with a severe infection may have to be retained in hospital for three months or longer. Where evidence of a myocardial lesion has been found the patient should not be discharged until the electrocardiogram has returned to normal.

I wish to express my thanks to Dr. J. A. Charles, medical officer of health, Newcastle-upon-Tyne, for permission to carry out the investigation, and to Dr. E. F. Dawson-Walker, medical superintendent of the Hospital for Infectious Diseases, Walker Gate, for assistance in the preparation of this article.

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A CASE OF INTRA-UTERINE INFECTION OF THE FOETUS BY GAS-GANGRENE ORGANISMS

BY

F. H. KEMP, M.B., M.R.C.P., D.M.R.

Assistant Radiologist to the Radcliffe Infirmary

AND

J. A. STALLWORTHY, F.R.C.S., M.R.C.O.G.

Assistant Obstetrician and Gynaecologist to the Radcliffe Infirmary

The following case is recorded as one of unusual clinical and radiological interest.

Case Report

The patient, a 2-para aged 30, was 16 weeks pregnant when she first attended the ante-natal clinic at the Radcliffe Infirmary in November, 1940. Her first child, weighing 6 lb. 11 oz., was born in 1930, and the second, weighing 9 lb. 8 oz., was stillborn the following year. Two months after the second confinement it was discovered that the patient was suffering from diabetes mellitus, and it would seem probable that this condition was present during the pregnancy and was responsible for its unfortunate ending. From the time diabetes was diagnosed in 1931 until the patient attended the Radcliffe Infirmary in 1940 she had required 30 units of insulin daily, and at her first ante-natal examination she was found to have just a trace of sugar in the urine, but no acetone or albumin.

Obstetrical progress was uneventful until Feb. 7, 1941, when complaint was made of sickness, and hydramnios was found to be present. The blood pressure was 110/80, and the urine was free of sugar and albumin. Foetal parts could not be felt, and, to investigate the cause of the hydramnios, a radiograph was taken. One apparently normal foetus presenting by the vertex was reported. The following week there was a considerable increase in the size of the uterus; acetone and sugar were present in the urine, but there was no albumin. The patient was more uncomfortable and was admitted to hospital. The foetal heart was audible and foetal movements were felt. In the next 10 days the abdomen increased rapidly in size and oedema of the lower extremities occurred. At this time the foetal heart could not be heard, so a second radiological examination was made on Feb. 27. It revealed a breech presentation but no overlapping of the skull bones or other features suggesting foetal death. On March 4 the patient stated that she could not feel any foetal movements, and no foetal heart could be heard.

On March 8 a further radiograph revealed a breech presentation with slight overlapping of the skull bones and a large bubble of gas within the shadow of the foetal head (see Fig.). Other films taken with the patient standing upright demonstrated gas and a fluid level within the foetal skull. The foetal brain and its investing membranes seemed to have collapsed, as the air bubble could readily be displaced to different positions by changing the woman's posture. No other bubbles of gas were seen within the foetus. The previous films were re-examined, and the second radiograph, taken on Feb. 27, showed several smaller gas bubbles within the shadow of the foetal skull which could not be accounted for by gas in the mother's

intestinal canal. The diagnosis was that of intra-uterine foetal death, and it was suggested that there was a gas infection of the foetal skull. Arrangements were made for the pathological laboratories to investigate the foetus bacteriologically as soon as it was delivered.

On March 16 spontaneous delivery of a macerated foetus occurred. The foetal body was soft but the skin was intact. Within an hour of delivery radiographs were taken of the foetal body and the presence of gas in the skull was confirmed. No

Radiograph taken on March 8. Intracranial gas bubble is well shown.

further collection of gas was seen in any situation. The skeleton was well developed and both lower femoral epiphysal centres were ossified. Dr. A. H. T. Robb-Smith opened the skull, and some of the macerated cranial contents were taken for bacteriological examination. There was extreme maceration but no naked-eye appearance of gas infection of the tissues. Sections from the brain and liver showed an extreme degree of autolysis, but no gas-forming organisms were seen. Bacteriological culture of the smears taken from the cranial contents was reported by Dr. Vollum to show a pure culture of an organism which was identified as *Cl. welchii*. The puerperium was uneventful, and except for a temperature of 99° on the third and fourth days it was apyrexial.

It is interesting to note that on Dec. 28, 1941, this patient was delivered of a healthy living female child after spending many weeks in hospital so that her diabetes could be controlled.

Discussion

This is a case of intra-uterine infection of the foetus with gas-forming organisms occurring in a woman suffering from diabetes mellitus. Hydramnios and increasing oedema of the lower extremities developed at the thirty-second week of gestation, and at this time there was considerable difficulty in controlling diabetes. A fortnight later, at the thirty-fourth week, there were signs suggesting foetal death, and radiographic examination revealed bubbles of gas within the foetal skull. Seventeen days after this a macerated foetus was delivered and a pure culture of *Cl. welchii* was obtained from its intracranial contents. There was no evidence of maternal toxæmia due to gas-forming organisms either before or after delivery. It would appear that the foetus died 17 or 18 days before delivery, as the heart had been heard on Feb. 25 but not on the 27th. The films taken on the 27th revealed small collections of gas in the foetal skull. Presumably the infection occurred after the death of the foetus, although it is possible that it was the cause of death. It is difficult to explain the path of

infection: there had at this time been no interference and no vaginal examination had been made. There was no evidence of a low-lying placenta and no apparent focus of infection elsewhere in either the mother or the infant. It would seem, therefore, that infection was blood-borne and transmitted through the placenta. Unfortunately the placenta was not examined bacteriologically. It is also difficult to know why infection was localized to the foetal skull, especially in view of the fact that gas was known to be present for 17 days before delivery and was detected in no other organ either by radiological examination or at necropsy. It is known that the liquor was not grossly infected, for no gas was present in the amniotic sac. Had the foetal skull been opened during the process of birth a pure culture of *Cl. welchii* would have been liberated in the genital tract. That this is possible should be considered when perforation is performed on a dead foetus or when Willett's forceps are applied to the scalp of such a foetus.

The relevant questions to be answered are: How often does gas infection of a foetus occur, and what is the path of infection? It is not uncommon for gas to be seen in all the principal vessels of the body within 24 hours of delivery, presumably secondary to infection of the placenta or the vessels of the umbilical cord; but one of us has investigated 3 cases, in addition to the one recorded, of suspected foetal death by examining the mother in the erect position, and no gas shadows have been observed.

THIOUREA AND WOUND REPAIR

BY

W. R. FEARON, M.B., Sc.D., F.I.C.

Department of Biochemistry, University of Dublin

The value of local applications of urea in the treatment of septic wounds was demonstrated in 1915 by Symmers and Kirk, and has been confirmed by many subsequent workers, including Millar (1933), Foulger and Foshay (1935), Robinson (1936), Muldavin and Holtzmann (1938), and Stonham (1941); while Cummins (1942) has shown that urea in concentrated solutions is an effective bactericide.

In 1929 Hammett reported that mitotic division and cell proliferation during wound repair were promoted by certain organic compounds containing a thiol, or sulphhydryl group, and he advanced the theory that tissue reconstruction was associated with the presence of free -SH groups (Hammett and Reimann, 1929), an explanation also put forward by Rapkine (1930), and accepted by Riley (1940) in an important survey.

Now, thiourea, the sulphur analogue of urea, resembles urea in many of its properties, and, furthermore, contains a latent or masked -SH group; consequently, its possible therapeutic effect in wound repair appears worthy of investigation. Thiourea is of very low toxicity, and may be obtained in a pure form, since its solubility in water at ordinary temperature is only about 1 in 30, which is much less than that of the ammonium thiocyanate from which it is prepared. Thiourea is much more stable than the typical thiol compounds. Its aqueous solution may be sterilized by boiling, and keeps well, although long exposure to air and light results in some decomposition, as shown by the gradual appearance of a precipitate of sulphur and dicyanamide.

Clinical Reports

For the preliminary investigation, ulcers of the static chronic type were selected for treatment. Two series of observations were made, the first being undertaken by J. G. Waugh, M.B., B.Ch., of this University, to whom I am indebted for the following report:

Fifteen cases were treated, in which the ulcers were characterized by extreme chronicity and recurrence due to fibrosis, exposure to trauma, poor blood supply, or polysepsis. After preliminary cleansing, the thiourea was applied in the form of a 1% aqueous solution on a gauze dressing kept freely moist with the reagent. Application in all cases was followed by a

brisk local reaction, accompanied by convergence of the epithelial margin. The response increased up to the eighth day and in some cases progress continued up to the twelfth day. After this, application of thiourea had no further obvious effect, and if persisted in merely tended to soften and macerate the epithelial margin.

The second series of cases was investigated by E. Kawerau, M.B., B.Ch., the treatments being carried out in Dublin at Dr. Stevens's Hospital and at the Adelaide Hospital.

Thirty-two cases were treated, the subjects being mostly working-class women beyond middle age. In all of them the ulcers were due to a varicose condition of the veins of the leg, and in more than half had a chronicity of over 5 years. Observation of all the cases showed that thiourea has a definite stimulative effect on the proliferating granulation tissue. When conditions are favourable the optimal response is reached within 12 days, although large ulcers of 0.5 cm. depth have filled with healthy granulation tissue up to their epithelial margins within a week. When this has occurred the treatment should be discontinued, as otherwise fibroblastic proliferation becomes exuberant and impedes epithelial growth, as already pointed out by Riley.

Method of Treatment

The procedure adopted in applying the thiourea is important. The most effective results followed the use of a 1% aqueous solution of thiourea (B.D.H.), applied on gauze or lint and kept moist by renewal every three to four hours. If the dressing is allowed to dry it adheres to the granulating surface, and is apt to cause damage when the dressing is renewed. If evaporation is prevented by use of a completely occlusive covering over the dressing, there may, for some unexplained reason, be considerable local pain. The difficulty of providing a continuously moist dressing for externe patients was overcome by the use of a hygroscopic paste, prepared by boiling 1 g. of thiourea and 2 g. of starch in 100 ml. of water. When the mixture had become of uniform consistency it was allowed to cool, and then 5 ml. of glycerol was added. This paste was applied on gauze or lint cut so as to fit the ulcer surface accurately. This was covered with a larger piece of lint, a thin layer of cotton-wool, and finally a broad bandage. No occlusive material is used. Where practicable the dressing is reapplied daily.

Conclusion

The mechanism of the action of thiourea and the other thiol compounds effective in promoting wound repair awaits elucidation. The only physiological property so far ascribable to thiourea is that of inhibiting the catalytic oxidation of ascorbic acid in aqueous solution (Fearon and Kawerau, 1942). As ascorbic acid is intimately associated with collagen formation and fibroblastic growth (Eddy and Dalldorf, 1941), the therapeutic action of thiourea may reside in its protective effect on the vitamin mobilized locally for tissue repair.

I wish to record my thanks to my two collaborators for the trouble they have taken in the clinical investigation of the action of thiourea; I also gratefully acknowledge the grant from the Medical Research Council of Ireland, which has made it possible for Mr. Kawerau to undertake his part in the work. The case histories and details of individual treatment will be published elsewhere.

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F. R. Whitehouse and C. H. Watkins (*Proc. Mayo Clin.*, 1942, **17**, 140) record a case of multiple diseases of the lungs treated by sulphadiazine. After the second course of this drug the patient had severe bleeding from the gums, and thrombocytopenia was detected, the platelets numbering on one occasion only 20,000 per c.mm. The value for Hb was 10.5 g. per 100 c.cm. of blood. The drug was discontinued, and improvement resulted from a transfusion. Four weeks after this the patient had to be given sulphadiazine again, and thrombocytopenia recurred. The authors urge that thrombocytopenia as the result of sulphonamide therapy should always be suspected when purpura occurs during treatment.