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# Transplacental Passage of Drugs and other Exogenous Compounds

## A Review—Part I†

By Gary A. Eckhoff,\* D.V.M., M.S.

### *Introduction*

It is the purpose of this paper to discuss selected aspects of placental drug transfer. Assessment in this area is important from several points of view. A discussion of the passage of pharmacologic agents between the pregnant female and her fetus brings forth the great inadequacy of our present knowledge in this area, particularly with regard to quantitative kinetic data which would permit calculation of transfer rates. A study of placental physiology also rapidly illustrates the fragmentary state of our knowledge of this subject.

Aspects of placental drug transfer are also important when one desires rapid placental passage of pharmacologic agents such as antibiotics. In cases of maternal transmission of syphilis or gonorrhea to the fetus it is desirable to achieve adequate fetal blood levels to ward off the infection. Prevention of intrauterine fetal infection during premature rupture of the membranes is another example of where rapid transplacental passage of a nontoxic antibiotic is needed<sup>29</sup>. Penicillin and its analogs appear to be ideal here and they are free of any undesirable effects on the fetus.<sup>28,29,30</sup>

A knowledge of various aspects of placental drug transfer takes on added importance when dealing with agents with potential harmful effects on the developing and mature fetus. It is well docu-

mented that various agents can have detrimental effects during all phases of fetal development.<sup>1,3,23,36,57</sup> Early embryonic cells proliferate rapidly and are, therefore, most sensitive to drugs that can act as teratogens in both animal and man. The thalidomide disaster of 1962 shall forever be a witness to this potential danger. Also, the pharmacodynamics of agents in the fetus is no doubt different from that in the mature individual. Few systemic investigations of metabolic capabilities of the fetus have been carried out with respect to pharmacologic agents. Thus many, many agents cannot be administered to the pregnant female. It would thus be extremely beneficial if the pharmacologist could readily manipulate placental drug transfer to exclude the passage of an agent which is harmful to the fetus but beneficial to the pregnant female. This can only be achieved after detailed knowledge is uncovered concerning the transport of pharmacologic agents across the placental membrane.

### *Anatomy and Physiology of the Placenta*

Both the macro and microscopic anatomy of placentation vary considerably depending upon the species involved.<sup>1,4,56</sup> One must always consider this comparative placentation when extrapolating drug transfer data from species to species. Man is like the monkey but has only one discoid patch. The rat, which is used extensively

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in placental drug transfer research, has a pair of discoid patches as does the monkey.

Placentas can be arranged in a series that is based on the degree of intimate contact existing between the chorion and the uterus; moreover, this is based on the minute histological relations established at this zone of junction of these two components: The sow and the mare have the epithelio-chorial type. Ruminants have the syndesmo-chorial type. The carnivore placenta is characterized as endothelio-chorial. Insectivores, bats, anthropods, man, and monkey have the hemo-chorial type of placenta and the rat, guinea pig, and rabbit have a hemo-endothelial type of placenta. Hemo-chorial and hemo-endothelial type indicates that maternal blood is in direct contact with fetal tissues and endothelium of fetal vessels respectively. Note that the rat, which is used extensively in placental drug transfer investigations, does not fall in the same histological class as man. The precise anatomic nature and thickness of the placental barrier varies in man according to the stage of pregnancy.<sup>57</sup> In the human placenta early in pregnancy there are four layers between the two circulations with a total thickness of about 0.025 mm. These consist of (a) syntrophoblast, (b) cytotrophoblast (which gradually disappears at about four months with only remnants present at birth. Both a and b together make up the trophoblast, (c) mesenchymal stroma of the chorionic villi, (d) endothelium of the fetal capillaries. At parturition the total thickness here has decreased by a factor of 10. The anatomical barrier to the passage of drugs from mother to fetus is thus considerable. The rate of passage of sodium does seem to bear a relationship to the thickness of the placenta.<sup>41,49</sup>

The physiology of the placenta makes it a unique organ. It can be thought of as an allograft that is resistant to immunological rejection and which functions almost autonomously and independent of the homeostatic regulations of the mother<sup>17</sup>. The blood of the mother and that of the fetus circulate independently in totally separate channels.<sup>1</sup> Fetal blood is pumped into the umbilical artery in the

umbilical cord, and is distributed by way of the chorionic plate to the chorionic villi. After passing through the capillary mesh of the villi the blood returns to the fetus by way of the umbilical veins. Maternal blood enters the placenta via spiral termination of the uterine arteries. The placenta functions primarily as an organ that permits exchange of materials carried in the blood of the mother and fetus. The placenta transfers nutrients and oxygen from the mother's blood to the fetus. Carbon dioxide and fluid waste products of fetal metabolism pass from the fetus to mother. The placenta exerts a kidney like function in this respect.<sup>1</sup> The placenta is also a synthetic organ for estrogen, progesterone, gonadotrophin, and certain food stuffs. It also has the ability to metabolize certain food stuffs, hormones, and even exogenous agents such as drugs.<sup>36,57</sup> The placenta also functions as a barrier and it is this function which is to be emphasized in this paper. It is the placental trophoblast that is chiefly important in placental interchanges, permeability, barrier functions and active enzyme transfer of certain materials.<sup>1,40</sup>

In light of today's knowledge, the term "placental barrier" must be used with great reservations. Arey states that the only substance absolutely barred from placental passage is particulate matter, such as bacteria.<sup>1</sup> It is well known that viruses, such as rubella and large protein molecules, such as antibodies, readily pass the placenta. It is also noted by Arey that large molecular nutrients such as proteins and fats are first broken down in the placenta to amino acids and fatty acids respectively and then transported to the fetus to be resynthesized to proteins and fats.<sup>1</sup> For years the concept was held that the placenta was a simple, passive, semi-permeable membrane across which substances passed largely by the process of diffusion.<sup>19,53</sup> This led to the idea that the placenta was an organ whose prime function was to protect the fetus against injury and infection, and provide a physical barrier to the passage of noxious substances from mother to fetus. The concept of a placental barrier has been abandoned for the following reasons. (a) Umbilical vein

blood does not represent an ultrafiltrate of maternal plasma.<sup>31,41</sup> (b) Placental transfer is not determined exclusively by such physical characteristics as thickness of the membrane, molecular weight of substance transferred, pore size, and maternal blood pressure.<sup>17,31,41</sup> (c) Few of the substances essential for fetal development cross the placenta by simple diffusion. Vitamins, amino acids, and certain ions are transferred against a concentration gradient. A continued selective action keeps essential nutrients at an adequate level on the fetal side of the placenta. (d) From a pharmacological standpoint, the placental barrier is also misleading. A review of the literature reveals that almost any drug given to the pregnant female can be expected to be found in the fetus.<sup>2,17,19,36,37,40,41,53,57</sup> Any agent present in the maternal or fetal bloodstream can be transferred across the placenta to some extent unless it is destroyed or is altered by metabolism during its passage. The important differences between drugs is the rate of transfer. With certain drugs this rate may be so slow that the amount transferred becomes pharmacologically undetectable.<sup>39</sup> Therefore, the term "placental barrier" should be modified to a sense of relative impedance to placental transfer of pharmacological agents.

Besides preventing bacterial passage, there are other isolated examples of where the placenta does act as a true barrier in defense of the fetus. Tetanus toxin does not pass the placenta membrane.<sup>16</sup>

#### *Techniques, Methods, and Procedures Used to Investigate Drug Transport Across the Placenta*

Various techniques have been used to study drug transfer across the placenta and these will be briefly reviewed below. (a) One of the simpler procedures known is to administer a drug to a pregnant laboratory animal, such as a rabbit or rat, and then analyze fetal tissues for presence of the agent.<sup>14</sup> (b) To detect passage from fetus to mother, one can surgically expose the fetus, inject them with the drugs, and then analyze maternal tissues.<sup>16</sup> (c) For larger animals and man, cord blood can

be sampled at the time of delivery for drugs which have been given maternally.<sup>29,30,43,51</sup> This is a common procedure when man is involved. Umbilical venous blood, compared to arterial blood, renders data more specific because it furnishes conclusive evidence of transfer from maternal to fetal circulations. (d) When animals are utilized the uterus and fetus can be surgically exposed and uterine and cord vessels cannulated.<sup>10,33,34</sup> An agent can thus be infused from either the maternal or fetal sides of the placenta. (e) Perfusion studies have also been carried out on isolated uterine and placenta preparations.<sup>15,24,42,45</sup> The chorioallantoic placenta of most mammals, including man, are particularly suitable for perfusion experiments. Mechanical pumps serve as the "artificial hearts" in these experiments.

The use of radioactive isotopes has been used extensively in many of the techniques outlined above. Antipyrine, a drug with high lipid solubility and low degree of dissociation, is utilized many times in these experiments to measure effective maternal and fetal placental flow rates.<sup>34</sup> Transplacental gradients of antipyrine are also used as indices of passive transfer characteristics of the placenta which provide a basis for the evaluation of possible active transport of agents.<sup>34</sup>

The development of gas phase methods, such as gas chromatography and gas chromatography—mass spectrometry, are providing new and highly effective ways for carrying out pharmacological and toxicological studies of drugs in the fetus and neonate.<sup>20</sup> The analytical separations are carried out by gas chromatography. The identification and structure studies of individual compounds are carried out by mass spectrometry. These procedures allow estimation of microgram amounts of drugs and drug metabolites and studies of the metabolism of drugs during multiple-drug therapy of the pregnant female.

#### *Fundamental Mechanisms of Placental Transfer of Foreign Compounds*

The main physiochemical processes which may pertain to placental transport may be considered, as with other mem-

branes, under seven main headings: ultrafiltration, simple diffusion, facilitated diffusion, active transport, pinocytosis, breaks in placental villi, and metabolic conversion.

Ultrafiltration has been largely abandoned. If the placenta were a simple semipermeable membrane likened to the endothelium of blood vessels, water, salts, and small organic molecules would pass with ease and the large molecules would be blocked. The umbilical vein would thus contain an ultrafiltrate of maternal plasma and the fetus would be dependent upon maternal blood pressure and flow for its supply of nutrients. Observations have been determined that this is not true.

In the process of diffusion, molecules move from an area of high concentration to one of low concentration and tend to assume equal concentrations on both sides of a membrane.<sup>48</sup> The driving force for diffusion is thermal agitation of the molecules.<sup>8</sup> The above comments are true for both kinds of diffusion (simple and facilitated).<sup>41,53</sup>

Most observations show that most drugs and foreign substances cross the placenta by simple diffusion.<sup>17,40,41,44,53</sup> This mechanism of transfer appears to be no different from that operating across other cell membranes.<sup>17,40,41,44,53</sup>

Very few vital substances essential to the fetus cross by simple diffusion.<sup>17</sup> Oxygen and carbon dioxide may be the only substances which cross the placenta via this mechanism. Preferential selective activity of the placenta is what is generally involved in transferring substances of physiological importance.

The process of facilitated diffusion, although not important in the placental transport of drugs, is important in the transfer of glucose and other sugars, amino acids, and salts which are relatively insoluble in the lipid membrane of cells.<sup>17,41,53</sup> The following evidence points to the fact that there may be a carrier molecule oscillating with great rapidity between the two surfaces of the placental membrane. The rate of transfer is influenced by the structure of the substance transferred. Agents, including some drugs, related structurally to the compound being

transferred may exhibit competitive inhibition for the transfer mechanism. The kinetics of the system shows a saturation phenomenon at high concentrations of substrate. The kinetics also deviate from Fick's Law, which is a mathematical equation that can be graphed showing the rate of transfer of a substance. Simple diffusion follows Fick's Law. The rate of transfer of facilitated diffusion is also more rapid than can be predicted on the physicochemical basis of simple diffusion.

Active transport mechanism seems to be involved in the transfer of vitamins, amino acids, sugars, and essential ions.<sup>7,17,42</sup> The transfer of sodium across the pig placenta was shown to involve active transport.<sup>3</sup> Kronfeld and his group have recently shown that calcium is also transported via an active process.<sup>10</sup> Drugs and foreign agents are not transported via this route unless they resemble very closely naturally occurring substances. Antimetabolites thus may be transported actively.<sup>8</sup> It is well known that the kidney, liver, and choroid plexus contain nonspecific active acid and base transport systems for exogenous compounds.<sup>34</sup> McNay has recently shown that these systems are probably lacking in the placenta.<sup>34</sup> There is, however, preliminary evidence to suggest that agents which are structurally related to endogenous compounds may be actively transported across the placenta.<sup>33</sup> In this study<sup>33</sup> it was shown that triameterene, a diuretic that is actively secreted by the renal tubules and which has a structure related to the purine nucleus, was actively transported across the near-term sheep placenta. A similar situation exist for pyrimidines (5-fluorouracil).<sup>27</sup>

Pinocytosis is another means by which substances might traverse the placenta.<sup>17,40,41,53</sup> Transportation of antibodies occurs via this route but pinocytosis appears not to function in the transfer of drugs and other exogenous agents.<sup>40,41,53</sup>

Physical breaks between the cells separating maternal and fetal blood (placental villi) are also known to occur and at times permit the passage of red blood cells.<sup>53</sup> The disease, erythroblastosis fetalis, of human babies and of foals is a possible result when fetal red blood cells cross the

placenta to the maternal side and the resulting isoantibodies return to cause hemolysis of fetal erythrocytes.<sup>19</sup> There is no evidence that these "holes" are significant in the passage of drugs.

Some endogenous substances are transferred by processes that involve the metabolic conversion of one substance into

another. Glucose is phosphorylated, converted to fructose and then secreted into the fetal compartment.<sup>18</sup> Several other examples similar to this exist. Placental drug metabolism also exists and this point will be discussed in greater detail in the next issue.

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## Diagnosis and Treatment of Disease in the Turtle

by Pete Henriksen\* and David L. Graham,‡ D.V.M.

Closely paralleling the tremendous boom in the cat and dog population in this country is an increased interest in exotic pets. The most commonly kept reptile pets include snakes, alligators, chameleons, iguanas, and turtles.<sup>13</sup> Of these, turtles are the most popular and it is certainly not unusual for the veterinary practitioner to be presented with an ailing turtle for treatment.

Many problems in turtles are related to poor nutrition. One very common ocular disease results is palpebral edema and hyperkeratosis of the Harderian glands. The nictitating membrane becomes inflamed, thickened, and easily visible with the naked eye. It fails to cover the eyeball completely and engorges with blood. Within a couple of days the upper and lower lids become swollen and fuse so that they cannot be mechanically separated even with a blunt instrument. The turtle, now totally blind, refuses to eat and usually dies of starvation. Recovery has been re-

ported, but untreated cases usually die. Sectioning the eye on post-mortem reveals an extensive change in the Harderian gland. The epithelium changes from glandular to squamous and the acini become dilated and distended by masses of keratin that cannot be expelled. The gland center becomes an accumulation of eosinophilic granulocytes forming a kind of abscess. The cause of this disease is generally thought to be a vitamin A deficiency. Other possible etiologies include: obstruction of the gland duct by bacteria or nematodes, faulty temperature regulation, or improper lime levels in the water.<sup>9</sup>

Treatment of this glandular disease usually consists of vitamin A supplementation in the form of cod liver oil (two drops daily). Success is reported in all but chronic cases.<sup>13</sup> Other remedies include sulfathiazole ointment daily, warm boric acid bath, or an hour a day swim in warm tea or aquarium salts.<sup>4</sup>

Another condition in turtles thought to be caused by vitamin A deficiency manifests itself as a patchy white discoloration of the carapace accompanied by listless-

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