cerebral vessels to vasoconstriction under these conditions (Lambertsen *et al.* 1953), it was felt important to obtain more experimental data before subjecting patients to this form of therapy.

Some preliminary experiments (Smith, Lawson, Renfrew, Ledingham & Sharp 1961) showed that when the carotid and vertebral arteries at the root of the neck were occluded in the dog the EEG flattened within three-quarters of a minute when the animal was breathing air at normal pressure. When this procedure was repeated with the animal breathing oxygen at two atmospheres the EEG remained, for all practical purposes, unchanged. One of the conclusions drawn from this experiment was that if cerebral vasoconstriction did take place with oxygen at high pressure it was not enough to negate the beneficial effects of thus increasing the arterial Po_2.

The next problem was to obtain quantitative data for cerebral blood flow in animals breathing air and oxygen at one and two atmospheres. Sokoloff (1959) has pointed out that a high arterial Po_2 at normal pressure causes cerebral vasoconstriction leading to a reduction in cerebral blood flow of about 12% to 15%. In experiments performed in this department, Jacobson, Harper, Lawson, McDowall & Norman (personal communication, 1963) using the krypton 85 clearance technique of Lassen & Ingvar (1961, Ingvar & Lassen 1962) could not demonstrate any further quantitive vasoconstriction with oxygen at two atmospheres. Intravenous sodium thiopentone was used as the anæsthetic agent in these animals and it may be that this agent, known to produce cerebral vasoconstriction by itself (Pierce *et al.* 1962), may have obscured the effect of oxygen at high pressure. Other anæsthetic agents are therefore being investigated to obtain more complete information.

One of the subjects which necessarily attracts close attention is that of prolonged administration of hyperbaric oxygen. This has been described as falling into two categories – neurological and pulmonary. Although oxygen at two atmospheres is not associated with convulsions in animals there are many reports of pulmonary damage occurring at this pressure in most animals. In this department McDowall & Karasewich (personal communication, 1963) have shown that conscious dogs exposed to 90% oxygen at two atmospheres die between ten and fourteen hours and that at autopsy their lungs are intensely congested and contain small areas of collapse with much frothy blood-stained mucus in the distal bronchioles. McDowall has further demonstrated that by anæsthetizing dogs with halothane and oxygen at high pressure using intermittent positive pressure respiration no lung changes are observed over the same period of time. The conclusion therefore drawn is that either halothane or intermittent positive pressure respiration prevents the damaging effect of oxygen at high pressure on the dog lung for this period of exposure. While this study as it stands at the moment does not greatly further our knowledge, extension of the work in this field is vital if the basic ætiology of oxygen poisoning is to be elucidated. It must be remembered that against this background of animal oxygen intoxication no patient so far exposed has shown either cerebral or pulmonary side-effects directly attributable to the oxygen administration.

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The Treatment of Carbon Monoxide Poisoning by Administration of Oxygen at High Atmospheric Pressure

During the period December 1960 to August 1962 all patients with a diagnosis of carbon monoxide intoxication who were brought into the Wilhelmina Gasthuis in Amsterdam were treated in the pressure chamber with administration of oxygen at a pressure of 3 atmospheres absolute (ATA). In all 40 patients were treated in this period. The cause of the intoxication in these patients is shown in Table 1.

On admission we divided our patients into three clinical groups. Group 1 contains 21 patients who were conscious or lightly comatose on admission; these patients had no hypotension, respiratory depression or neurological abnormality. Table 2 shows the frequency of the signs and symptoms that were present. Group 2 contains

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Table 1
Causes of the intoxication

	No. of cases	
Attempted suicide		
Coal gas	11	20
Coal gas in combination with an overdose of barbiturate	9	
Accidental		
Improperly ventilating stove	11	20
Leaking gaspipe	5	
Fire	3	
Improperly ventilated garage	1	

10 patients who were in deep coma when brought into hospital; there was no respiratory depression in this group either, but in some a hypotension

Table 2
Signs and symptoms in group 1: 21 patients

	No. of cases
Grade of consciousness	
Light coma	3
Stuporous	5
Conscious	13
Symptoms	
Headache	15
Nausea, vomiting	6
No symptoms	1

was present and all had some neurological abnormalities (Table 3). Group 3 consists of 9 patients who attempted to commit suicide by a combined intoxication with coal gas and an overdose of

Table 3
Signs in group 2: 10 patients

	No. of cases
Deep coma	10
Hypotension	3
Pulmonary symptoms	6
Hyperpnœa	4
Positive Babinski reflex	5
Tendon reflexes: hyperactive	6
diminished or absent	3
Hemiparesis	3
Hemianopsia	1
Muscular spasms	5

barbiturate; in this group depression of respiration and circulation were prominent and frequent signs, but there were only minor abnormalities on neurological examination; signs of regional damage such as a hemiplegia were not found (Table 4).

Table 4
Signs in group 3: 9 patients

	No. of cases
Deep coma	9
Hypotension	6
Vasopressor required	3
Respiratory depression	7
Muscular spasms	2

Table 5
Cause of the intoxication and HbCO content on admission, in the three groups of patients

	Group 1	Group 2	Group 3	Total cases
Attempted suicide	6	5	9	20
Accident	15	5	—	20
Total number	21	10	9	40
HbCO content %				
1–10	3	—	1	4
11–20	1	—	—	1
21–30	5	1	1	7
31–40	7	5	2	14
41–50	4	3	3	10
51–60	1	1	1	3
61–70	—	—	1	1
Average	28·9%	38·6%	38·3%	33·4%

Table 5 shows the HbCO content on admission in the various groups of patients. In relation to the low HbCO content in some of our patients it should be mentioned that the HbCO content of the blood sample which was taken on admission was usually not determined before treatment in the chamber. This was only done in cases in which the diagnosis was not quite certain. In this way precious time was saved, especially when the determination could not be carried out at once, as for instance during the night.

The duration of treatment was twenty minutes as a minimum and sixty minutes maximally at full pressure. The duration of compression was twelve minutes. In comatose patients the ear-drums were perforated before starting. Oxygen was administered by way of a Waters' system connected to a mask and a Ruben non-return valve.

Results

The clinical results of the treatment were excellent in group 1 (Table 6). Headache and nausea disappeared and did not return. All patients were fully conscious after treatment. Only one patient did not improve, but started complaining of a headache during the treatment.

The results in group 2 were much less favourable (Table 7); in only 4 out of 10 patients was there any improvement in the grade of consciousness. There was no change in the neurological abnormalities in any of them. Three times a convulsion occurred during treatment. Two patients died, one of them during treatment and the other

Table 6
Results in group 1

	No. of cases
Complete recovery	16
Partial recovery	4
No change	—
Deterioration	1

Table 7
Results in group 2

	No. of cases
Grade of consciousness	
Complete recovery	0
Partial recovery	4
No improvement	6
Neurological abnormalities	
No improvement	10
Complications	
Convulsions	3
Final outcome	
Complete recovery	7
Death	2
Permanent damage not excluded	1

Blood pressure in patients with hypotension on admission (mm Hg)

Before treatment	*During treatment*	*After treatment*
100 systolic	130 systolic	240/125
90/70	125/90	95/70
95/70	120/80	100/65

four weeks after the intoxication. In one patient permanent damage could not be excluded.

In group 3, judgment of the effect of the treatment was hampered by the co-existing barbiturate intoxication. All these patients remained comatose. If respiratory and circulatory depression were present on admission, an increase in the respiratory rate and a rise in blood pressure could always be observed. Both these effects were partially or completely annihilated during decompression.

In a number of patients EEG and ECG were recorded during treatment. In group 1 the clinical improvement was accompanied by an improvement in the EEG. The most characteristic sign was an increase of the voltage of the alpha waves during treatment in patients who were conscious but complained of a severe headache (Fig 1).

In groups 2 and 3 no improvement could be observed. In group 2 (Fig 2) the EEG was composed of theta and delta waves with some very fast beta activity superimposed. The delta waves had a slightly angular form and the voltage was low. In group 3 (Fig 3) the EEG was dominated by the barbiturate intoxication. Beta activity was absent, the voltage of the delta waves was high and the form was round and not angular.

An abnormal ECG was observed in 5 out of 8 cases. There was a marked improvement in all pathological cases, which did not recede during or after decompression (Figs 4 and 5).

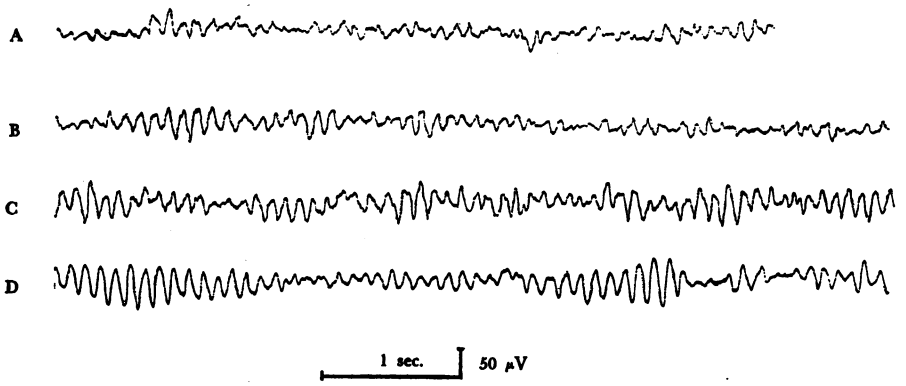

Fig 1 *C M, aged 52, group 1. Increase of voltage of alpha rhythm during the treatment.* A, *before treatment; HbCO content 27%.* B, *after compression.* C, *30 min at 3ATA.* D, *after decompression*

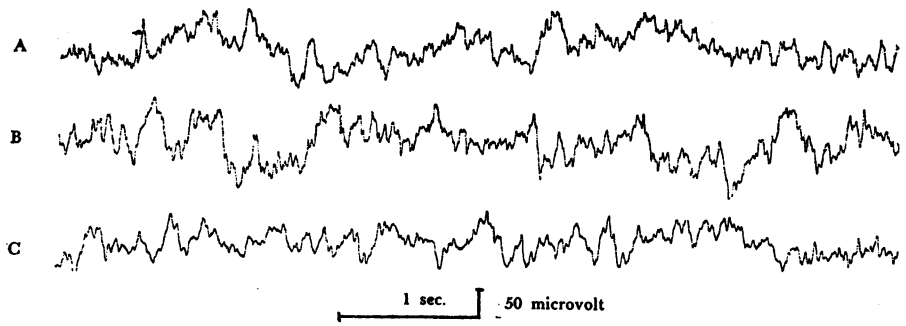

Fig 2 *F V S, aged 70, group 2. Delta and theta waves; beta activity superimposed. No change during treatment.* A, *before treatment.* B, *20 min at 3 ATA.* C, *after decompression*

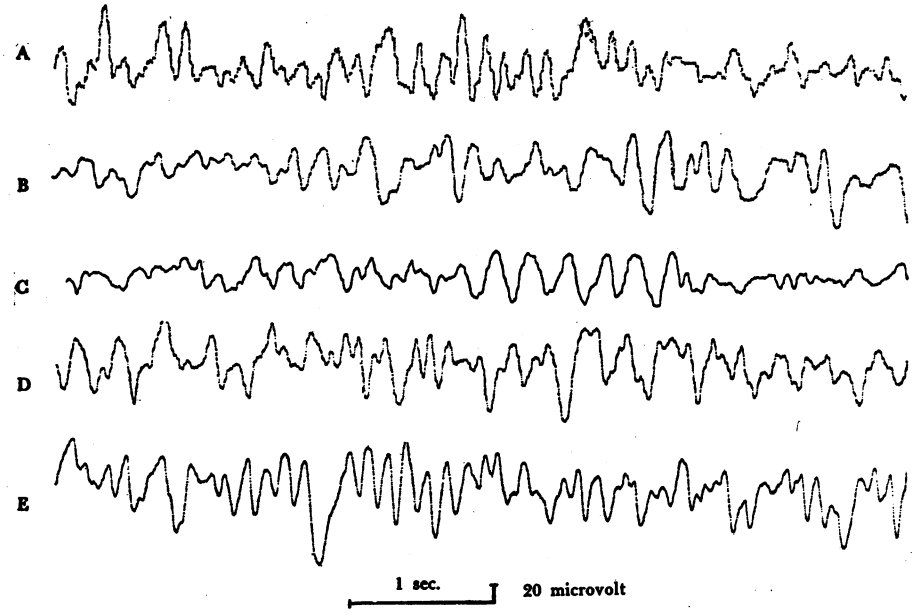

Fig 3 *E K, aged 46, group 3. Delta and theta activity. Beta waves are absent altogether. After 45 min at 3 ATA* (C) *a series of consecutive similar waves of 4–5 c/s. From time to time during the rest of the compression period such a complex of waves was observed.* A, *before treatment.* B, *5 min at 3 ATA.* C, *45 min at 3 ATA.* D, *55 min at 3 ATA, before decompression.* E, *after decompression*

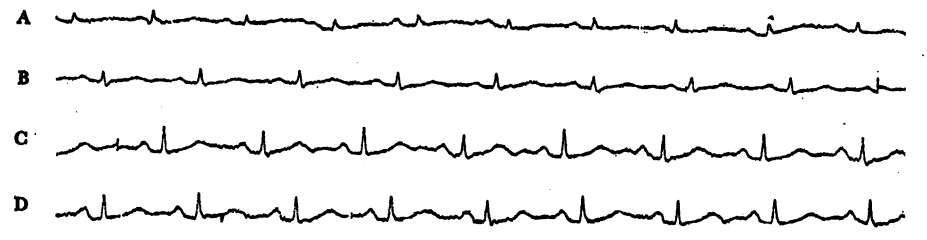

Fig 4 *B S, aged 80, group 2. Improvement of the voltage and of the T waves during treatment.* A, *before treatment.* B, *after 10 min at 3 ATA.* C, *35 min later, before decompression.* D, *after decompression*

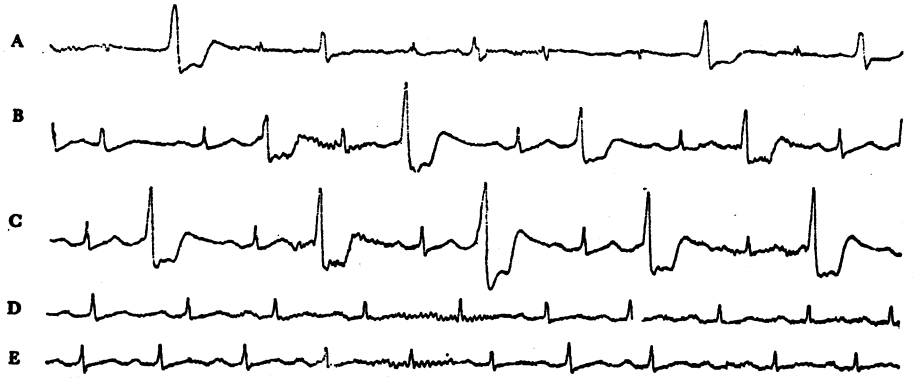

Fig 5 *F V S, aged 70, group 2. A low voltage and multifocal ventricular extrasystoles before treatment. During the treatment normal sinus rhythm is resumed.* A, *before treatment.* B, *10 min at 3 ATA.* C, *15 min at 3 ATA.* D, *18 min at 3 ATA.* E, *25 min at 3 ATA*

Discussion

Some important conclusions may be drawn from these results in relation to both the pathophysiology of carbon monoxide poisoning and the value of the treatment with high pressure oxygen. There cannot be any doubt about the latter's mode of action, if it can be started without delay. The oxygen transport function of the blood is immediately restored and the period of tissue hypoxia is thus shortened. Unfortunately most intoxications do not occur opposite a hospital where a pressure chamber is available. Transport of the patient and preparations for treatment usually take a considerable time. In the meantime oxygen is administered and part of the carbon monoxide present in the blood is already eliminated. In this respect treatment of these patients is very different from all the experimental work which has been carried out.

The administration of high pressure oxygen has a second effect, however. Following carbon monoxide hypoxia there is a tendency for cerebral swelling to occur. This effectuates an increase in the oxygen pressure gradient between capillary and cells and thus produces a secondary hypoxia, which is caused by tissue factors and is independent of the oxygen transport function of the blood. This secondary hypoxia causes the post-anoxic headache, which is such a characteristic symptom after carbon monoxide poisoning but is not a part of the symptomatology of carbon monoxide hypoxia itself. In many cases it only starts later, after a completely symptomless period.

Secondary hypoxia is opposed by the application of high pressure oxygen. Our results in group 1 demonstrate this very clearly; first, because the effect on the typical post-anoxic headache was very favourable and, secondly, because this effect was equally favourable in patients in whom practically all carbon monoxide had been eliminated before treatment started.

These results in group 1 justify two important conclusions: (1) They are a strong argument in favour of the existence of secondary hypoxia and suggest that it plays an important part during the recovery period. (2) If high pressure oxygen treatment cannot be carried out at once, the favourable effect should be mostly if not completely ascribed to the abolition of secondary hypoxia.

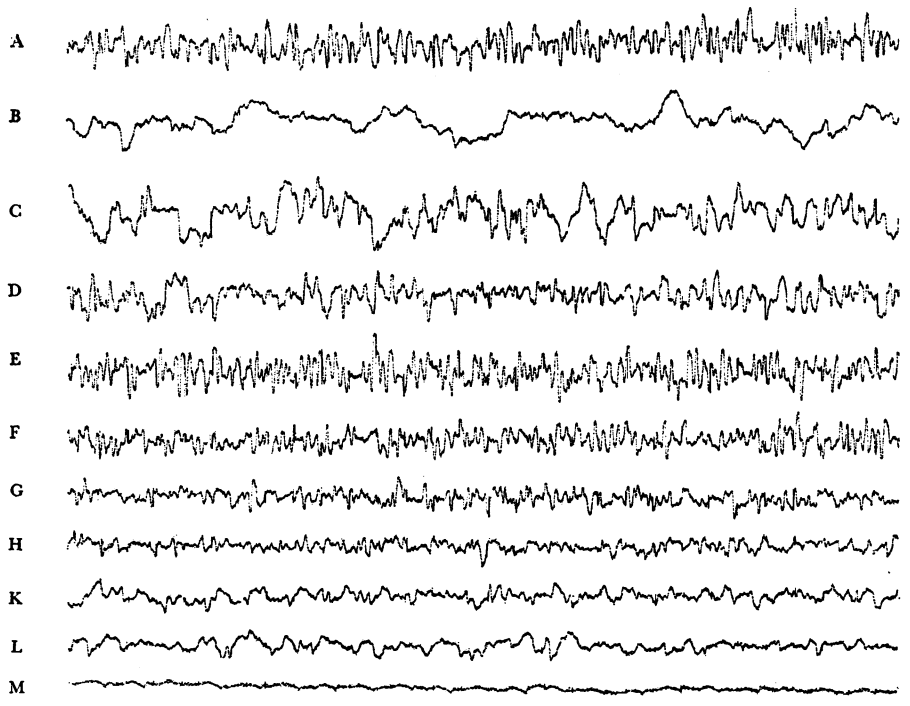

Fig 6 *Marked secondary decrease of the voltage of the EEG after an intoxication of 30 min duration. HbCO content during the intoxication 75%.* A, *before the intoxication.* B, *at the end of the intoxication period. After the intoxication period:* C, *5 min, pupils wide, fixed;* D, *10 min;* E, *15 min, pupils narrow, good reactions to light;* F, *20 min, voltage slightly decreasing;* G, *30 min;* H, *50 min, pupils half-wide;* K, *60 min;* L, *90 min, pupils wide, fixed;* M, *120 min, iso-electrical EEG*

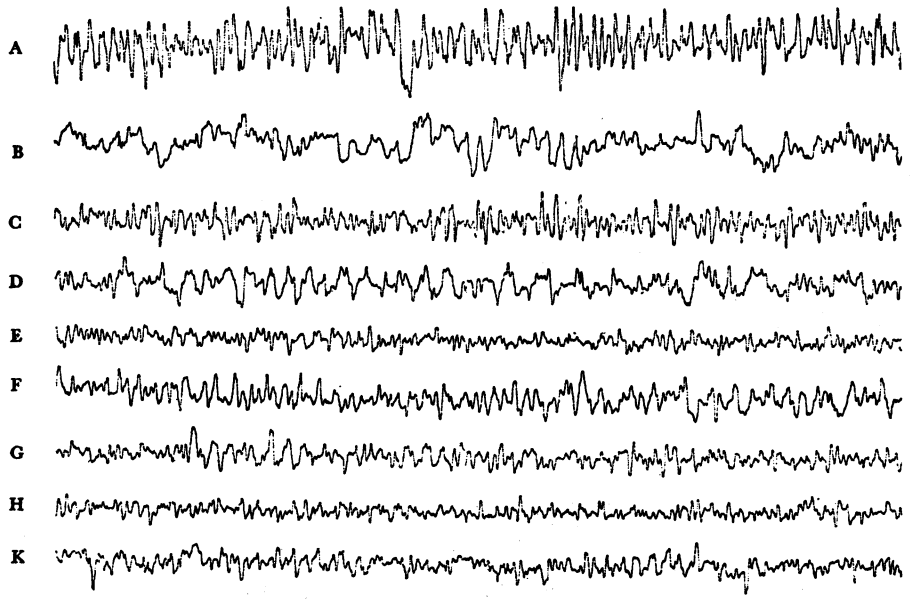

Fig 7 *Effect of the administration of oxygen at a pressure of 3 ATA, two hours after the intoxication period. Duration of the intoxication 60 min. HbCO content during the intoxication 74%.* A, *before the intoxication.* B, *at the end of the intoxication period.* C, *50 min after the intoxication period.* D, *120 min after the intoxication, secondary decrease of the voltage.* E, *after compression.* F, *15 min at 3 ATA.* G, *30 min at 3 ATA, some improvement of the EEG.* H, *during decompression at a pressure of 1·6 ATA.* K, *after decompression*

This is the situation as far as a mild intoxication is concerned. After a serious intoxication of long duration the effect of the treatment is more difficult to evaluate and the two stages in the recovery period are not quite so clear. This is probably due to a number of circumstances: (1) Part of the damage can be expected to be irreversible, no matter what therapeutic measures are taken. (2) The latency factor in the recovery after serious anoxic damage complicates the situation. After minor damage the latency period does not play such an important part and an improvement in the condition of the cell is then reflected in an improvement of the functional state. If, however, the damage is more serious, this sequence of events cannot be expected. If there is any improvement, this does not correlate in time in any consistent way with the therapeutic measure employed. (3) A deterioration in the condition of the central nervous system during the recovery period is much more difficult to detect in serious cases. If there is a persisting coma, only an extensive degree of deterioration due to secondary hypoxia is likely to be noticed. Milder forms would probably be masked by the serious clinical picture which results from cerebral damage.

In our opinion, however, secondary hypoxia is likely to play an important part after serious intoxications also. First, a number of case histories both from our own series and in the literature point in this direction, showing a marked deterioration of the clinical condition during the first hours or days of the recovery period. Second, this opinion is supported by our experimental findings.

In order to determine the effect of high pressure oxygen when administered some time after a serious intoxication, a number of experiments on dogs were carried out. We devised a method which enabled us to follow the EEG before, during and after the intoxication. The grade of intoxication was determined on the EEG and once a certain level of hypoxia was reached the HbCO content was kept at a constant level for a certain period of time. Oxygen at normal pressure was then administered for two hours and the recovery of the EEG was followed.

Fig 6 shows what happened time and again after an intoxication of long duration. The EEG returns to normal within a surprisingly short time. The HbCO content may still be as high as 45% when the EEG has recovered completely. But afterwards the EEG deteriorates again, and in this extreme case even became iso-electric.

After two hours, high pressure oxygen was administered. In this way we tried to imitate the real time relations as closely as possible. It appeared that the effect of high pressure oxygen on this secondary deterioration of the EEG was minimal. In only 1 out of 7 cases could some improvement be observed (Fig 7).

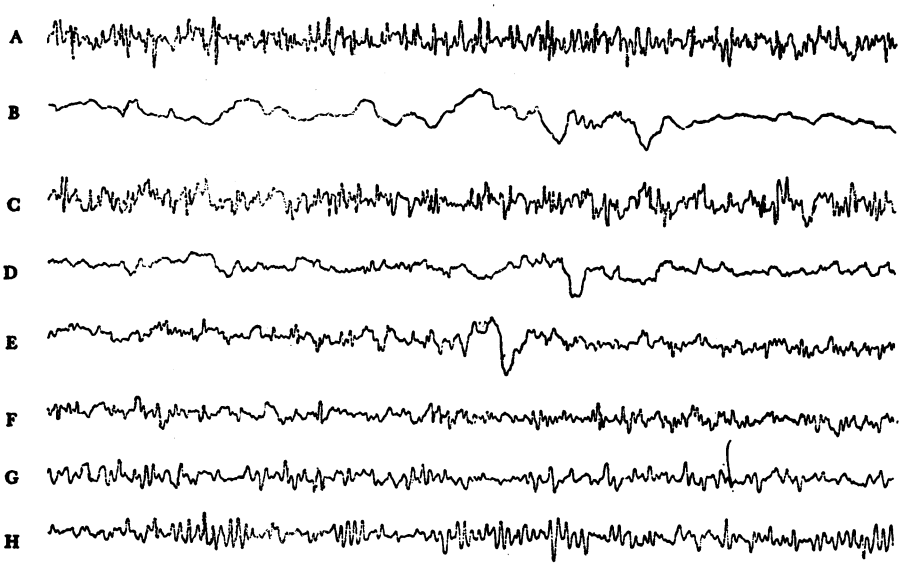

Fig 8 *Effect of hypothermia on the EEG two hours after the intoxication period. Duration of the intoxication 30 min. HbCO content during the intoxication 80%.* A, *before the intoxication.* B, *at the end of the intoxication period. After the intoxication period:* C, *60 min;* D, *120 min, secondary decrease of the voltage, temperature 37·4°C;* E, *150 min, 35°C;* F, *165 min, 33°C; G, 190 min, 31°C;* H, *210 min, 31°C, marked improvement of the EEG*

Fig 8 shows that the effect of hypothermia is much more spectacular in these cases. This is probably due to a decrease of brain volume and an improvement of the capillary circulation.

In conclusion, our findings support the opinion that the administration of high pressure oxygen after carbon monoxide hypoxia may be effective in two different ways, mainly dependent on the moment at which the treatment can be started. If it can be started immediately, as happens on rare occasions, it restores the oxygen transport function of the blood. In the majority of cases, however, it can only be started after some time. In this event it appears that, when oxygen at normal pressure is administered, relatively little time is needed for recovery of the oxygen transport function to an extent sufficient for a proper oxygenation of the tissues. There is, however, a strong tendency for secondary hypoxia to develop due to cerebral swelling. Following a mild intoxication, the administration of high pressure oxygen opposes this secondary hypoxia completely. Following a serious intoxication it takes a subsidiary position. In our opinion, therefore, high pressure oxygen should be combined with or followed by hypothermia in those cases which completely fail to improve with high pressure oxygen alone.

Acknowledgments: The Tables and Figures illustrating this paper are reproduced from Dr Sluijter's thesis 'The Treatment of Carbon Monoxide Poisoning by Administration of Oxygen at High Atmospheric Pressure' (1963, Amsterdam).

Meeting February 1 1963

A Discussion was held on the **Sterilization of Anæsthetic Apparatus**; the opening speakers were Dr J R E Jenkins (*Cardiff Royal Infirmary, Cardiff*) and Dr W M Edgar (*Royal Infirmary, Bradford*).

Among those who took part in the subsequent discussion were Professor E A Pask, Dr S R Williams, Dr B G B Lucas, Dr S Galloon, Professor B W Lacey and Professor W W Mushin.

The papers by Dr Jenkins and Dr Edgar will be published in *Anæsthesia.*

Meeting April 5 1963

The following papers were read:

The Susceptibility of Nerve Fibres to Local Anæsthetics
Dr P W Nathan and Mr T A Sears (*National Hospital, London*)
(See *Anæsthesia*, 1963, **18**, 467)

Some Problems of the Clinical Evaluation of Relaxant Drugs in Man, with Special Reference to a New Competitive Agent
Dr Ian Verner (*St Mark's Hospital, London*)