A FATAL CASE OF SUBACUTE YELLOW ATROPHY OF THE LIVER AFTER CINCHOPHEN

BY

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Cases of toxic cirrhosis with jaundice following the use of cinchophen (atophan), whether fatal or non-fatal, are very infrequently met with in this country or reported in our literature. Most of our knowledge on the subject is obtained from cases reported in the American clinics. The case to be recorded is of interest owing to the fact that toxic symptoms appeared after a dose of only 37½ grains had been taken during a period of five days.

Weir and Comfort¹ published an account of 117 cases of toxic cirrhosis due to cinchophen; nineteen of the cases were seen at the Mayo Clinic, and ninety-eight were collected from the literature on this subject: of the 117 sixty-one were fatal. According to Weir and Comfort the toxic symptoms arose after doses ranging from 54 grains in five weeks to 7,200 grains in four months; but they mentioned that fatal results have also occurred with relatively small doses.

Various explanations have been given as to the action of this drug, and as to why it has such profound toxic properties in some cases. Its use in rheumatic affections has been based on the property which it exerts as an eliminating agent of uric acid, and on this its efficiency principally depends. To the property which the liver has for the breaking up of such chemical agents may be attributed the toxic action of the drug. This view was propounded by Rake.² The chemical formula of cinchophen shows it to be a combination of benzene and pyridine, as follows:

Under liver influence the compound becomes broken up and the benzene ring element separated off. The benzene element is then considered to attach itself to or combine with the liver cells, in which destruction and atrophy is produced, with general toxic characters. Similar behaviour had been noted in connexion with cases of trinitrotoluol poisoning, which occurred during the war.

In cases of jaundice associated with a gastro-duodenal catarrh it has been put forward that certain toxic substances can give rise to a phlegmonous gastro-enteritis, and this condition is regarded as responsible for the obstructive or intense character of the jaundice. This view has been prominently held by Perman and Goehring³ in connexion with the two cases they have reported.

History of Case

The patient, a female aged 38, saw her doctor at the beginning of April, 1934, and complained of sore throat and acute pains in the joints. She was given aspirin and methyl salicylate applications on account of a previous rheumatic history. After a few days this treatment was changed, and sodium salicylate (15 grains) and sodium bicarbonate (20 grains) were administered four times a day. She made a fairly good recovery, the temperature settling and the pain disappearing from her joints, which, however, still remained stiff. She went back to work against her doctor's orders.

About three weeks later she again saw her doctor, who gave her twelve tablets of cinchophen (7½ grains each), with

instructions to take one nightly and to stop immediately if any gastric symptoms should appear. After five days she visited him again, when he noticed very faint jaundice. He stopped the cinchophen and prescribed mistura alba. Altogether she had taken only five tablets of the drug. The jaundice progressed slowly, but the patient continued at her work until May 25th, 1934—that is, twenty-five days after the onset of jaundice—when, owing to weakness, she had to take to bed. Four days later she became partially comatose, and was removed to hospital.

She was admitted on May 30th, and her condition then was as follows. She was deeply comatose and continually spitting, yawning, and rubbing her nose. The skin and eyes were intensely jaundiced, and she vomited several times. Some paresis of the right side of the face was present. Temperature was 99.2° F., and the pulse 104. The urine contained bile. The liver dullness did not appear to be altered. The following day she developed a cerebral cry, the right knee-jerk became very brisk, both plantar responses were extensor, and bilateral ankle-clonus was elicited. The temperature rapidly rose to 104.7° F., and the pulse and respirations to 144 and 40 respectively. The patient never regained consciousness, and died that evening.

Post-mortem Findings

Necropsy revealed the following points: lividity of the face and lips, a condition of intense generalized jaundice, and a number of petechial haemorrhages in the skin.

Some bile-stained fluid was present in the pericardial, pleural, and abdominal cavities. The heart was normal, but a number of small areas of extravasated blood were seen in the endocardium of the left ventricle at the septum. The lungs were congested and oedematous, and petechial haemorrhages were present on their surface, while the bronchi contained blood and bile-stained mucus. The stomach was normal. There was no evidence of gastritis. There were a few haemorrhages in the serous coat of the intestines, but no lesion of the mucosa.

The liver was reduced in size and weighed 36 oz. Although it felt somewhat soft and was finely nodular on surface, it appeared firm on section. It had a yellowish brown coloration, with areas of congestion, but the softened yellow areas of acute yellow atrophy were not a feature. The bile ducts on section were dilated. The gall-bladder was normal; no stones. The spleen was slightly enlarged, firm, and congested. The kidneys were bile-stained, and there was evidence of cloudy swelling; there were a few small haemorrhages in the pelvis. The bladder was slightly distended, and there were several small haemorrhages on the mucosa and some degree of cystitis. The brain was congested and oedematous, and a few small haemorrhages were observed at the base and over the cerebellum.

Histology.—Sections of the liver revealed a generalized necrosis of liver cells with an increase of the fibrous tissue between areas of necrotic cells. In places the fibrosis was more apparent, and a large number of bile ducts were recognized. Small aggregations of round cells were noted in different parts of the section. The appearances were those of a case of subacute liver atrophy. There was a marked degree of cloudy swelling of the epithelium of the convoluted tubules of the kidneys: a similar condition, but of less degree, was observed in the straight tubules. The glomeruli were only slightly affected, and for the most part seemed normal. Congestion and minute extravasations of blood were also a feature. In the spleen there was some proliferation of the stroma cells and well-marked congestion. The heart muscle was unaffected.

Summary

1. This was a case of acute rheumatism which failed to respond properly to the usual remedies, and was then treated with cinchophen.

2. The total amount of cinchophen taken was only 37½ grains, at the rate of one tablet on five successive days.

3. The early appearance of jaundice—namely, five days after the beginning of treatment—is worthy of note.

4. The question of idiosyncrasy has been raised by some authorities (Rabinowitz,⁴ Weir and Comfort), and

probably had some connexion in this case on account of the small dose of the drug that was taken.

5. The pathological features are quite classical and are similar to those of other reported cases; they are of interest from the close resemblance to the condition met with in cases of trinitrotoluol poisoning.

6. The advisability of the abandonment, or at least better control, of the administration of cinchophen should be considered.

I should like to thank Dr. Buchanan for notes of the case prior to admission, Dr. Mackenzie for permission to record the case, and Dr. Anderson for notes on the post-mortem report and histological findings.

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- ² Quoted by Sutton, Don C.: *Journ. Amer. Med. Assoc.*, August 4th, 1928.
- ³ Perman and Goehring: *Arch. Int. Med.*, September, 1933, lii.
- ⁴ Quoted by Weis, Clifford R.: *Journ. Amer. Med. Assoc.*, July 2nd, 1932.

THE ADVANTAGES OF NITROUS OXIDE AND AIR ANALGESIA IN THE MIDWIFERY OF GENERAL AND HOSPITAL PRACTICE

BY

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The value of nitrous oxide and oxygen anaesthesia and analgesia in maternity has been recognized for some years, and yet because of certain technical difficulties this relief could never become available for all women in their confinements. But by making use of air instead of oxygen Dr. Minnitt of Liverpool has devised an apparatus which appears to fulfil all the necessary requirements.

The apparatus is an adaptation of a McKesson oxygen therapy apparatus.¹ Gas flows from the cylinder through a reducing valve into a bag contained in a metal drum. The flow of gas is controlled by an automatic valve so that it stops when the patient ceases to inhale.

A mixture of approximately 35 per cent. nitrous oxide in air is delivered to the patient. The method of administration is simply to turn on the gas, give the face-piece to the patient, and tell her to breathe in and out when a pain comes on, ceasing to make use of the apparatus when the pain goes away.

The Minnitt gas and air apparatus has been in use at the Wellhouse Hospital, Barnet, for the past eleven months, where I have been privileged to observe its use, and from personal observation of some 250 cases, both in this hospital and in private maternity work, I feel convinced that we have now come to the time when there can be no reasonable objection to all women enjoying the relief which gas and air can give.

Any method which is to be of general value for relieving the pain of maternity must fulfil certain requirements. These may be briefly enumerated as follows: (1) There must be satisfactory relief to the patient. (2) The normal process of labour must not be interfered with. (3) There must be no danger to mother or child. (4) The technique of administration must be one that can be used by midwives and nurses without constant medical supervision, and must be one which will assist the nurses in their work. (5) The apparatus must be readily portable, and not too expensive either to buy or to use. Let us now consider these requirements, and see how far they are fulfilled.

Relief from Pain in Normal Labour

The first 200 patients to receive gas and air at the Wellhouse Hospital were asked to give their own opinion of the method. Eighty-eight stated that they felt no pain whatsoever, 106 that they found great relief, and six that they found some relief. The almost complete silence that reigned in the ward while patients were having gas and air in the second stage of labour was most noticeable. This in itself was an eloquent testimony to the value of this form of analgesia.

In both hospital and private cases there was no evidence that labour was in any way prolonged. Patients being relieved of all, or much, of their pain were enabled to make great use of their voluntary muscles, thus helping delivery. Instead of an excited hysterical woman we found that we had a patient silent and contented, doing her utmost to assist. In 250 cases, some 60 per cent. of which were first confinements, there were nineteen forceps deliveries.

Safety of Mother and Child

Scientific work at Liverpool has shown that there is no danger to mother or child by the use of gas and air.^{2,3} Electrocardiograms for series of patients showed that they did not appear to be influenced to any significant extent as a result of their experiences. The alteration in the mother's pulse and the foetal heart rates estimated at approximately equal intervals during analgesia were within normal limits.

A biochemical study was made of the blood taken from a maternal vein and the umbilical cord in a number of patients immediately after delivery with and without analgesia, and conclusions were drawn that although the administration of gas and air reduced the oxygen content of the mother's blood that of the umbilical cord did not show any marked alteration. Clinically it was observed at the Wellhouse Hospital that with all five air ports of the machine open it was not possible to obtain full surgical anaesthesia in a normal healthy woman. Further, when the patient was breathing regularly in and out cyanosis did not occur, but when she held her breath and pushed down in the second stage of labour cyanosis did occur in a few cases, although this was not of a dangerous degree.

In the first 200 cases at this hospital there were four stillbirths; these were in no way due to the administration of the gas and air.

Is the Method a Help to the Nurse or Midwife?

We now come to a most important consideration, and one which, in my opinion, makes the gas and air technique of Dr. Minnitt superior to any other method.

At the Wellhouse Hospital for the first fifty cases a medical officer was present during the entire time gas and air was being administered. Gradually, however, as time went on and greater confidence was felt in the safety of the method the nurses took more charge, until it became evident that they were perfectly capable of managing a case on their own responsibility. The nursing staff now administers the gas and air to the patients after receiving instruction in its use, so that there is no need for the medical man or woman to be constantly present at the bedside of the patient.

According to the present rules of the Central Midwives Board there must be medical supervision when a nurse or midwife administers any form of anaesthesia or analgesia, but with gas and air the supervision can be very much reduced, thus assisting greatly in the administrative problems of a medical superintendent of a municipal hospital. Without this assistance it would be impossible for the general use of analgesia in labour in these hospitals.