily, had also drunk heavily on the day after the poisoning (February 2.). With another of his friends he had drunk a bottle of gin (750 cm^3, 45 vol. per cent. of ethyl alcohol) and had also drunk an unknown quantity of beer. He had thus drunk at least 170 cm^3 of pure ethyl alcohol on this day. This person suffered no ill effects from the poisoning.

In case Nr. 3, the patient stated that he had drunk less methyl alcohol than the other three, and this statement was confirmed later by the two who recovered completely. Unlike his boon companions, this patient had not drunk ethyl alcohol either before or after drinking methyl alcohol.

A sister of the patient who died stated that he had remained at home on the day after the spree, and had not drunk alcohol.

The two who recovered completely from the poisoning drank a considerable quantity of alcohol the first two days after the poisoning.

In case Nr. 7, the patient stated that he had drunk in the course of two days about 300 cm^3 of pure methyl alcohol, i. e. many times the fatal dose which, according to Poulsson (38), is about 50—75 g. On the second day, when he began to feel ill, the patient drank five glasses of port wine (about 300 cm^3 18 vol. per cent. of ethyl alcohol). On the morning of the third day, he drank a tumblerful of gin (about 150 cm^3 45 vol. per cent. of ethyl alcohol), as well as some concentrated alcohol in an equal quantity of coffee. He could not say how much he had drunk of this mixture. But it is certain that he drank altogether considerable quantities of ethyl alcohol. Yet there were no permanent ill effects from the poisoning.

The observation that ethyl alcohol is an antidote to methyl alcohol is apparently supported by some experiments by Asser (1). He found that less formic acid was excreted in the urine of dogs given ethyl alcohol together with methyl alcohol than in the controls given methyl alcohol alone. Amyl alcohol and acetone influenced the excretion of formic acid in the same way.

Asser envisaged three possible explanations of this phenomenon:

a) increased oxidation of HCOOH
b) reduced formation of HCOOH
c) a change in the mode of oxidation of methyl alcohol.

Accordingly he investigated the action of ethyl alcohol, amyl alcohol and acetone on the excretion of formic acid after the administration of 2 g of sodium formiate, and he found that less was excreted than when the same quantity of formiate was given alone. Hence his conclusion that an increased oxidation of formic acid was also the cause of the diminished excretion observed in the first experiments in which ethyl alcohol, amyl alcohol and acetone was given at the same time as the methyl alcohol.

The oxidation of the formiate must depend on the degree of its penetration into the cells, and alcohol may be assumed to make the cell membranes more permeable for the formiate.

This experiment does not prove that ethyl alcohol promotes oxidation of the formic acid in methyl alcohol poisoning when the formation of this acid is intracellular.

Probably the reduction in the excretion of formic acid effected by ethyl alcohol in methyl alcohol poisoning is due to a reduced formation of this acid. The following is an attempt to find a theoretical basis for this hypothesis.

According to Traube's rule, ethyl alcohol reduces the surface tension of aqueous solutions more than methyl alcohol, and Livingstone and his associates (30) have found this difference to be in the ratio of two to one.

Ethyl alcohol will therefore loosen the adsorption of methyl alcohol to the respiration enzyme, thereby checking its oxidation to formic acid.

The protection given by a single dose of ethyl alcohol will be limited to the time taken to oxidize it, and the manifestations of methyl alcohol poisoning may develop after this time. But during it, some of the methyl alcohol will, however, be excreted. According to Völtz and Dietrich (53), about one-quarter of the methyl alcohol given was excreted during the first two days, mainly by the lungs. A patient who has drunk ethyl alcohol will therefore be exposed to the action of a smaller quantity of methyl alcohol than would otherwise have been the case. If ethyl alcohol is taken repeatedly, there may be no signs whatever of poisoning in spite of large quantities of methyl alcohol having been taken.

One might expect a recurrence of the acidosis when the ethyl alcohol was oxidized, and this would seem to have been so in case Nr. 7. On the morning of the second day in hospital, the alkali reserve had risen to 44 vol. per cent. At this stage the methyl alcohol in the blood was 0.14 per cent. On the third day, the alkali reserve had again fallen to 31 vol. per cent. in spite of the administration of bicarbonate.

A chronic drunkard does not seem to be less predisposed than others to the action of methyl alcohol if he omits to drink ethyl alcohol when poisoned by methyl alcohol. Case Nr. 5 demonstrates this point.

It may be assumed from the above investigations that ethyl alcohol has a favourable effect on methyl alcohol poisoning. *The explanation of this must primarily be found in the capacity ethyl alcohol*

possesses to displace methyl alcohol from the inner surfaces of cells, its oxidation to formic acid being thereby checked. Nor can one neglect the capacity of ethyl alcohol to reduce metabolism as a factor influencing the course of the poisoning favourably.

C. *The Influence of the Supply of Much Fluid on the Acidosis.*

Völtz and Dietrich (53) found that while under normal conditions only about 1.5 per cent. of the methyl alcohol taken is excreted in the urine, up to 15 per cent. may be so when diuresis is much increased.

Pohl (36) found that the quantity of formic acid excreted rose with the intravenous injection of normal saline solution.

The favourable course of the poisoning in case Nr. 10, may partly have been due to the large intake of fluid, and the same observation applies to this patient's companion, O. H., and to the two persons who drank methyl alcohol with the patient in case Nr. 3, for they had drunk much beer as well as more concentrated ethyl alcohol. In case Nr. 7, in which no beer was drunk, the supply of fluid can hardly have affected the issue appreciably.

One of the most constant manifestations of acidosis is dehydration of the organism which is increased by frequent vomiting. The relationship between the amount of fluid taken and the diuresis on the first day in hospital in some of the cases in which these items were recorded can be seen in the following table:

Case	Supply of Fluid	Diuresis	Chlorides in Blood Plasma
7	2600	1700	337 mg per cent.
9	4750	2100	
10	5685	900	282 » » »
11	3800	950	323 » » »
12	2400	800	

As this table shows, the quantity of urine was small in spite of considerable intake of fluid. It must therefore be abundant if diuresis is to be profuse.

VIII. The Pathogenesis of Amblyopia.

A. *The Possibility of a Causal Relationship of Acidosis to Amblyopia.*

As already mentioned, all the patients with severe acidosis suffered from serious visual disturbances which developed, as a rule, after the general manifestations of the poisoning had lasted some time. In two cases of moderate acidosis — about 30 vol. per cent. — in which there had been no signs of severe acidosis before admission to hospital, diminution of vision was not demonstrable.

In the three cases ending in death, the pupils were dilated and did not react to light.

A relationship having thus been established between the degree of the acidosis and the amblyopia, one may ask whether the former may be a contributary cause of the latter.

It may be noted in support of this hypothesis that a similar degeneration of the retina is quite often observed in several conditions associated with acidosis. It is not surprising, after what has already been said of the check to cell-respiration in this form of poisoning, that similar amblyopia occurs in cases of formalin and carbon monoxide poisoning. It is remarkable that the amblyopia of diabetes is always associated with acidosis, as emphasized by Rönne, Holth and others. Among other diseases which are apt to favour acidosis, and in which degeneration of the retina also occurs, may be mentioned the toxaemia of pregnancy, the cachexia of cancer, and extensive burns of the skin. In experimental thyreoidin poisoning, degeneration of the retina with secondary optic atrophy has been observed. Occasionally amblyopia follows loss of blood, nearly always in persons already very debilitated (Röe, 40). Acidosis may also occur in such cases, and its degree depends not only on the severity of the haemorrhage, but also on other factors, notably the state of the heart (Jervell).

It is remarkable that in several cases blindness has followed venesection of patients suffering from cholera which is often associated with severe acidosis.

Considering that the metabolism of the retina is more lively than that of any other normal tissue, it seems reasonable to suppose that the reduction of the buffer capacity of the bicarbonates, phosphates and proteins provoked by the acidosis may injure the retina

more easily than other structures. One may therefore assume that the acidosis injures the retina by virtue of an increase in the hydrogen ion concentration.

This does not, however, explain the fact that the amblyopia of methyl alcohol poisoning is, as a rule, much more severe than that of the above mentioned morbid conditions.

The marked predilection shown by methyl alcohol for the retina in comparison with all other tissues can hardly be due to a greater accumulation of the alcohol in the retina. According to Pohl (37) Nicloux has not found any marked difference in the concentration of methyl alcohol in the various organs, and Pohl himself has found less of it in the cerebrum than elsewhere. Yant and Schrenck (55) found that, when methyl alcohol was inhaled by dogs, and its concentration in the blood was put at 100, its percentage distribution elsewhere was as follows:

Contents of the stomach	103	per	cent.
Aqueous humour and corpus vitreum ..	93.9	»	»
Heart muscle	84	»	»
Hemispheres of the cerebrum	86	»	»
Kidneys	95	»	»
Urine	108	»	»

The concentration of methyl alcohol in bone marrow and fat was low. They came to the conclusion that the concentration of methyl alcohol is practically the same in all the tissues and cells in relation to their water content. We must, therefore, seek other explanations for the markedly selective action of methyl alcohol on the retina.

In the higher animals, Otto Warburg has shown that the retina has, as compared with other organs, a much greater consumption of oxygen in relation to its iron content, i. e. 100,000 mm^3 of O_2 calculated per milligram of iron per hour.

The explanation of this selective action on the retina is, I believe, to be found precisely in what has just been said and in connexion with the severe acidosis. When the iron in the respiration enzyme is paralyzed, defective oxygen activation must occur earlier in the retina than in other organs.

B. *The Part Played by Light in the Pathogenesis of Amblyopia.*

In this study there are two patients whose vision declined before the general symptoms occurred, i. e. at a time when the acidosis must have been slight or moderate. In both these cases the eyes were exposed to strong light.

In case Nr. 1, the patient noticed diminution of vision when he was by the sea on a sunny day. All the three observations made

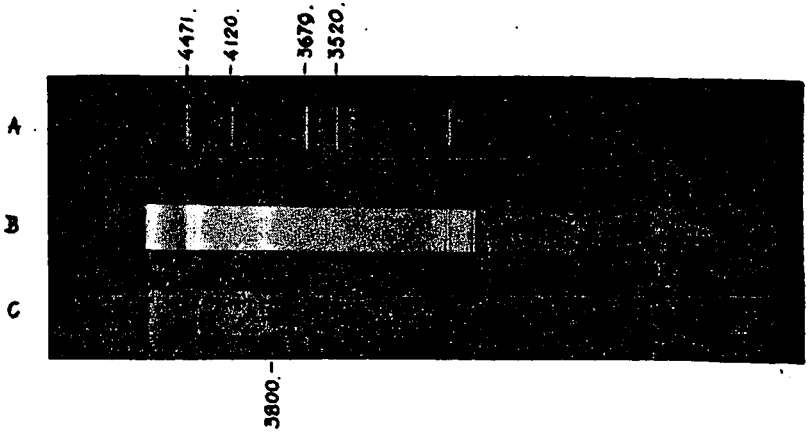

Fig. 14. A: Neon light. B. Autogen light, duration of exposure 16 seconds. C. Autogen light with filter, duration of exposure 16 minutes.

by the Meteorological Institute on this day confirmed this point. The patient's eyes must have been exposed to much light, both directly and by reflexion from the surface of the water. General symptoms appeared some hours later.

In case Nr. 6, the diminution of vision followed the exposure of the eyes to autogen light. The patient wore the protective spectacles he was accustomed to use. Their green glass was about 2 mm thick, and the spectacles fitted so as to shut out all light round the eyes.

Schanz (46) has maintained that the ultraviolet rays injure the retina in this form of poisoning. This is improbable, for under ordinary conditions the rays in question are absorbed by the refraction media of the eye.

Autogen light is very rich in active rays, and it would be interesting to learn how much of them could penetrate the glass of the

spectacles in question. This problem has been studied by Cand. Real. Frans Aubert at the University Physical Institute, Oslo. As the photo shows, no rays with a shorter wave-length than 3800 Ångström penetrated the glass even after prolonged exposure.

On the assumption that the amblyopia is due to inhibition of the processes of oxidation, the injurious action of light would naturally seem to depend on the increased calls on oxidation evoked by the visible rays of the spectrum.

According to Sattler (45), Schwarzkopf found no differences in the degree of the degenerative changes in the retinas of both eyes of animals poisoned with methyl alcohol when only one eye was exposed to light. This observation cannot forthwith be accepted as proving that light plays no part here. When poisoning is severe, the changes in the retina may attain the maximum limit independently of light. Further, when only one eye is illuminated, there will, to a certain extent, be increased glycolysis in the other, witness the observation that the cones in the retina contract even when only one eye is exposed to light (Fuchs).

When death occurs during the acute stage of poisoning, the degenerative changes in the retina are not limited to any definite part of it (Pick & Bielschowsky, Birch-Hirschfeld). The last-named made a point of insisting that the appearance of the central area and its immediate neighbourhood does not differ from that of the peripheral parts of the retina. The degeneration of the medullary sheaths of the optic nerve is no more prominent in the macula-papillary fibre bundle than in the other parts of the nerve.

This runs counter to the general opinion that these fibres are primarily most injured by methyl alcohol. It may be assumed that the central part of the retina later on shows the greatest loss of function and degenerates to a greater degree than the peripheral parts because of the great claims made by light on the processes of oxidation in the former.

As illumination of the retina increases the formation of lactic acid in it, and as oxidation and thereby also resynthesis are inhibited, the hydrogen ion concentration will increase. This is probably why severe amblyopia may occur even during a slight degree of acidosis if the eyes are exposed to strong light as in the case of the last two patients.

C. *The Causes of the Characteristic Course of Amblyopia.*

It may seem strange that vision improves gradually even after prolonged amaurosis, but this tallies with the findings of Goldschneider and Flatau who, — according to Birch-Hirschfeld (4) — have shown that definite structural damage to the ganglion cells can be repaired. The last-named worker found in cases of methyl alcohol poisoning that the nuclei of the ganglion cells retained their normal structure for a remarkably long time. This may explain the tendency to undergo repair shown by the cells in question.

It may seem more difficult to understand the secondary failure of vision.

This failure began from six to 12 weeks after the poisoning in the patients whose amblyopia persisted and who were periodically re-examined. It is not till this stage is reached that definite pallor of the optic discs is, as a rule, observed; and in two cases (Nrs. 3 and 6) there was at the same time marked irregularity of the calibre of the larger blood vessels with thickening of their walls. These changes resemble those seen in the blood vessels of the retina in arteriosclerosis. It is not till later on that thin, atrophic blood vessels are seen.

The latest changes in the blood vessels were seen in case Nr. 6 in which the failure of vision was least. In the left eye, in which the diminution of vision began earlier than on the right side, the changes in the blood vessels were also detected earlier.

In case Nr. 9, in which the poisoning was very severe, the diminution of vision of the left eye began already after the sixth week when the optic disc was pale, whereas there were no definite changes visible in the large blood vessels. The optic disc on the right side was pale eight weeks after the poisoning, and when, two weeks later, he was re-examined, there was considerable limitation of the field of vision (Fig. 11).

There would thus seem to be a causal relationship between the degree of the amblyopia and the length of the interval preceding the onset of diminution of vision, and about the same time changes in the blood vessels (pallor of the optic discs and calibre variations) are seen.

As it must be assumed that the oxidation capacity of the degenerated cells is reduced, the eyes of these patients must be pro-

tected against strong light even after the acute stage of the poisoning. This precaution should delay failure of vision. According to Settler (45) Schieck has observed strikingly rapid failure of vision, after it had again become quite good, in a patient whose eyes had been exposed to strong sunlight.

Patients do not object to wearing dark glasses as they find that they often see better in weak than in strong light, — a phenomenon often observed in tobacco and alcohol amblyopia (Fuchs). The rapid failure of vision accompanying high fever in case Nr. 5 was striking. These observations can be explained as a sequel to the reduced oxidation capacity of the cells of the retina.

In some of these cases of amblyopia, the patients have traced failing vision to severe muscular exertion, and records of such cases are to be found in the literature (Wood and Buller). It is natural to explain this phenomenon as a result of the decreased buffer capacity which is induced by the formation of lactic acid during muscular exertion.

A secondary decline of vision was observed in this study in all the cases in which the amblyopia persisted. *This decline, and the gradually developing limitation of the field of vision, are presumably due to atrophy of the blood vessels. Strong light, fever and muscular exertion can hasten this decline.*

IX. The Treatment of Amblyopia.

The treatment of amblyopia must consist of the rapid correction of the acidosis, the supply of large quantities of fluid, and the protection of the eyes against light. The most rational way in which to correct the acidosis is to administer an isotonic (1.3 per cent.) solution of sodium bicarbonate, the total dose of which should be calculated according to Van Slyke's nomogram.

It is not necessary to give the whole of this dose at the outset of treatment, but in every case one should aim at reducing acidosis from a severe to a moderate degree, i. e. the bicarbonate content of the plasma should be raised to 12—14 millimol (Kirk), a figure corresponding to an alkali reserve of about 30 vol. per cent.

For an intravenous injection it is sufficient to use solutions of the best quality of powdered sodium bicarbonate in sterilized water without any special sterilization of the powder itself (Kirk).

As the acidosis of methyl alcohol poisoning can recur rapidly, the alkali reserve should be investigated frequently during the early stages of hospital treatment, and the dosage of the bicarbonate regulated accordingly.

As Jervell (23) has shown, treatment with the bicarbonate increases the excretion of lactic acid in the urine. Probably the same is the case with formic acid.

In the absence of serious cardiac complications, the injection can be given at the rate of 1 litre per 10—15 minutes (Kirk). In several cases there were electro-cardiographic signs of myopathic changes. These signs, which disappeared in a few days, do not contra-indicate the treatment, though a certain cautiousness should be shown in the timing of the injection.

Even if the alkali reserve cannot be determined, it is safe to give a couple of litres of this solution provided there are definite clinical signs of acidosis. In addition, the bicarbonate should be given by the mouth until the reaction of the urine becomes alkaline.

As a supplement to this treatment of acidosis, it may be convenient to give ethyl alcohol so as to check the oxidation of methyl alcohol. This measure is of special importance when it is impossible to give an intravenous injection of the bicarbonate in adequate doses, as, for example, during prolonged transport to hospital. But the dosage of alcohol must not be such as to raise its concentration in the blood to more than 0.1 to 0.2 per cent. Later on, the amount of alcohol given should correspond to the amount oxidized (about 7 g per hour).

Profuse diuresis may be obtained by giving normal saline solution which corrects any hypochloraemia present. As, according to Völtz and Dietrich (53), methyl alcohol behaves like ethyl alcohol and acetone in being re-absorbed from the bladder, care must be taken to keep it always empty.

Gastric lavage is indicated as Yant and Schrenck (55) have shown that methyl alcohol is excreted into the stomach. As they have found that the concentration of methyl alcohol in the gastric juice is slightly higher than that in the blood, such treatment cannot be expected to remove much methyl alcohol. It does not, for that matter, constitute any immediate danger for the patient, *and gastric lavage should therefore not be carried out before, but after, an intravenous injection of bicarbonate.*

The above considerations point to the treatment being carried out on the medical side of a hospital during the acute stage of the poisoning, even in the cases in which the clinical signs of acidosis have disappeared on the patient's admission.

The eyes must be protected against light, particularly during the acute stage, but also later on if there is amblyopia.

Lewis Ziegler (57) recommends sweat baths and thyroid extract. Both are contra-indicated for reasons already mentioned.

Lumbar puncture is said by some (Pincus, Zethelius and Wersén) to influence the course of the amblyopia favourably. But as, under ordinary conditions, there is gradual improvement during the first few weeks, it does not necessarily follow that it is due to this treatment. The observation period was too short, only 1—2 months, to warrant drawing conclusions as to the final results. In most of the cases observed by these writers, the cerebro-spinal fluid was normal, and only in a few cases was the pressure slightly raised (between 150 and 200 mm H_2O).

It was particularly in their sixth case that Zethelius and Wersén noted an apparently favourable reaction to lumbar puncture. Just before he noticed diminution of vision, the patient had drunk ordinary alcohol and thereupon half a tumbler of spirits whose taste was queer. Half an hour later he noticed diminution of vision. These writers evidently jumped to the conclusion that this last beverage was wood spirits, and that it was responsible for the rapid development of amblyopia. They must surely have been mistaken to judge by the common experience concerning the latent period of methyl alcohol poisoning. It is probable that in this case the methyl acohol had been drunk at an earlier stage, possibly the day before. The large quantity of ordinary alcohol consumed may well have contributed to the favourable outcome of this case.

Schieck (48), who saw no benefit follow lumbar puncture in three cases, is not impressed by the favourable results claimed by these writers for this treatment.

X. Conclusions.

A. *Pathogenesis.*

1. The action of methyl alcohol is explained by inhibition of the processes of oxidation caused by formic acid. This probably forms — by a reversible process — a complex compound with the iron in the respiration enzyme.

2. Acidosis follows inhibition of the processes of oxidation and is mainly due to lactic acid.

3. Amblyopia does not, as a rule, appear till acidosis has become severe, i. e. some time after the development of general symptoms.

4. If the eyes are exposed to strong light, amblyopia may precede clinical signs of acidosis.

5. Increase of metabolism favours acidosis and may thereby provoke amblyopia or aggravate it if already present.

6. A milder course is given to the poisoning if ethyl alcohol is consumed just before or, better still, just after the drinking of methyl alcohol whose oxidation is thereby checked. All signs of poisoning may be averted if ethyl alcohol is drunk repeatedly on the first few days after the drinking of methyl alcohol even though it has been consumed in large quantities.

7. The intake of much fluid may be assumed to exert a beneficial influence on the course of the poisoning.

8. A secondary diminution of vision was observed in all the cases in which normal acuity of vision was not restored. The gradual decline of the retina's functional capacity is probably due to atrophy of its blood vessels.

9. The patients who regained normal vision retained it, and they showed no morbid changes in the blood vessels.

10. The selective, destructive action of methyl alcohol on the retina is presumably due to the retina's great need of oxygen in relation to its iron content. The acidosis in itself must be assumed to play a large part in the development of this serious symptom.

11. The great variations in tolerance to methyl alcohol shown by different individuals are primarily due more to the part played by the factors mentioned under headings 4, 5, 6 and 7 in the course of the poisoning than to individual predisposition as has been commonly held.

B. *Treatment.*

1. The acidosis should be rapidly corrected by bicarbonate whose dosage is calculated according to Van Slyke's nomogram. Treatment should begin with the intravenous injection of an isotonic (1.3 %) solution of sodium bicarbonate.

2. Liberal flushing with fluid to combat dehydration and promote profuse diuresis is indicated. Hypochloraemia is an indication for normal saline solution, and signs of inanition for an intravenous injection of a 5 per cent. solution of glucose.

3. Ethyl alcohol helps to prevent a recurrence of acidosis.

4. Gastric lavage should not be undertaken till an intravenous injection of a bicarbonate solution has been given.

5. Treatment should at first be given in a medical ward and not in an eye department.

6. The eyes require protection against light, notably during the acute stage of the poisoning, but also later on if amblyopia persists.

7. There is no reliable evidence in support of the assumptiou that lumbar puncture is beneficial in amblyopia.

8. Treatment with sweat baths and thyroid extract seems to be contra-indicated.

A perusal of newspaper accounts of methyl alcohol poisoning in different parts of Norway leaves one with the very definite impression that the treatment these patients receive at first is very inadequate. The rapidity with which the manifestations of the poisoning may develop, and the often lengthy journey to hospital, may explain why so many patients die on the way. Much would be gained if the doctor first summoned to the patient at once started to correct the acidosis instead of contenting himself with washing out the stomach. It is, therefore, urgently essential that every doctor should be familiar with the principles of the treatment. I hope that this preliminary study of methyl alcohol poisoning will have contributed to this end.

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