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PRESENT STATUS OF CYCLOPROPANE*

BY

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Several reports have been published^{1 2 3 4 5 6 7 8 9} covering the past studies of cyclopropane at the University of Wisconsin. It is not the purpose of the present communication to repeat what has already been published, but rather to describe further experiences, experimental and clinical, which may serve to bring up to date what is now known about this agent.

Physical and Chemical Properties

The solubilities reported by Henderson and Lucas in 1929¹⁰ were determined upon specimens of gas known to be impure. The solubility of present market samples at 37.5° C. per c.cm. of fluid has been determined by Orcutt¹¹ as follows: 1 c.cm. of water dissolves 0.204 c.cm., 1 c.cm. of oil dissolves 6.99 c.cm., and 1 c.cm. of human blood dissolves 0.457 c.cm. of cyclopropane. These figures give an oil-water ratio of 34.3. The figures compared with those for older agents, methods of determination, and comment of the physiological chemist will be found in his report when it is published.

A method of manufacture by what has been referred to as the "chloride process" has been patented by the Purdue University Research Foundation. Since such a method promises a reduction of cost of clinical supplies the successful production under this process is awaited with interest but with some trepidation. Past experience with other new agents leads to the fear that new methods, and the employment of chemists inexperienced in production, may result in dangerous impurities. There are already several manufacturers producing cyclopropane in the United States by the method suggested by Freund.¹² Differences in such physical properties as odour are already leading to speculation as to the possibility of the presence of toxic chemical impurities. For the protection of the careful manufacturer, as well as the patient, a reliable and authoritative chemical analysis of market samples should be available in each country. When dealing with a new and experimental therapeutic agent it is extremely important that the drug in its purest state be available.

An early report from our laboratories¹ contained erroneous figures of the explosive range of mixtures of cyclopropane and oxygen. This error in publication is regretted in the interest of scientific accuracy, although we deny the clinical importance of such knowledge. Effective concentrations of any hydrocarbon used for anaesthesia vary widely. The more dilute concentrations outside the respiratory apparatus are quite as likely to come in contact with sources of ignition as are those in the respiratory tract. Concerning the fire hazard from anaes-

thetic agents in general, the policy seems safe to look upon ether, ethylene, and cyclopropane as always a potential source of danger. If one remembers that ethylene is slightly lighter than air, whereas ether vapour is some two and a half times as heavy, and cyclopropane one and a half times as heavy as air, one may then intelligently guard against contact of explosive mixtures with sources of flame or spark. We believe the completely closed carbon dioxide absorption technique to be the greatest safeguard against this danger.

Pharmacology

Effective Concentration.—Seevers and Bennett during the past year have conducted a comparative study of the analgesic properties of cyclopropane, nitrous oxide, and ethylene in normal subjects. They found that concentrations of cyclopropane ranging from 1½ to 4 per cent. definitely depressed or abolished sensory stimuli from

FIG. 1.—Composite graph, taken from Seevers, showing comparative rates of saturation and desaturation of tissues (peritoneal cavity).

skin and mucous membranes without interfering with consciousness or volition. On the basis of their findings we have instituted a clinical comparison of the usefulness of cyclopropane and nitrous oxide analgesia during labour.

The previously reported figures⁴ for effective mask concentrations in surgical anaesthesia gave averages of 7.4 per cent. for light surgical anaesthesia, advancing through 13.1 per cent. for second plane, and 23.3 per cent. for third plane, an average of 42.9 per cent. being found necessary to cause respiratory arrest. It will be remembered, however, that the maximum and minimum concentrations found in the mask during each plane of anaesthesia varied widely from these averages. Subsequent work sheds some light on the subject. Seevers *et al.*⁵ studied the rate of saturation and desaturation of animals with ethylene and cyclopropane by means of tissue gas depots, the technique being based on that described by Argyll Campbell. Fig. 1 is a rough graph based on two of theirs, plotting the relative saturation of the rabbit's peritoneal cavity (chamber tension divided by peritoneal tension) during two hours in a chamber containing an anaesthetic concentration of the gases. The

* Read in opening a discussion in the Section of Pharmacology and Therapeutics with Anaesthetics at the Annual Meeting of the British Medical Association, Oxford, 1936.

relative rate of desaturation is also shown. The diffusibility of cyclopropane through rubber has been shown,⁴ and diffusion through skin similar to that of nitrous oxide¹³ may occur. These findings indicate that the constant reduction of gas tension during anaesthesia, due to escape from the blood, and varying in rate with changes in circulation to the various parts of the body, may offer partial explanation of the widely variant effective concentration necessary in the mask to produce a given degree of narcosis. If induction were made by very gradually and slowly increasing the cyclopropane concentration in the anaesthetic atmosphere, allowing time for at least a partial equilibrium to become established between alveoli, blood, and tissues, doubtless the wide variation in maximum and minimum effective concentrations for the different degrees of narcosis found previously might be minimized. Probably much lower averages would be found. Further reference will be made to the matter in the following discussion of effects on respiration.

It is interesting that Burford recently reported before the American Society of Anesthetists a technique for cyclopropane administration agreeing with this reasoning. He recommends that just sufficient concentration of gas be added at the beginning of induction to ensure unconsciousness, after which the flow is reduced to between 10 and 100 c.cm. per minute, with the hope of balancing the loss to body tissues until an approximate equilibrium is built up in a gradual manner between blood and tissues. Clinical experience has taught that the temptation to use higher concentrations than are necessary is very difficult to resist. The abundant oxygen possible in the anaesthetic atmosphere gives the average anaesthetist a feeling of confidence and at the same time of impatience at waiting for the effect he desires. The irritant property of ether vapour prevents a similar mistake being made with that agent. Extremely rapid induction with dangerously high concentrations is impossible. Cyclopropane is practically devoid of irritation.

Respiration

It is evident to the casual observer that cyclopropane does not cause the early stimulation of respiration seen when nitrous oxide, ethylene, or ether is inhaled.

FIG. 2.—Graphic representation of changes in minute-volume respiratory exchange, depth of anaesthesia and respiratory rate during slow and gradual induction with cyclopropane to the point of respiratory arrest.

Whether an actual reduction in minute-volume respiratory exchange takes place during induction and light surgical anaesthesia has been in dispute. In order to secure more definite evidence we have induced anaesthesia with various agents in the following manner. A tight-fitting face mask, with a minimum of dead space, was fitted directly to a soda-lime canister and these to a water spirometer arranged to trace respiratory excursions on a revolving drum from which respiratory rate and tidal volume could be measured and minute-volume exchange calculated.

In Fig. 2 are shown graphically the measurements taken from such a record of cyclopropane anaesthesia.

A woman, 36 years of age, weight 105 lb. (48 kilograms), had been given paraldehyde, 1 oz., and scopolamine, 1/150 grain (0.0004 gram), one and a half hours before anaesthesia. Four thousand cubic centimetres of oxygen were run into the spirometer before connecting it to the soda-lime canister and mask in air-tight contact with the patient's face. Oxygen added at the rate of 150 c.cm. per minute replaced that used by the patient in metabolism. After four minutes the flow of oxygen was stopped and exactly the same rate of flow of cyclopropane begun; thus anaesthesia progressed slowly through the various stages and planes, reaching the point of respiratory arrest in twenty-eight minutes. At this point 900 c.cm. of oxygen was run into the spirometer and the flow of cyclopropane stopped. Within thirty seconds respiration was resumed spontaneously.

It will be observed that a return through the various planes of third-stage anaesthesia took place in approximately one-half the time required to reach respiratory arrest after cyclopropane was started. One may assume that a portion of the gas in the blood at the time of respiratory arrest was, during the ten minutes following respiratory arrest, rapidly diffusing into the tissues and cavities of the body.

It will be noted that no increase in either rate or tidal volume of respiration occurred after cyclopropane flow was begun, but rather a very gradual decrease in depth, but not in rate until the fourth plane was reached with intercostal paralysis. At this point a period of increased rate began, insufficient in depth to maintain efficient exchange. We may conclude from this experiment and others like it that cyclopropane as a rule causes no respiratory stimulation even during induction, that there is a slight depression during the first and second planes of surgical anaesthesia and that, if increasing dosage is gradual, very slight respiratory depression occurs until a concentration is reached that will shortly result in respiratory arrest. If we could always effect a very slow gradual induction, avoiding high concentrations at any time, a more complete stabilization of tensions in various parts of the body would result. The added safety is manifest. A concentration which will arrest respiration quickly (within three to five minutes) may be extremely toxic to the heart.

Circulation

The Heart.—It is important to watch carefully and continuously the peripheral pulse when there is marked respiratory depression during cyclopropane anaesthesia. Previous publications^{2, 4, 8} have called attention to the occasional recording of ventricular tachycardia in electrocardiographic tracings taken during cyclopropane anaesthesia in both animals and clinical patients. Since a ventricular tachycardia has been recognized as occurring previous to ventricular fibrillation from whatever cause, cardiac studies have continued. Clinical interest has been focused on arrhythmia as noted by pulse palpation. In Table I the percentage incidence of arrhythmia observed in clinical cases during operation with cyclopropane and with ether is listed in order of occurrence in the

TABLE I.—Cases with Arrhythmia during Operation according to Plane of Anaesthesia, 1935

Plane	CsH ₆			Ether		
	Cases	No.	Per cent.	Cases	No.	Per cent.
I	635	13	2.22	31	2	6.45
II	1,263	72	5.70	275	7	2.54
III	471	37	7.86	305	8	2.62
IV	298	38	12.72	115	2	1.74
Total ...	2,667			726		

four planes of anaesthesia. It will be noted that incidence of palpable arrhythmia with cyclopropane increases with depth of anaesthesia, whereas with ether the incidence decreases as narcosis becomes more profound.

The experimental work of Levy¹⁴ showed that under light anaesthesia with chloroform animals became much more sensitive to certain sensory stimuli and to non-fatal doses of epinephrine. Ventricular fibrillation could be quite regularly produced by such means but always under light chloroform, never when the anaesthesia was profound. Meek, in collaboration with our department, has administered non-fatal doses of epinephrine intravenously (0.01 mg. per kilogram) to dogs under both light and deep cyclopropane narcosis. Ventricular tachycardia has frequently resulted. Ventricular fibrillation has not been observed unless the animal was in respiratory arrest, and then on one occasion only. This work is being continued to include other of the commonly used agents. At present we can only say that doses of intravenous epinephrine which frequently precipitate ventricular fibrillation in dogs during light chloroform fail to do so under light cyclopropane. However, under very deep cyclopropane with high concentrations and respiratory arrest, epinephrine has caused ventricular fibrillation.

During over 7,200 clinical administrations of cyclopropane at the Wisconsin General Hospital three patients have died. The condition of the patient before anaesthesia accounted for one of these fatalities, circulatory depression before anaesthesia being sufficient to make a blood pressure reading impossible. The other two were credited at the time to technical errors in administration. Analysed in the light of more recent experimental evidence, however, these deaths may have been caused by ventricular fibrillation. High concentrations of the gas were administered for induction in each case. A closed mask and bag was used, allowing rebreathing without carbon dioxide absorption. Depth of anaesthesia progressed rapidly to marked respiratory depression before intubation. After intubation in each case no respiration was present and no pulse could be palpated. Intracardiac epinephrine was used in one case and the other was subjected to extreme psychic shock before induction, with possible resultant excess secretion of epinephrine. These cases will be reported in detail later. It seems possible that these two cases may illustrate the clinical parallel of the one animal in Meek's series in which ventricular fibrillation was precipitated by intravenous epinephrine administered during extremely profound cyclopropane anaesthesia. Further study of the mechanism of cardiac damage is indicated and will be continued.

Comment.—From the experimental and clinical evidence available at this time we may say that in normal individuals (animal or man) cardiac damage is not likely to precede respiratory arrest if extremely rapid induction with high concentrations is avoided. A safe reaction includes a moderate decrease in pulse rate. Beyond this, if cardiac damage is occurring, the sequence of events is probably as follows: first, a further slowing of the pulse from 60 to 50 or below; then either an arrhythmia or a tachycardia (ventricular) may occur, presumably to be followed by ventricular fibrillation. If it is not the anaesthetist's custom to follow the pulse with constant palpation at least he should do so throughout any period of extreme depression of respiration under deep cyclopropane anaesthesia. *The instant extreme bradycardia, arrhythmia, or tachycardia appears the concentration should be markedly reduced at once.* Present knowledge would point to the inadvisability of rapid inductions, the use of high carbon dioxide tensions, and the administration of epinephrine as a resuscitative measure.

Blood Pressure.—For the belief that cyclopropane raises blood pressure we can find no clinical or experimental

evidence. Blood pressure is occasionally seen to rise after induction of anaesthesia, but never have we failed to explain the rise on other grounds than drug action. The common causes of rising systolic pressure in anaesthesia are carbon dioxide excess, oxygen want, or respiratory obstruction. Seevers⁵ has shown the tissue gas tensions of carbon dioxide to range between 50 and 75 mm. of mercury under cyclopropane anaesthesia (distinctly above normal) and between 35 and 50 under ethylene (normal or below).

My associates Hathaway and Orcutt have studied changes in the gas content of the blood of patients under anaesthesia with several agents. In Fig. 3 are graphically

FIG. 3.—Results of analysis of venous and arterial blood and bronchial samples of oxygen, carbon dioxide, and cyclopropane during a cyclopropane administration.

represented analyses of the venous, arterial, and bronchial content found in a patient before and during cyclopropane anaesthesia. Values are expressed in volumes per cent.

The patient was a man weighing 114 lb. (52 kilograms) undergoing a herniorrhaphy. One and a half hours after the administration of morphine 1/6 grain (0.01 gram) and scopolamine 1/150 grain (0.0004 gram), anaesthesia was induced with cyclopropane by means of a closed technique without soda-lime. Narcosis was carried rapidly to the third plane of surgical anaesthesia with extreme depression of respiration.* After intubation, bronchial gas specimens were taken. (A small catheter passed inside the endotracheal airway deep into a bronchus permitted the removal of a small amount of the anaesthetic atmosphere at the height of expiration during several respiratory cycles). Concentration of cyclopropane was probably much higher at the time of intubation than during the taking of bronchial samples later in the anaesthesia. The first set of blood samples were taken before the mask was applied and the second at the deepest plane of anaesthesia during intubation and with marked respiratory depression. Although the depth of anaesthesia was lighter thereafter the third set of samples, including bronchial, were taken during another short period of respiratory depression. The fourth and fifth sets of samples were taken during normal surgical anaesthesia with a respiratory rate of approximately 20 per minute.

The tendency toward a high bronchial and arterial carbon dioxide in the above experiment will be seen. A tendency for venous oxygen to approach the arterial will be noted. Our present view is that this may be the manifestation of an increased peripheral blood flow. A similar result is characteristic of ethylene anaesthesia and is not due to the high oxygen tension in the alveoli, since the same change has been found when cyclopropane was administered by pharyngeal insufflation with air alone as a vehicle. The quiet breathing without exaggeration of minute-volume under cyclopropane permits a small amount of respiratory obstruction to be more easily overlooked. For the same reason the dead space of even the

* The technique of rapid induction without soda-lime here described is no longer considered safe or desirable. Slow, gradual saturation produces safer and more satisfactory anaesthesia.

best face mask available may afford too much rebreathing and a toxic "piling up" of carbon dioxide. Further experimental evidence will be necessary to determine whether reduced minute-volume respiration is the sole cause of high carbon dioxide or whether changes in blood flow or in tissue metabolism may be concerned. The possibility that an extremely high oxygen tension in the anaesthetic atmosphere may result in interference with carbon dioxide elimination must be considered.

Before considering direct drug action to be the cause of a rise of blood pressure under cyclopropane anaesthesia very careful consideration should be given to possible technical faults and particularly to the likelihood of inefficient carbon dioxide control.

Gastro-intestinal

In vitro experiments have been reported from Leake's laboratory,¹⁶ showing stimulation of isolated intestinal muscle by cyclopropane. Meek, at Wisconsin, has studied normal dogs with Thiry and Thiry-Vella intestinal loops. Both circular contraction and propulsion phenomena are inhibited or arrested in deep cyclopropane anaesthesia. Rather prompt return to normal activity was observed after removal of the mask. Six experiments out of fourteen showed a distinct increase over the normal both in propulsion activity and in circular contraction during recovery.

The customary use of opium for post-operative pain in our hospital doubtless has a greater influence on gastro-intestinal morbidity than does the agent used. Of the 10,638 cases analysed in the accompanying tables roughly 3 per cent. of the nitrous oxide, 7 per cent. of the ethylene, 13½ per cent. of the cyclopropane, and 16½ per cent. of the ether cases were followed by sufficient distension to be mentioned and recorded. The latter two agents only were used for abdominal work. The percentage of patients, for each agent, who were nauseated or vomited at least once after leaving the operating room were roughly as follows: nitrous oxide 23 per cent., ethylene 33 per cent., cyclopropane 39 per cent., and ether 56.5 per cent. The average incidence of nausea or vomiting for the 10,638 cases was 40.6 per cent.

Genito-urinary

Cyclopropane has been used for Caesarean section. Uterine activity can be inhibited and, we believe, abolished with deep anaesthesia when necessary. Early recovery of tone in light anaesthesia and following has, in our experience, prevented post-partum haemorrhage. In normal labour we prefer nitrous oxide except for slight additions of cyclopropane late in the second stage or during perineal repair in particularly difficult cases. An investigation of the effect of cyclopropane on kidney function and bladder musculature is planned for the coming year. Clinical experience has not pointed to serious interference with ether function. The records show that either mild or severe urinary retention was recorded in 7.5 per cent. of cyclopropane cases, 5.4 per cent. for ether, 2.1 per cent. for ethylene, and 2.8 per cent. for nitrous oxide. Again, the incidence follows the type of operation, and is probably little influenced by the anaesthetic agent.

Clinical Experience

A comparison of the relative frequency of administration of the various inhalation agents at Wisconsin General Hospital over a three-year period is set down in Table II. The total death rate includes all known fatalities, whether during the hospitalization period or later, whatever the cause. The relative frequency of administration in the three separate years and the totals are shown in Table III. During 1935 a prearranged effort was made to use

ether as frequently as possible in order to secure case records of a similar number of ether and cyclopropane administrations. The effort failed.

The relative incidence of post-operative respiratory and circulatory complications, expressed in percentages, is shown in Fig. 4. Total respiratory complications, including cough, pharyngitis, etc., as well as pneumonia, are represented by the unshaded blocks. Major respiratory complications only—namely, pneumonia and atelectasis or massive collapse—are represented by the shaded section.

TABLE II.—Clinical Use of Cyclopropane, 1933-5

	Cases	Per cent.
Inhalation anaesthesia	10,638	
CO ₂ absorption technique	9,025	84.8
Ethylene		9.5
Nitrous oxide		12.2
Ether		22.8
Cyclopropane	5,889	55.3
Died within two weeks	222	2.08
Total deaths	355	3.33

TABLE III.—Total Cases by Agents

	1933	1934	1935	Total
Cyclopropane	860	2,343	2,686	5,889
Ether	1,165	531	735	2,431
Nitrous oxide	481	476	342	1,299
Ethylene	785	189	43	1,019
Total	3,291	3,539	3,808	10,638

Deaths from respiratory causes are represented in black. Circulatory complications are not separated into major and minor disability, the plain blocks representing total percentages of circulatory abnormalities following operation from simple tachycardia (pulse rate of over 100 after return to the ward) or bradycardia (pulse rate below 60 after return to the ward) to fibrillation, cardiac dilatation, and shock. The black blocks, again, represent deaths from

FIG. 4.—Post-operative respiratory and circulatory morbidity and mortality. White = total morbidity. Shaded portion = major morbidity. Black = mortality.

circulatory causes. The other agents used are included with cyclopropane for comparison. While the latter drug has been used for all types of operations, as has ether, for obvious reasons the use of ethylene and nitrous oxide was confined to operative procedures demanding little or no relaxation. Under these circumstances the effect of the operation itself and the condition of the patient is probably a larger factor in resulting morbidity and mortality than is the agent used. For this reason little discussion of these figures seems justified. Records are kept with considerable care by the anaesthesia department personnel. Hollerith punch cards are used for final record and for convenience in sorting and compiling.¹⁸

There is, however, probable justification in these records for the following statement. Cyclopropane has, in our hands, resulted in no increase in death rate from anaesthesia, as such, over the older agents in common use. It certainly has carried its share of bad risk cases. It has, in our hands, a definitely lower major respiratory morbidity than we have experienced after ether or spinal anaesthesia. Due to the difference in operative procedures for which other agents and methods are used further comparison is difficult.

Conclusion

After six years' experience with cyclopropane in laboratory and operating room we still consider it an experimental drug. There are many things about it which are yet to be learned. At the same time, we feel justified in continuing its clinical use and recommending it to others who are competent to study its effects and recognize its dangers.

The author regrets injustice to several of his associates as well as inconvenience to readers through failure to cite references to published papers in every case. Much of the work here presented in outline has been accomplished during recent months, and is either incomplete or in manuscript only at this time.

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L. B. Ellis and Soma Weiss (*Arch. Neurol. and Psychiat.*, August, 1936, p. 362) have continued the discussion on vasomotor disturbances and oedema associated with cerebral hemiplegia. They have compared the arterio-venous oxygen difference, obtained from measurements of the oxygen tension of blood from an artery and from the ante-cubital and femoral veins of thirty-five cases of hemiplegia. The position of the lesions causing the hemiplegia was not mentioned. In all the cases the arterio-venous oxygen difference was decreased in the paralysed arms, and in many of the cases in the legs also. There was no significant difference in blood pressure, venous pressure, skin temperature, or capillary resistance between the two sides. In thirteen of sixteen cases examined oedema of varying degree was present in the affected side. Its absence on the normal side is not recorded. The authors assume that alteration in the arterio-venous oxygen difference implies an alteration in the rate of blood flow. This would be so if the metabolic requirements of the normal and paralysed limbs were identical. Using this assumption, they conclude that the rate of blood flow is increased on the hemiplegic side. They state that this "is due to a vaso-dilatation involving the arteries and arterioles, resulting from altered vasomotor reflexes of cerebral origin." Some of the very conflicting literature on the subject of cerebral vasomotor control is also discussed.

ACUTE RHEUMATIC MENINGITIS

BY

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Rheumatic meningitis is mentioned by the writers of older textbooks of medicine, but of recent years the condition is so rare that the occurrence of a case merits a detailed description. The fact that acute rheumatic fever is itself less common and less severe may account for the rarity of the condition, but it is curious that it is not more often seen. On the analogy of tuberculosis and pneumococcal infections, which have a predilection for the pleura, peritoneum, pericardium, meninges, and synovial membranes of joints, it would be reasonable to expect to find that the rheumatic inflammation which commonly attacks all of these except the meninges would also from time to time be found to affect the latter situation.

Case Record

The case here described was that of a man aged 34. He had previously been in good health, having never suffered from attacks of rheumatic fever, chorea, scarlet fever, or recurrent tonsillitis. There was, however, a marked history of alcohol for a few years previous to the present illness. He was suddenly taken ill. There was high fever; the joints of the wrists, the left elbow, the knees, and the right ankle were acutely inflamed; and there was profuse sweating. The joints became swollen in succession, not simultaneously. They were acutely painful and excruciatingly tender. They were reddened and warm to the touch, and the knee-joints contained some fluid. He was given 150 grains of sodium salicylate a day, and within three days the tenderness, swelling, and pain had completely disappeared. Fever, however, persisted at about 102°, and the case was investigated with a view to discovering the cause of this. The blood count was: red blood cells, 3,300,000; colour index, 0.94; white blood cells, 8,600. Blood culture was sterile, and the agglutination reactions were negative against the typhoid group, *B. abortus*, and *B. melitensis*.

It was on the seventh day of his illness that I was first asked to see him. He was mentally clear and had no headache, and his only complaint was of a slight pain felt centrally in the left chest and radiating to the back; this was worse on taking a deep breath. A slight cough was present. The only abnormal physical signs were those concerning the heart and the left lower lobe of the lung.

The apex beat was flabby, but localizable three-quarters of an inch outside the left mid-clavicular line in the fifth space. The area of cardiac dullness extended upwards to the second left space, and the cardio-hepatic angle was obtuse. In the fourth and fifth spaces a distant pericardial friction was audible. This disappeared in three days. At the apex of the left lower lobe posteriorly the percussion note was slightly impaired, and the respiratory murmur was broncho-vesicular in character. No rheumatic nodules were found. A diagnosis of rheumatic pericarditis was made.

Five days later the patient was again seen. He looked extremely flabby and ill. He had no mental or physical energy. The heart was still enlarged, and its rhythm suggested a partial heart-block. An electrocardiograph tracing proved the presence of this, the P-R interval increasing to 0.4 of a second before the dropped beat. It was assumed that this confirmed absolutely that the condition was one of rheumatic fever with a pancarditis. Five days later the patient was again seen. He had for the previous three days complained of pain at the back of the neck. This had come on gradually, and simultaneously there had developed a change in the patient's mental state. He was in a rambling, restless condition, but was not excited; indeed, at times he was semi-comatose. He was very confused. There were no hallucinations or delusions. Headache was not complained of, and there had been no vomiting.