Discussion

DISCUSSION

Nanna Svartz (Stockholm): *Autoradiographic investigations on the penetration of medical drugs to the fetus*

In addition to the common types of testing remedies, I should like to emphasize another possibility of estimating the risks for the fetus of the maternal medication.

Several years ago we reported some experiences with fluorescence microscopy which had made it possible to study the affinity of some drugs to certain tissues of the body.

At the Veterinary school in Stockholm S. Ullberg and collab. have during the last years elaborated a still more advantageous method for studying the pathways of a compound in the body. The compound to be investigated is labelled with C^{14} or S^{35} or Tritium. The radioactive compound is injected intravenously into mice. The animals are sacrifized by immersion in a cold liquid 5, 20, 30, 60 and 120 minutes or more after the injections. By aid of Ullberg's method sagittal sections are made through the entire body of the mice. The sections are put on films. The autoradiographic pictures are studied 4–8 weeks after the injections. By this method it is f.i. possible to establish whether a drug is penetrating or not into the fetus.

A few examples from investigations that I have carried out together with *Ullberg*, *Hanngren* et al. will be demonstrated in the following. The first picture (Fig. 1) shows

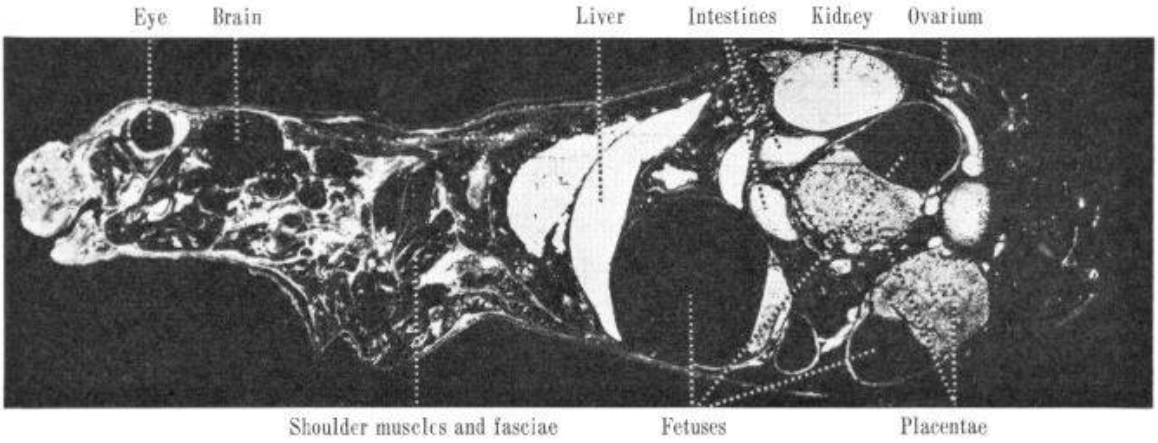

Fig. 1. Mouse, injected with S^{35} labelled salicyl-azo-sulphapyridine 5 minutes before the animal was sacrificed. The compound has already passed the intestinal wall and a strong radioactivity is seen in the lumen of the intestines. Strong radioactivity in the connective tissue and the liver, no radioactivity in the brain and in the foetus.

the distribution of an azo compound between salicylic acid and sulphapyridine (Salicyl-azo-sulphapyridine) 5 minutes after injection. The drug is already accumulating in the connective tissue, the liver and the intestines. It does not penetrate to the fetus or the brain. The next picture (Fig. 2) shows the distribution 30 minutes after injection of labelled azo compound. The distribution is about the same as after 5 minutes. — Pure Sulphapyridine on the other hand is rapidly penetrating into the fetus and is diffusely distributed in the whole body, as is demonstrated in Figure 3.

As to Salicylic acid it is also diffusely distributed in the body. Amino-salicylic acids, on the other hand, show about the same localization as azo-compounds with one exception: they are penetrating to the fetus (Fig. 4).

Ullberg, *Schmiterlöw*, *Hanngren*, *Hansson* et al. have investigated the distribution of many different compounds, f.i. phenothiazine derivatives. As to the accumulation in the fetus these authors have a.o. demonstrated differences between Promethazine (Lergigan) and Aprobit (Soventol). Aprobit does not penetrate to the fetus, while Promethazine does.

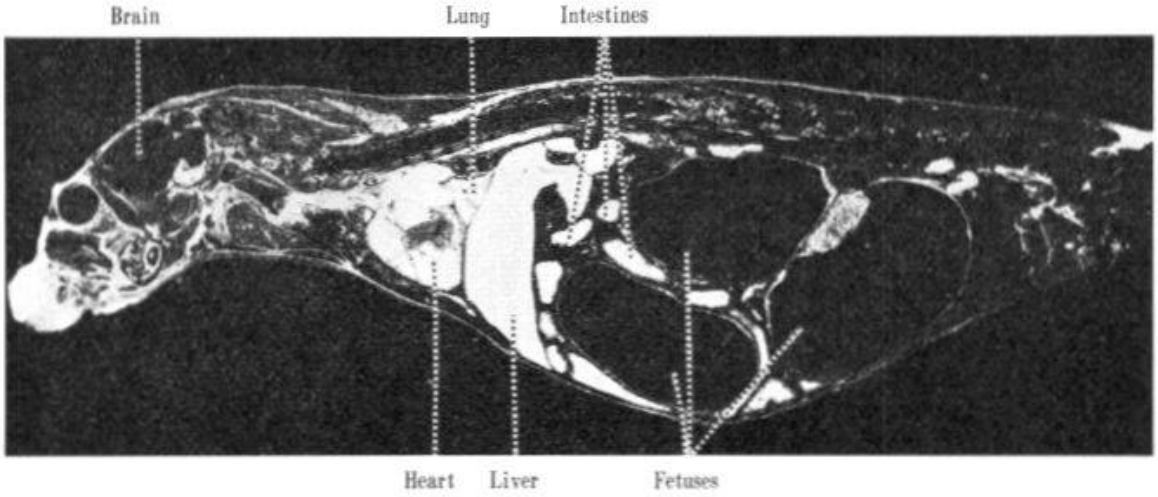

Fig. 2. The distribution 30 minutes after injection is about the same as in Figure 1.

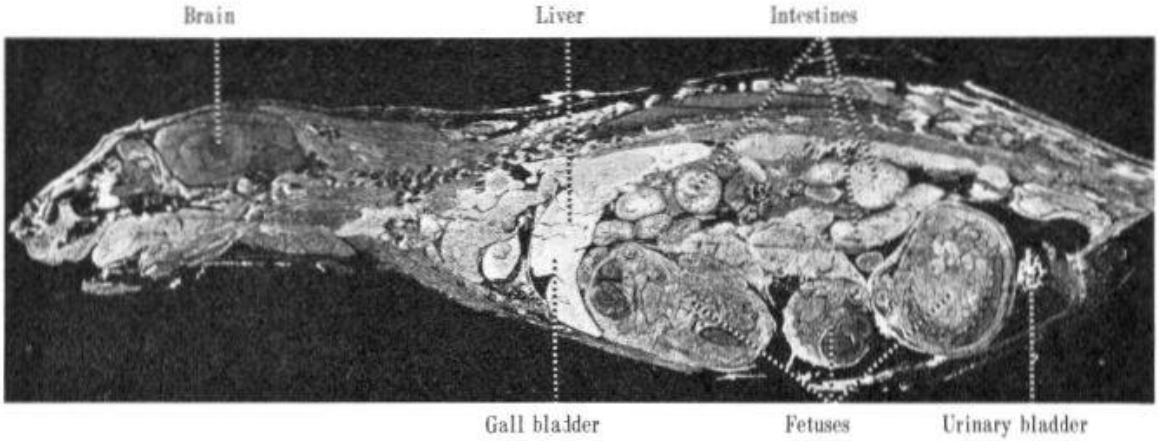

Fig. 3. S^{35} Sulphapyridine is diffusely distributed in the body, thus, also to the brain and the fetus.

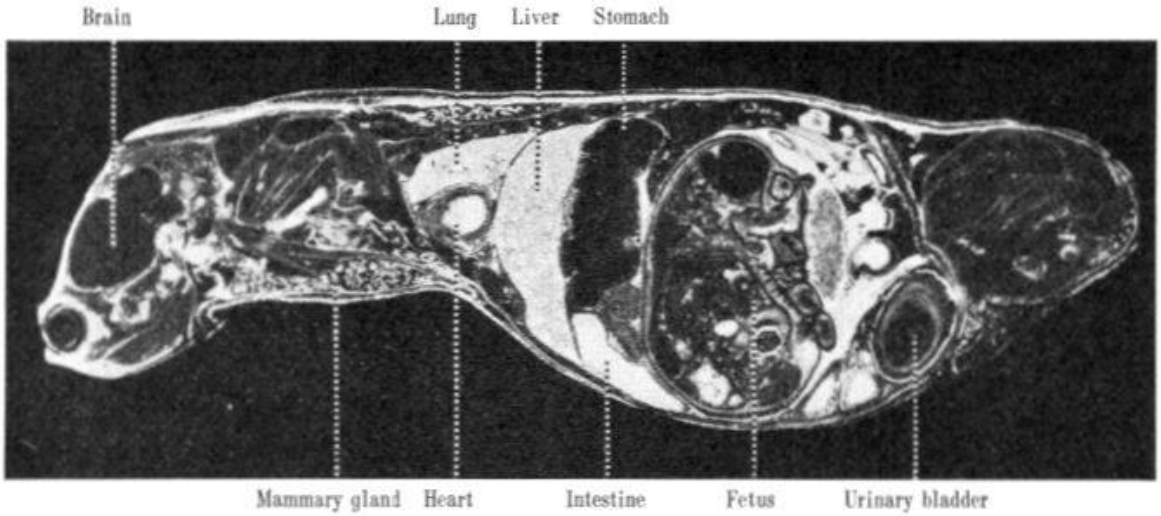

Fig. 4. Autoradiogram showing the distribution of C^{14}-5-amino-salicylic acid 1 hour after intravenous injection. The compound shows the same affinity as salicyl-azo-sulphapyridine with one exception. The drug has penetrated to the fetus.

According to *Schmiterlöw*, Nicotine shows a rapid penetration into the brain and the suprarenals and the kidneys. Radioactive metabolites were also found in the fetus.

It is somewhat aside from the subject to-day, but I want to mention that by aid of the Ullberg laboratory I have been able to study the tissue affinity of that macroglobulin, called the Rheumatoid Factor, that we have isolated from the blood in Rheumatoid Arthritis. The macroglobulin in question was labelled with J 125 by L. Plantin. This radioactive substance is known to damage proteins, but in our tests, however, the characteristic biologic properties of the Rheumatoid factor were left unchanged. Two days after injection radioactivity was demonstrated nearly only in the connective tissue of the skin (Fig. 5) and in the fasciae of the muscles and in the joint capsule. From other experiments it seems already to be established that macromolecules do not penetrate to the fetus.

In our opinion it would be important to use as a routine method this possibility of studying the distribution in the body of different substances and particularly medical drugs and establish among others their penetration to the fetus.

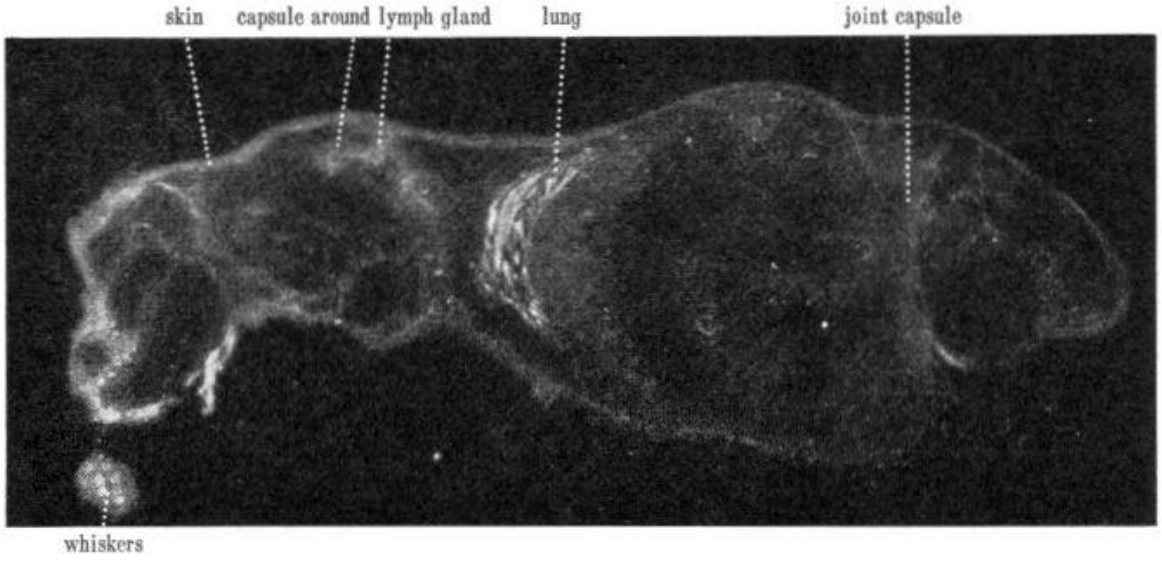

Fig. 5. Autoradiogram showing the distribution of the Rheumatoid factor, labelled with J 125. The factor is concentrated to the connective tissue. No affinity to the liver, the spleen, the lymphatic glands.

Appelgren L.-E., Hansson E. and *Schmiterlöw C. G.:* Acta physiol. scand. **56,** 249 (1962). – *Hanngren Å., Hansson E., Svartz N.* and *Ullberg S.:* Acta med. scand. **173,** 61, 391 (1963). – *Helander S.:* Acta pharmacol. (Kbh.) **6,** 97 (1950). – *Schmiterlöw C. G.* and *Hansson E.:* Arch. int. Pharmacodyn. **18,** 431 (1956). – *Svartz Nanna:* Gastroenterologia (Basel) **86,** 683 (1956). – *Ullberg S.:* Acta radiol. (Stockh.) Suppl. 118 (1954). – *Ullberg S.* and *Bengtsson G.:* Acta endocr. (Kbh.) **43,** 75 (1963).

H. Tuchmann-Duplessis (Paris): Signale qu'il existe de nombreuses circonstances dans lesquelles des substances qui ne pénètrent pas dans l'embryon ou le fœtus, déterminent néanmoins des malformations.

Le cas le plus simple est représenté par le bleu trypan. Ce colorant diazoïque reste localisé dans les membranes fœtales, respecte l'embryon lui-même et détermine cependant un fort pourcentage de malformations du système nerveux et des viscères.