INDUCTION OF DECIDUOMATA BY INTRAUTERINE COPPER IN THE RABBIT

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In the course of a study on the dissolution of copper in the rabbit uterus (Tobert, 1974), it was observed that copper intrauterine devices (Cu-IUDs), inserted into rabbits 1 day after induction of pseudopregnancy, consistently elicited what appeared to be deciduomata in the endometrium adjacent to the device. Four rabbits, each with an IUD bearing 42 mm² of copper in one horn and an IUD bearing 14 mm² of copper in the other, were found to have nodular endometrial masses in the vicinity of the IUD in seven of the eight horns when killed 14 days after insertion of the devices. Subsequent histological examination confirmed that in all seven cases the endometrial masses were composed of decidual cells.

In view of the use of copper as an intrauterine contraceptive agent (Tatum, 1973) and the paucity of information on experimental decidualization in the rabbit, this phenomenon appeared to merit further investigation. The purpose of this study was to determine whether the decidual cell reaction is a specific response to copper, by comparing the decidualogenic capacity of physically similar IUDs bearing copper, platinum, zinc or nickel. Platinum is too noble to be attacked by body fluids and provides an inert control. Zinc is a reactive metal that dissolves readily in biological fluids (Clarke & Hickman, 1953) and is an effective intrauterine contraceptive agent in rabbits (Zipper et al., 1969). Nickel was used because it was suspected that the decidual cell response might be a consequence of the endometrial trauma produced by copper (Tobert & Davies, 1975); nickel is reported to produce endometritis and pyometra in the rabbit (Carleton & Phelps, 1933) and to cause even more tissue necrosis than copper when implanted into rabbit abdominal muscle (Wu et al., 1967).

The IUDs consisted of acrylic rods, 21 mm long and 2-4 mm in diameter, onto which rectangular pieces of metal foil, 6 x 7 mm, were mounted so as to form a metal sleeve 6 mm long at one end of the rod. Details of the construction and surgical insertion of the Cu-IUDs are described elsewhere (Tobert, 1974; Tobert & Davies, 1975), and the Pt, Zn and Ni IUDs were constructed and inserted in the same way. The foils used (Goodfellow Metals) were all at least 99-9% pure and were of the following thicknesses: Cu 6·5 µm, Pt 7·5 µm, Ni 10 µm, Zn 25 µm. Thin foils were used because thicker foils of the harder metals tend to form sharp edges along the ‘seam’ of the sleeve which might

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injure the endometrium. This design was adopted in preference to the wires more commonly used in order to minimize physical differences between the IUDs resulting from the different flexibility of the various metals.

Twelve virgin New Zealand White rabbits, 3·1 to 3·7 kg, caged singly and on 14 hr daylight/24 hr, were used. Pseudopregnancy was induced by the intravenous injection of 50 i.u. HCG. The next day the animals were subjected to laparotomy under aseptic conditions and sodium pentobarbitone/halothane anaesthesia, and the ovaries inspected to confirm the presence of ruptured follicles and the absence of CL from a pre-existing spontaneous pseudopregnancy. The IUDs were then inserted, one into each uterine horn; all possible combinations of the four metals were used twice, so that each metal was inserted into six rabbits. The metals were all distributed equally between the right and left horns. Twelve days after HCG injection, at which time deciduomata reach maximum development (Beasley & Davenport, 1970), the animals were killed by overdose of sodium pentobarbitone, and the uteri removed, opened antimesometrially, and inspected for the presence of deciduomata.

The results of the experiment were clearcut; deciduomata were present in 5/6 copper-containing horns, and none was present in any of the other horns, with the exception of one Zn- and one Pt-containing horn, both of which contained minute nodules adjacent to that end of the device distant from the metal sleeve. These were probably the result of irritation by the tip of the device since they were well away from the metal sleeves. The deciduomata in the Cu-containing horns were all related to the metal and ranged in size from a few small nodules to a massive deciduoma occupying over half the length of the horn. In two cases the decidual tissue was found above and below the metal but not actually in contact with it; possibly copper ions in very high concentrations inhibit the response.

In 4/6 Ni-containing horns, small soft pads of tissue were found in contact with the metal. These were unlike the harder, mostly nodular deciduomata in the Cu-containing horns and consisted of hyperplastic but not decidualized stroma. The epithelium and glands had largely disappeared and an intense infiltration of leucocytes was evident at the luminal surface of the endometrium. In these four horns the nickel was almost exhausted, indicating a dissolution rate several times faster than that of copper (Tobert, 1974).

Since the IUDs were almost identical in physical form, the deciduomata are attributable to the chemical nature of the Cu-IUD and probably to the copper ions released from it, although other products of the reaction between the metal and the uterine fluid could possibly be involved (Oster, 1972; Oster & Oster, 1974). A gross pyometra was observed in all the Cu-containing horns but was not consistently present in the horns bearing any of the other metals. This was not due to bacterial infection, since pus from 4/6 Cu-containing horns was cultured aerobically and anaerobically on blood agar with uniformly negative results. It was attributable to inflammation and ulceration of the endometrium adjacent to the device (Tobert & Davies, 1975). Possibly it is this tissue damage that induces the decidual cell response by the same mechanism as other forms of endometrial trauma such as incisions or threading (De Feo, 1967). On the other hand, a more specific pharmacological action of copper
Fig. 1. Uterus (× 1·4) 12 days after HCG injection with IUDs in situ. The Cu-IUD has produced a massive deciduoma with well-marked placental folds (PF). No decidual tissue was found in the horn bearing the Pt-IUD. The corroded appearance of the platinum is an artifact caused by reflections in the metal surface.

Fig. 2. Tissue adjacent to a Cu-IUD, showing decidua and pus in the lumen and glands. H & E, × 120.

Fig. 3. Tissue adjacent to a Ni-IUD, showing loss of epithelium and glands and intense leucocytic infiltration of the stroma. H & E, × 120.

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may be involved. The fact that nickel caused considerable inflammation and epithelial destruction without producing deciduomata constitutes some evidence for the latter interpretation.

The importance of the time of insertion remains to be determined. We have observed that insertion of Cu-IUDs 5 days before mating does not regularly produce decidualization (J. A. Tobert, unpublished observations). Zipper et al. (1969) and Johnson (1972) also inserted Cu-IUDs before mating or induction of pseudopregnancy and reported stromal hypertrophy though not decidualization 9 to 10 days later. However, the deciduomata in the present experiments cannot be attributed to the trauma of insertion since none was produced by any of the other metals, and in any case the time of insertion in the present study precedes the sensitive period for deciduoma induction in the rabbit (Hafez & Pincus, 1956; De Feo, 1967). The endometrium may become less sensitive to the presence of copper after a sufficient time in situ, or the dissolution rate may fall as the fresh surface is corroded, so that earlier insertion would reduce the copper levels to which the prostegational endometrium was exposed. Copper wire, inserted into the uterus 6 days after HCG injection, appears to be more effective than silk thread or silver wire controls in inducing deciduomata, though intraluminal injections of copper acetate (1 ml of 1 mg/ml or 10 mg/ml solution 6 days after HCG) were ineffective (J. A. Tobert, unpublished observations).

The results of this study in the rabbit contrast with observations on the rat (Chang et al., 1970; Webb, 1973), in which intrauterine copper, inserted on Day 1 of pseudopregnancy (Day 0 = oestrus), not only fails to elicit decidualization but inhibits the response to subsequent uterine trauma. However, this is consistent with the fact that premature insertion of a thread into the rat uterus inhibits the response to subsequent trauma (De Feo, 1967), whereas there is some evidence that in the rabbit this manoeuvre facilitates deciduoma production (Marston & Chang, 1969).

There are several reasons why the above results may be of interest. Firstly, Sturgis-Arias Stella changes with marked decidual formation have been reported in a few patients using the copper IUD (Salaverry et al., 1973). Secondly, insertion of a Cu-IUD may be a useful experimental technique for producing deciduomata in the rabbit, a species for which few reliable methods are available (De Feo, 1967). Thirdly, if the action of copper can be demonstrated to be due to more than mere epithelial trauma, this may shed some light on the induction mechanism of the decidual cell reaction.

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