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First studies on foetal organotropism of cephalosporin, streptomycin and rifamycin SV under physiological conditions

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DRUGS exert an action on foetal organism which depends mainly on the stage of pregnancy, on the transplacental passage and on the distribution and localisation in the blood and different foetal organs.

Drug concentration has been extensively investigated in foetal and maternal blood, but scantily at the level of foetal organs (organotropism)[1].

Since 1964,[2–5] we have been carrying out a systematic research on foetal organotropism, by studying drug organotropism under different conditions (physiological, pathological and artificial) and at different times after drug administration.

MATERIAL AND METHODS

Eighty eight Dutch rabbits, weighing 2400 ± 200 g, were used within the period from the 25th to the 30th day of pregnancy. The following drugs were administered to rats which had been fasting for 18 hr: cephalosporin hydrochloride (50 mg/kg i.m.), or streptomycin sulphate (300 mg/kg i.v.), or rifamycin SV Na salt (50 mg/kg i.v.). Animals were killed by bleeding 1/2, 1,2, 4 or 8 hr after streptomycin injection, 1/2, 1, 2, 4, 8 or 14 hr after cephalosporin injection and 1/4, 1/2 or 1 hr after rifamycin SV injection.

The assay of antibiotics was performed by a microbiological method, employing as test-organism *Staph. Curcio* for cephalosporin and rifamycin SV and *Myco. paratubercularis* ATCC 607 for streptomycin. The following organs: kidney, liver, lung, brain, muscle, placenta were aseptically homogenized for 5 min with a M/20 buffer phosphate solution pH 7 (Na_2HPO_4, $12H_2O$ and KH_2PO_4). The homogenates were centrifugated for 10 min at 3000 rev/min. Assays were performed on the supernatants.

RESULTS AND CONCLUSIONS

The results obtained are shown in Figs. 1–3.

1. From a quantitative point of view, blood and organs show, in all three cases an antibiotic activity which is much lower but more lasting in the foetus than in the mother.

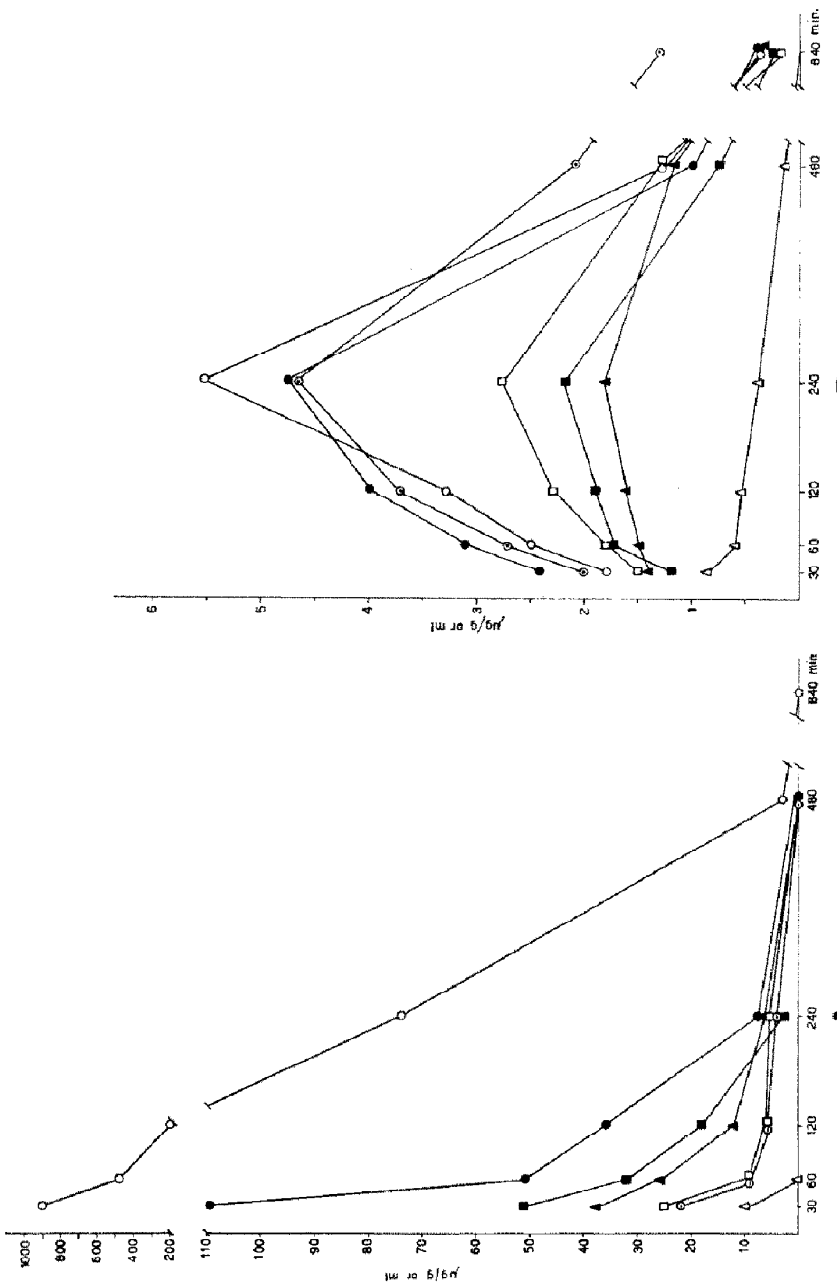

FIG. 1. Distribution of cephalosporin hydrochloride in the maternal (A) and foetal (B) organs after i.m. injection of 50 mg/kg.

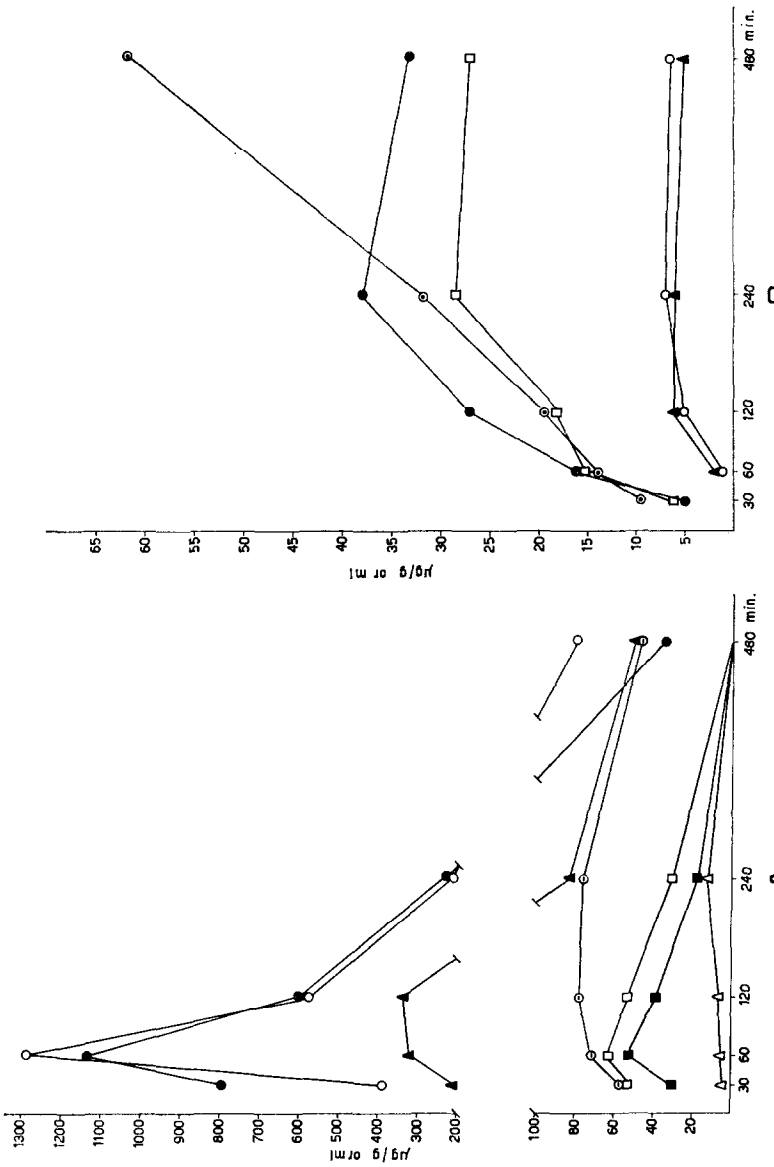

FIG. 2. Distribution of streptomycin sulphate in the maternal (A) and foetal (B) organs after i.m. injection of 300 mg/kg.

2. From a qualitative point of view, remarkable and interesting differences are observed between distribution of drug in maternal and foetal organs in the case of streptomycin and cephalosporin, but not of rifamycin SV.

For example, streptomycin shows a physiological organotropism for the maternal lung, but not for the foetal lung.

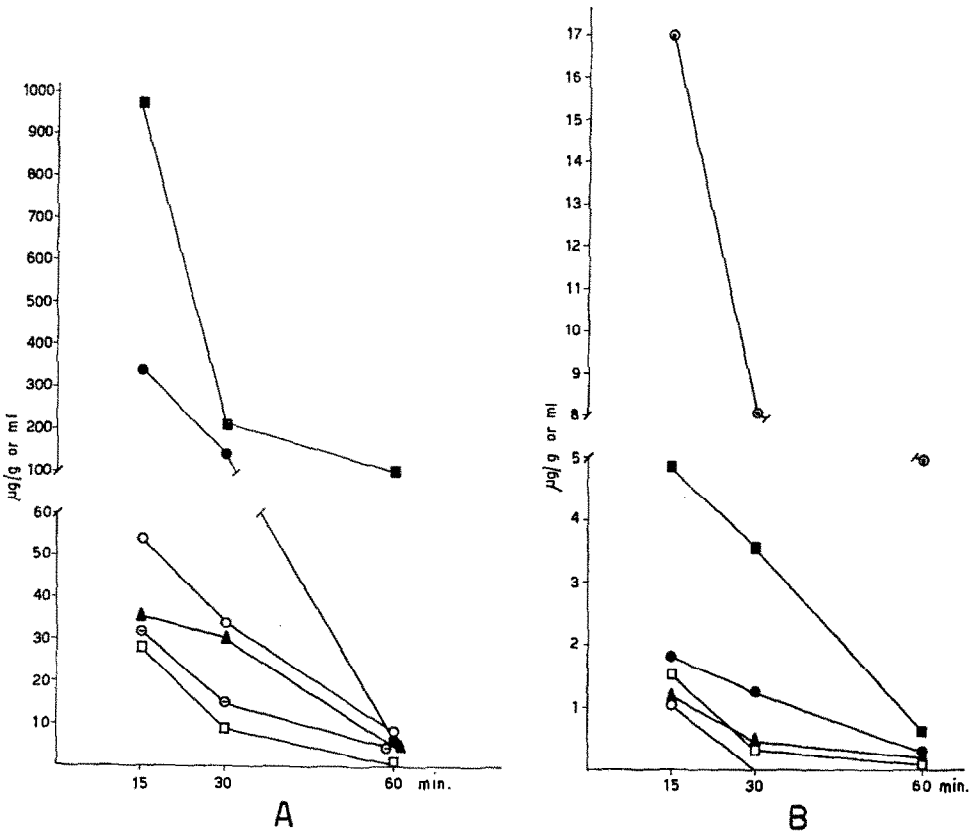

FIG. 3. Distribution of rifamycin SV Na salt in the maternal (A) and foetal (B) organs after i.v. injection of 50 mg/kg.

The above mentioned results are likely to be related to particular excretory and disintoxicating mechanisms to morphological structure, and to functional state of each maternal and foetal organ.

The results of these preliminary experiments justify the undertaking of other investigations, carried out with drugs of different chemical structures and animals of different species at various stages of pregnancy.

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Effect of vitamin K deficiency on the adenosine nucleotide content of chicken liver

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A VITAMIN K deficiency produces a hemorrhagic tendency resulting from a depressed synthesis of clotting factors; however, the details concerning the mechanism have not been elucidated. Martius and Nitz-Litzow reported that mitochondria from the livers of vitamin K-deficient animals were uncoupled[1] and suggested that, as a result, the energy supply would be decreased, which in turn would result in a depression of protein synthesis. However, other investigators found the P-O ratio of mitochondria from vitamin K-deficient animals to be no different from that of normal animals.[2, 3] In the present studies, a different approach was used to obtain information concerning this point. Assuming that a depression of the high-energy phosphate content would serve as an index of uncoupling, the adenine nucleotide content of normal and vitamin K-deficient animals was compared. No difference was found between the adenine nucleotide content of control and vitamin K deficient-animals.

MATERIALS AND METHODS

A vitamin K deficiency was produced by placing one-day-old white leghorn chicks (Duckworth Hatcherys, Hanover, Md.) on a vitamin K-deficient diet (General Biochemicals, Chagrin Falls, Ohio). On the basis of preliminary trials, the diet appeared to be deficient in other vitamins as well. The diet was therefore, supplemented with vitamins in the amount and quantities reported by Griminger.[4] The diet of the control animals was supplemented with vitamin K_1 in the form of stabilized beadlets (Hoffman-LaRoche, Inc., Nutley, N.J.), with the equivalent of 2·7 mg vitamin K_1/kg food. The diets and tap water were given *ad libitum* throughout the experimental period. All chicks were reared in electrically heated thermostatically controlled brooders with a screen bottom.

At four weeks of age, blood was collected from the carotid artery of ether-anesthetized chicks and prevented from clotting by the use of sodium citrate. Plasma prothrombin times were determined by the one-stage procedure, with acetone-dehydrated chick brains as a source of thromboplastin.

Immediately after the blood samples were obtained, liver samples of approximately 100 mg were removed rapidly and frozen in liquid nitrogen in order to minimize any changes in nucleotide content that might occur during the period of handling. The tissues were then pulverized in a − 17° room and extracted with $HClO_4$ as described elsewhere.[5]

ATP, ADP, and AMP were assayed by the enzymatic procedure of Kalckar.[6] Adenylic acid deaminase (preparation A) and adenyl pyrophosphatase were prepared as described by Kalckar.[7]

Myokinase was obtained from Boehringer and Soehne. The nucleotide content is expressed as micromoles per gram fresh weight. Glycogen was determined by the procedure of Seifter *et al.*[8] Inorganic phosphate was determined by the method Fiske and Subbarow.[9]

RESULTS AND DISCUSSION

After four weeks on the diet, the chickens weighed about 210 g and all appeared healthy. However, those on the vitamin K-deficient diet had a prolonged prothrombin time, while those on the diet