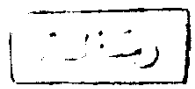
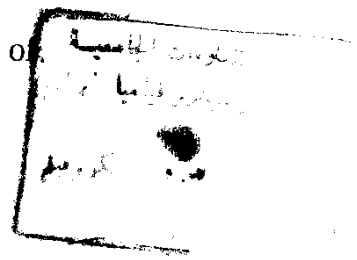
EFFECTS OF ALCOHOL ON UPTAKE OF IMMUNOGLOBULIN G BY ENDOMETRIUM



THESIS

Submitted For Partial Fulfilment of
The PH. D. Degree **(Anatomy)**



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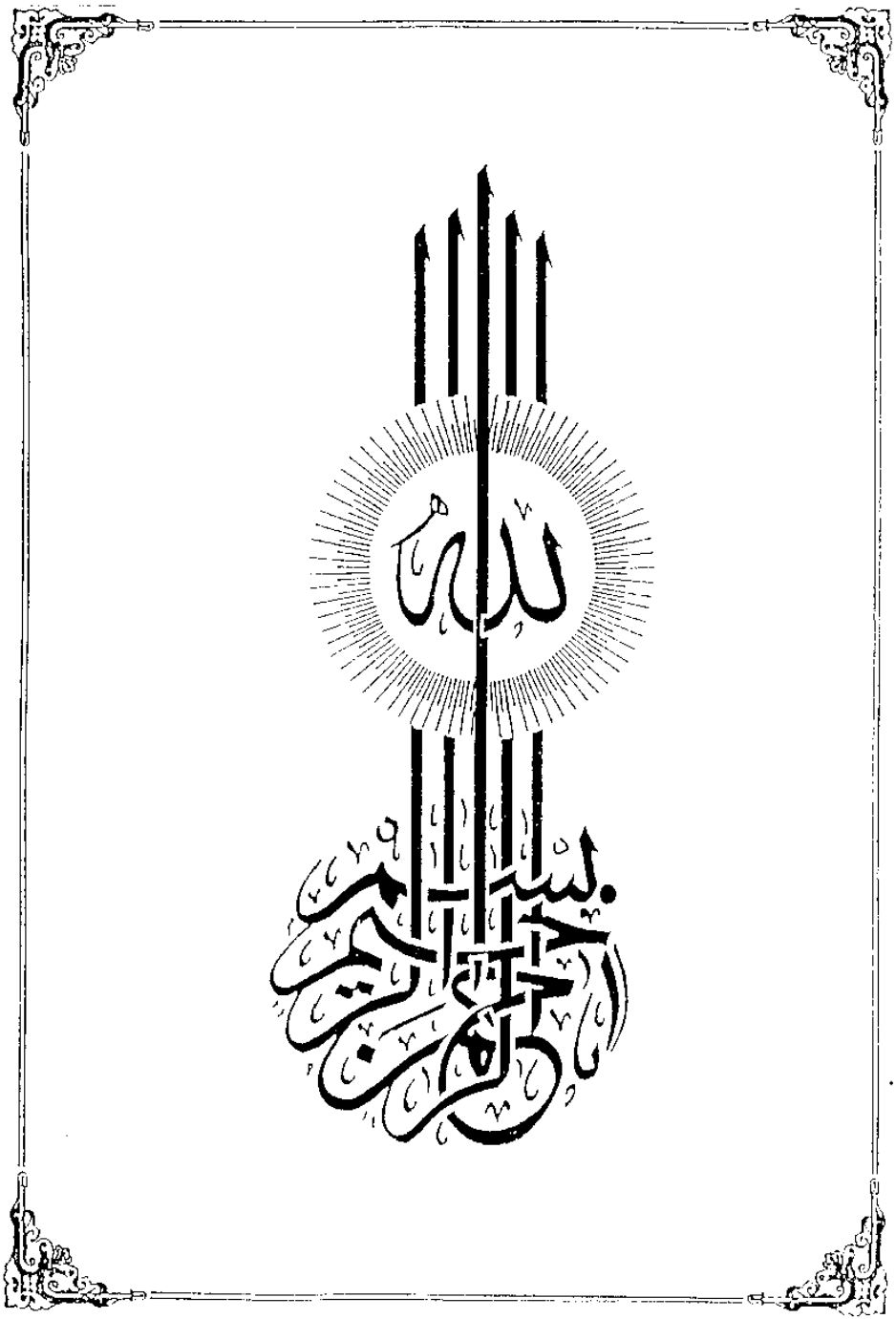

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To Whom
I am proud Being Their Daughter
To
My Father and Mother
Thanks for everything

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INTRODUCTION

INTRODUCTION

The principal function of the uterus was the sustenance of the developing embryo, and in mammals this involved the attachment of the blastocyst to the wall of the endometrium. Most of the cellular changes taking place in the tissues of the uterus were concerned with preparation for this event or with regession if it did not occur. Thus when considering the endometrium during implantation, we were concerned with a series of cellular changes culminating in the formation of the placenta; and, as would be expected, there was considerable variation between different species. Implantation of the blastocyst was normally the central event of the fertile estrus cycle, and the sequence of cellular changes in the endometrium during the cycle were adaptations to allow it to take place. In the interim, of course, the uterine lumen had to provide a suitable environment for the sperm during their transport to the oviduct.

This event required very different conditions from those required for implantation. Viewed from this perspective the build-up and breakdown of the endometrium during every cycle seemed more understandable. Also, the endometrium had been considered as a special tissue during pregnancy, forming the

feto-maternal interface and having a dual function. It might serve to protect the mother from excessive trophoblastic invasion and the fetus from any maternal immunological attack. Moreover, there was substantial evidence to suggest that a local secretory immune system was present in the female genital tract in many species *(Parr and Parr, 1985a)*. Immunoglobulins and/or secretory components had been detected in the uterine lumen, in gland lumina, in plasma cells in endometrial stroma and in luminal and/or glandular epithelial cells. However, less information was available concerning the transport of immunoglobulins into the uterine lumen, especially in the case of immunoglobulin G(IgG), *(McAnulty and Morton, 1978; Schumacher, 1980 and Rachman, Casimiri, Psychoyos and Bernard, 1983)*. IgG was of particular interest since materno-fetal transport of this class of immunoglobulin provided neonatal immunity. Studies of the localization of all classes of immunoglobulins in the reproductive tract epithelium were relevant to this question. Rachman et al (1983), detected immunoglobulin A (IgA) in mouse uterine gland epithelium at proestrus, but not in luminal epithelium and did not observe immunoglobulin G in either cell type. Canning and Billington (1983), reported constant staining for immunoglobulin A and immunoglobulin G in mouse uterine lumina and glandular epithelial cells throughout the estrus cycle. In other species,

immunoglobuins or secretory components had been reported in uterine luminal or glandular epithelia in mares *(Kenney and Khaleel, 1975)*, rats *(Wira, Sullivan and Sandoe., 1983)*, Sows *(Hussein, Newby and Bourne., 1983)*, rabbits *(Symons and Herbert, 1971)* and humans *(Kelly and Fox, 1979 and Suzuki, Ogawa, Tamada, Nagwa and Watanabe, 1984)*. A clarification of whether immunoglobulin G was present in epithelial cells of the rat uterus would contribute to a better understanding of the pathway of immunoglobulin G transport into the uterine lumen.

Most of the ultrastructural studies designed to ivestigate the mechanisms of neonatal immunity in the rat were through utlilizing electron-opaque proteins (ferritin or horseradish peroxidase) as simulants for immunoglobulin. Moreover, most studies were concerned with the near-term stages of gestation and little attention was paid to the earlier endometrial function as a route for transport of immunoglobulin g(IgG) in the rat. Furthermore, reviewing the current literature, it was found that alcohol abuse during pregnancy has been reported to produce intrauterine growth retardation, fetal alcohol syndrome (FAS) or fetal alcohol effects (FAE) *(Stein and Susser, 1984; Lin, 1985; Halmesmaki, Autti, Granstom, HeiKenheimo, Raivio and Ylikorkala, 1986; and Synder, Singh and Pullen, 1986)*.

Moreover, in newborn infants associated with intrauterine growth retardation, immunoglobulins concentrations was known to be suppressed *(Yang, Lin, River and Moawad,1983).* Although it has been found that serum levels of immunoglobulins in alcoholics were abnormal, however, it was the level of IgA that increased: IgG level was unaltered *(Drew Clifton, Labroog and Shearman., 1984).*Since it was the transport of IgG across the placental membrane that provided humans with neontal immunocompetence before birth if indeed the concentration of IgG in maternal blood remained unaffected by alcohol, then a failure in the acquisition of neonatal immunity was likely the result of failure in mechanisms for materno-fetal exchange of this immunoglobulin class *(Burnett, 1968).* Moreoever, alcohol consumption had been shown to have an acute deleterious effect on the fine structure of the human placenta *(AmanKwah and Kaufman, 1984).*

The controlling cellular mechanisms for placental transport of IgG during pregnancy were very poorly understood; the effects of chronic alcohol intake on such mechanisms were unknown. After the human, the laboratory rat had been the animal model of choice for such studies, as alcohol could be self-administered in pharmacologically significant amounts from a

liquid, nutritionally adequate diet that contained ethanol as a fixed percentage of total daily caloric intake. Maintenance on such a system over time assured that any variations in the transfer of immunity to the fetus were a result from alcohol, not from malnutrition. Moreover, it had been known for more than 30 years that in rats, like in humans, neonatal immunity was acquired by transfer of antibody as IgG from maternal to fetal blood compartments just before term *(Bramble, 1958; Mayersbach, 1958)*. Accordingly, the aim of the present work was to study the ultrastructure of the endometrium in the rat as well as to ascertain, assess and evaluate the controlling cellular mechanisms for uptake and materno-fetal translocation of immunoglobulin G (IgG) across the endometrium by utilizing immunocytochemical methods. In addition, it was possible to examine the effect of chronic alcohol intake on the ultrastructure of endometrial cells as well as on the controlling mechanisms for the uptake and the transport of IgG across endometrium.

REVIEW OF LITERATURE

THE MORPHOLOGY AND ORGANELLAR ARCHITECTURE OF THE ENDOMETRIUM

Krehbiel (1937) showed that in the uterus of the rat, there were two major areas of decidualized tissue: an antimesometrial decidual region consisting of primary and secondary zones and a mesometrial decidual region. The secondary decidual zone occurred on day 6 of pregnancy in the rat stromal cells surrounding the primary decidual zone as result of a subsequent phase of hyperplasia and hypertrophy.

Enders and Schlafke (1967) established many of the essential features of implantation in Holtzman rats using electron microscopy. The intial stages in implantation in the rat were designated pre-implantation stage, implantation stage 1, implantation stage 2 and implantation stage 3. On the late afternoon of day 5 of pregnancy most of the blastocysts had lost their zonae, but were still unimplanted. By the evening of day 5 in most of the rats the blastocysts were held in position within the uterine lumen starting implantation (implantation stage 1) but decidualization of stromal cells was just beginning. In the second stage of implantation the decidualized cells formed a cup around the luminal epihelium. This stage was well developed by the afternoon of day 6, a time at which the