

Conclusion

We have attempted to provide the practitioner a foundation upon which indication for fluid therapy and proper selection of fluid may be considered when confronted with the clinical case. Simplicity in approach and efficient use of the practitioner's time can be maintained if initial time is spent preparing formulations and equipment. The addition of a regimen of supportive fluid therapy to one's armament of therapeutic measures will add a very professional and rewarding dimension to the rural practice of bovine medicine.

REFERENCES

1. Benjamin, M. M. 1961. Outline of Veterinary Clinical Pathology, 2nd. ed., Iowa State University Press, Ames.
2. Donawick, W. J. and Christie, B. A. 1971. Clinicopathologic conference. J.A.V.M.A. 158: 501-510.
3. Fisher, E. W. 1969. Hydrogen ion concentration— anion—cation (acid-base) balance. In Veterinary Clinical Pathology. W. Medway, J. E. Prier and J. S. Wilkinson eds., Williams and Wilkins, Baltimore.
4. Hammond, P. B. 1962. Supportive therapy in the rural practice. Minn. Vet. 2: 20-22.
5. Schalm, O. W. 1965. Veterinary Hematology, 2nd ed., Lea and Febiger, Philadelphia.
6. Tasker, J. B. 1971. Fluids, electrolytes, acid-base balance. In Clinical Biochemistry of Domestic Animals Vol. II, 2nd. ed., J. J. Kaneko and C. E. Cornelius eds., Academic Press, New York.
7. Tenney, S. M. 1970. Respiration in mammals. In Dukes' Physiology of Domestic Animals, M. J. Swenson ed., Cornell University Press, Ithaca.

Transplacental Passage of Drugs and Other Exogenous Compounds: A Review-Part II

by Gary A. Eckhoff,* D.V.M., M.S.

METABOLISM OF DRUGS BY THE PLACENTA

In addition to and in conjunction with its transport functions, the placenta possesses metabolic activity consisting of many enzyme systems which function in the biosynthesis, degradation, and biotransformation of numerous endogenous compounds. Claude Bernard was the first to discover glycogen in the placenta⁵⁷. The role of placental glycogenolysis in maintaining early fetal glucose stores has also been elucidated⁵⁴. In 1965 Mori discovered protein biosynthesis in the placenta³⁸. This study utilized rabbits and involved placental S³⁵ incorporation into protein. Numerous active enzyme systems exist which function in the biosynthesis and degradation of steroids. It was also discov-

ered that conjugation of steroids markedly decreased their placental transfer^{26,11}. Thus there are extensive enzymatic capabilities in the placenta for endogenous compounds. It would be interesting to speculate on the effects of drugs on these metabolic activities of the placenta. This is an area with very little investigative effort and resultant alteration in placental function could be of considerable importance to fetal physiology.

Only within the last five years has investigative effort revealed the ability of the placenta to function in the biotransformation of drugs and other foreign compounds. Consideration of molecular change of pharmacologic agents given to the pregnant female and assayed in the fetus have led workers toward investigate efforts in this area. As noted above, pharmacologically administered steroids to the mother are generally considered to pass through the placenta only in a nonmetabolized state²⁶. It is thus essential to under-

* Dr. Eckhoff is an instructor of Veterinary Physiology and Pharmacology, Iowa State University.

† Presented as a partial fulfillment of a master's degree from the University of Minnesota, College of Veterinary Medicine, St. Paul, Minnesota.

stand how placental biotransformation of other drugs may affect their transplacental passage. It is also of interest to note that the varied drug metabolizing capabilities of placental tissue once again suggests a regulatory role of the placenta. This context would infer more of a physiological barrier than an anatomical barrier. There can be no doubt that placental biotransformation influences the form and quantity in which certain foreign agents ultimately reach the fetal compartment.

Preliminary evidence indicates that placental drug metabolism resembles that associated with the very familiar hepatic microsomal cytochrome P-450 drug metabolism system. The placenta, after the twelfth week of gestation, contains the pigment P-450, numerous mitochondria and microsomes, and significant quantities of smooth endoplasmic reticulum in the trophoblastic cells^{22,35,50}. In vitro metabolism of certain drugs also occurs with placental microsomal fractions and homogenates²¹. For instance, pentobarbital and amphetamine metabolism and hydroxylation and demethylation of polycyclic hydrocarbons has been demonstrated with rat and human placentas^{52,56}. As in the case for hepatic microsomal drug metabolism, these placental enzyme systems can be induced under certain circumstances. Smoking mothers have more ability for placental metabolism of certain agents⁵⁶. Chlordane pretreatment also induces the metabolism of certain substrates such as hexobarbital¹². Phenobarbital, which is a very familiar inducing agent in hepatic microsomal drug biotransformation, does not appear to induce the analogous systems in the placenta^{12,46}.

It is thus quite evident that the placenta does have the ability to metabolically alter drugs and other foreign compounds. How these systems effect drug transport across the placenta must await further investigation. Knowledge thus gained should aid not only in helping to understand how drugs are transported across the placenta, but also how certain drugs produce toxic effects on the fetus and how drugs may someday be employed for their therapeutic effects in the fetus.

FACTORS WHICH GOVERN THE DIFFUSION OF DRUGS ACROSS THE PLACENTA

Before proceeding to factors which govern the diffusion of drugs across the placenta, it should be pointed out that placental transfer of endogenous and some exogenous compounds is a two-way street. Although transfer to the fetus of endogenous agents is important, the equally vital passage from fetal to maternal compartments does exist. For instance, an active pump is known to exist which functions in transferring sodium from fetal to maternal blood streams³. Although we are most concerned with maternal-to-fetal passage of drugs, fetal-to-maternal passage exists as well. As noted above, most drugs pass across the placenta via simple diffusion and, therefore, a dynamic equilibrium occurs across the placental membrane which eventually reaches a steady state condition. In many cases in the laboratory it is the fetal-to-maternal passage that is studied in order to gain evidence of placental passage. There are also isolated examples of preferential placental transfer from fetal to maternal circulations. Triamterene, a diuretic, was transferred much more rapidly from the fetus than to the fetus³³. It was postulated that possibly an active transfer process exists for this purine-like compound.

Since most substances foreign to the body traverse the placenta via simple diffusion, it is pertinent that factors which determine the rate of this transfer be discussed. Almost all substances cross the placenta, and what becomes important, therefore, is the rate of their passage to the fetus.

The law which encompasses most of the factors which govern placental drug transfer is Fick's Law^{8,9,40,41,44,53}. The rate of diffusion is a function of the surface area available for transfer, the concentration gradient between maternal and fetal blood, the thickness of the membrane, and the diffusion constant of the drug, which takes into account its lipid solubility, degree of ionization, molecular weight, and spatial configuration. The following formula bears these relationships out:

$$\text{rate of diffusion} = K \frac{A(C_m - C_f)}{X}$$

K = diffusion constant

A = surface area

X = membrane thickness

($C_m - C_f$) = concentration difference between maternal and fetal blood

Of the basic mechanisms of placental transfer discussed above, only simple diffusion follows Fick's Law. It does not take into account the effects of maternal and fetal blood flow, solubility of the drug in fetal blood compared to maternal blood, and the intervillous space—fetal blood concentration gradient⁴⁰. Solubility differences are of particular interest when considering the uptake of anesthetics⁴⁰. Blood flow is very important with highly fat soluble poorly ionized agents which penetrate the placenta with ease⁴¹. The rate of placenta passage in this case is largely determined by the volume of blood perfusing the placenta. Changes in blood flow resulting from uterine contractions, cord compression, position of the mother or any insult on blood flow to and from the placenta can thus affect placental drug transfer.

The placenta can be thought of as a lipid membrane or barrier when one discusses placental permeability^{6,39,40,41}. Highly ionized acids and bases traverse the placenta slowly and changes in pH which increase the concentration of the undissociated form favors the passage of these drugs. One would expect poor fetal penetration with drugs of low lipid solubility. The ideal situation for rapid passage is low dissociation at physiological pH and high lipid solubility. Thiopental and antipyrine are two such drugs which penetrate the placenta very rapidly and achieve equilibrium with the fetus within 1 to 2 minutes^{31,32}. On the other hand tubocurarine and succinylcholine, two drugs with a great deal of dissociation at body pH and highly lipid insoluble, traverse the placental membrane at an extremely slow rate^{6,39}.

The few studies that have been done

on placental drug transfer strikingly resemble the transfer of materials across the blood-brain barrier or gastrointestinal epithelium⁶. However, quantitative studies are still too few to provide a sound basis for the placenta as a lipid membrane. Predictions regarding the rate of transplacental passage of drugs must await further investigation.

The lipid theory would make it unlikely that an analgesic could be developed for maternal pain and not cross the placenta, since an agent that would cross the blood-brain barrier would also cross the placenta.

As noted in the formula above, the rate of placental drug transfer is partially dependent on the concentration gradient between fetal and maternal blood. It appears that a high concentration gradient can over-ride the effects of lipid solubility and ionization. This seems to be the case for curare and succinylcholine^{28,47}.

Molecular size of the drug also determines its diffusibility. Drugs with a molecular weight of less than 600 diffuse across easily, but with increasing size the factor of lipid solubility becomes progressively more important⁴⁰. A molecular weight of 1000 seems to be the point at which compounds become nearly impassible⁴⁰. If the placental membrane does indeed fit the widely held classical concept that the plasma membranes are composed of fat-like layers interspersed with pores, drugs with molecular weight under 100 could apparently pass through these pores bypassing the lipid region³². Larger drugs must pass through this region.

Surface area and thickness of the placental membrane also have a theoretical bearing on the rate of transplacental diffusibility of drugs. Theoretical because this area is virtually unstudied in the light of drug passage. The surface area of the placenta increases and the villous membrane becomes thinner as gestation progresses⁴⁰. These processes should tend to favor the transfer of pharmacological agents across the placenta.

To conclude the discussion of factors which determine the rate of transplacental drug transfer it can be said that this trans-

fer rate is governed chiefly by the lipid solubility of the unionized drug molecule with other factors, such as molecular size, blood flows, concentration gradients, and surface area and membrane thickness, usually of secondary importance.

Summary

Various aspects of transplacental passage of pharmacological agents have been discussed and reviewed. Essentially all drugs can traverse the placenta but there are notable differences in the rate of transfer. The scarcity of quantitative data does not allow predictions to be made concerning the specific rate of transfer of a new drug. The foregoing discussion of placental pharmacology serves to illustrate the fragmentary knowledge on this subject and thus emphasizes the need for future investigations before this area of pharmacology is fully understood.

REFERENCES

1. Arey, L. B.: *Developmental Anatomy*. W. B. Saunders Co., Philadelphia, 1965: 119-150.
2. Baker, J. B.: The Effects of Drugs on the Fetus. *Pharmacological Reviews*, 12, (1960): 37-90.
3. Crawford, J. D. and McCance, R. A.: Sodium Transport by the Chorioallantoic Membrane of the Pig. *J. Physiol.*, 151, (1960): 458-471.
4. Crawford, J. M.: Vascular Anatomy of the Human Placenta. *Am. J. of Obstet. and Gynecol.*, 84, (1962): 1543-1567.
5. Crawford, J. S.: Some Aspects of Obstetric Anesthesia. Part II: The use of Relaxant Drugs. *Brit. J. Anesth.*, 28, (1956): 154-158.
6. Dancis, J.: *The Placenta and Fetal Membranes*. Ed. by C. A. Villee. Williams and Wilkins Co., Baltimore, 1960: 85-99.
7. Dancis, J. Money, W., Springer, D., and Levitz, M.: Transport of Amino Acids by the Placenta. *Am. J. Obstet. Gynecol.*, 101, (1968): 820-829.
8. Danielli, J. F.: *Recent Developments in Cell Physiology*. Ed. by J. A. Kitching. Academic Press, New York, 1954: 1-14.
9. Davson, H. and Danielli, J. F.: *The Permeability of Natural Membranes*. 2nd Ed., Cambridge University Press, 1952: 38-56.
10. Delivora-Papadopoulos, M., Ramberg, C. M., Crandall, E. D., Kronfeld, D. S.: Placenta Calcium Transfer in Sheep Near Term. *Fed. Proc.* 29, (1970): 775.
11. Diczfalussy, E.: Symposium on Placental Physiology: Endocrine Functions of the Human Feto-placental Unit. *Fed. Proc.*, 23, (1964): 791-798.
12. Dixon, R. L. and Willson, V. J.: Metabolism of Hexobarbital and Zoxazolamine by Placental and Fetal Liver Supernatant Fraction and Response to Phenobarbital and Chlordane Treatment. *Arch. Intern. Pharmacodyn.*, 172, (1968): 453-466.
13. Done, Alan: Perinatal Pharmacology. *Annual Review of Pharmacology*, 6, (1966): 189-208.
14. Douglas, B. H. and Hume, A. S.: Placental Transfer of Imipramine, A Basic, Lipid-Soluble Drug. *Am. J. Obstet. Gynecol.*, 99, (1967): 573-575.
15. Faber, J. J. and Hart, F. M.: Transfer of Charged and Uncharged Molecules in the Placenta of the Rabbit. *Am. J. Physiol.*, 213, (1967): 890-894.
16. Fedinec, A. A.: Observations on the Passage of Tetanus Toxin Through the Placenta and Fetal Membranes of the Rat. *Lab. Invest.*, 11, (1962): 536-543.
17. Ginsberg, J.: Placental Drug Transfer. *Annual Review of Pharmacology*, 11, (1971): 387-408.
18. Hagerman, D. D., Roux, J., and Villee, C. A.: Studies of the Mechanism of Fructose Production by the Human Placenta. *J. Physiol.*, 146, (1959): 98-104.
19. Hagerman, D. D. and Villee, C. A.: Transport Function of the Placenta. *Physiological Reviews*, 40, (1960): 313-330.
20. Horning, M. G., Waterbury, L. D., Horning, E. C. and Hill, R. M.: Placental Transfer of Drugs: Drugs and Drug Metabolites in the Neonate. *The Feto-Placental Unit*. Ed. by A. Pecile and C. Finzi. Excerpta Medica Foundation, Amsterdam, 1969: 305-312.
21. Juchau, M. R. and Yaffee, S. J.: Biotransformation of Drugs Substrates in Placental Homogenates. *The Feto-Placental Unit*. Ed. by A. Pecile and C. Finzi. Excerpta Medica Foundation, Amsterdam, 1969: 260-270.
22. Juchau, M. R., Niswander, K. R., and Yaffee, S. J.: Drug Metabolizing Systems in Homogenates of Human Immature Placentas. *Am. J. Obstet. Gynecol.*, 100, (1968): 348-356.
23. Karnofsky, D. A.: Drugs as Teratogens in Animals and Man. *Annual Review of Pharmacology*, 5, (1965): 447-472.
24. Krantz, K. E., Panos, T. C., and Evans, J.: Physiology of Maternal-Fetal Relationship Through the Extracorporeal Circulation of the Human Placenta. *Am. J. Obstet. Gynecol.*, 83, (1962): 1214-1228.
25. Kvisselgaard, N. and Moya, F.: Investigation of Placental Thresholds to Succinylcholine. *Anesth.*, 22, (1961): 7-10.
26. Levitz, M. and Dancis, J.: Transfer of Steroids Between Mother and Fetus. *Clin. Obstet. Gynecol.*, 6, (1963): 62-75.
27. Long, R. F. and Marks, J.: The Transfer of Drugs Across the Placenta. *Proc. Roy. Soc. Med.*, 62, (1969): 318-321.
28. MacAulay, M. A., Abou-Sabe, M. and Charles, D.: Placental Transfer of Ampicillin. *Am. J. Obstet. and Gynecol.*, 96, (1966): 943-955.
29. MacAulay, M. A., Berg, S. R., and Charles, D.: Placental Transfer of Dicloxacillin at Term. *Am. J. Obstet. and Gynecol.*, 102, (1968): 1162-1168.
30. MacAulay, M. A. and Charles, D.: Placental Transfer of Cephalothin. *Am. J. Obstet. and Gynecol.*, 100, (1968): 940-946.
31. McGaughey, H. S., Jones, H. C., Talbert, L., and Anslow, W. P.: Placental Transfer in Normal and Toxic Gestation. *Am. J. Obstet. Gynecol.*, 75, (1958): 482-495.
32. McKechnie, F. B. and Converse, J. G.: Placental Transmission of Thiopental. *Am. J. Obstet. and Gynecol.*, 70, (1955): 639-644.
33. McNay, J. L. and Dayton, P. G.: Placental Transfer of a Substituted Pteridine from Fetus to Mother. *Science*, 167, (1970): 988-990.
34. McNay, J. L., Fuller, E., Kishimoto, T., Malveaux, E., and Dayton, P. G.: Lack of Active Transfer of ¹⁴C Tetraethylammonium and Paraaminohippuric Acid by the Term Sheep Placenta. *Soc. for Exper. Biol. Med. Proc.*, 131, (1969): 51-56.
35. Meigs, P., Ryan, K. J.: Cytochrome P-450 and Steroid Biosynthesis in the Human Placenta. *Biochem. Biophys. Acta.*, 165, (1968): 476-482.
36. Mirkin, B. L.: *Developmental Pharmacology*. *Annual Review of Pharmacology*, 10, (1970): 255-271.
37. Mirkin, B. L.: Effects of Drugs on the Fetus and Neonate. *Postgraduate Medicine*, 47, (1970): 91-96.
38. Mori, M. and Iso, H.: Study of Protein Biosynthesis in Fetus and Placenta. *Am. J. Obstet. Gynecol.*, 93, (1965): 1164-1180.
39. Moya, F. and Kvisselgaard, N.: Placental Transmission of Succinylcholine. *Anesthesiology*, 22, (1961): 1-6.
40. Moya, F. and Smith, E.: Placental Transport of Drugs and Anesthetics. *Anesthesiology*, 26, (1965): 465-476.
41. Moya, F. and Thorndike, V.: Passage of Drugs Across the Placenta. *Am. J. Obstet. and Gynecol.*, 84, (1962): 1778-1798.
42. Nixon, D. A.: The Transplacental Passage of Fructose, Urea, and Meso-Inositol in the Direction from Fetus to Mother, as Demonstrated by Perfusion Studies in the Sheep. *J. Physiol.*, 166, (1963): 351-362.
43. Noddle, B. A.: Transfer of Oxytocin from Maternal to Fetal Circulation in the Ewe. *Nature*, 203, (1964): 414.
44. Page, E. W.: Transfer of Material Across the Human Placenta. *Am. J. Obstet. Gynecol.*, 74, (1957): 705-718.

45. Panigel, M.: Placental Perfusion Experiments. *Am. J. Obstet. Gynecol.*, 84, (1962): 1664-1683.
46. Pecile, A., Chiesara, E., Finz, C., and Conti, F.: Induction of Drug-Metabolizing Enzymes in the Feto-Placental Unit. *Internat. Symposium Feto-Placental Unit*. Ed. by A. Pecile and C. Finzi, Excerpta Medica Foundation, Amsterdam, 1969: 225-259.
47. Pittinger, C. B. and Morris, L. E.: Placental Transmission of D-Tubocurarine Chloride from Maternal to Fetal Circulation in Dogs. *Anesthesiology*, 14, (1953): 238-244.
48. Schanker, L. S.: Passage of Drugs across Body Membranes. *Pharmacological Reviews*, 14, (1962): 501-530.
49. Sternberg, J.: Placental Transfer: Modern Methods of Study. *Am. J. Obstet. and Gynecol.*, 84, (1962): 1731-1748.
50. Strauss, L., Goldenburg, N., Hirota, K., and Okukaria, Y.: Symposium on the Placenta. In *Birth Defects*, original articles Series I. National Foundation Pub., New York, 1965: 13-26.
51. Usubiaga, J. E., La Tuppa, M., Moya, F., Wikinski, J. A., and Velazco, R.: Passage of Procaine Hydrochloride and Paraaminobenzoic Acid across the Human Placenta. *Am. J. Obstet. Gynecol.*, 100, (1968): 918-923.
52. Van Petten, Hirsch, G. R. and Cherrinton, A. D.: Drug-Metabolizing Activity of the Human Placenta. *Can. J. Biochem.*, 46, (1968): 1057-1061.
53. Villee, C. A.: Placental Transfer of Drugs. *Ann. N. Y. Acad. Sci.*, 123, (1965): 237-244.
54. Villee, C. A.: Regulation of Blood Glucose in the Human Fetus. *J. Appl. Physiol.*, 5: 437, (1953): 437-444.
55. Welch, R. M., Harrison, E., Gommi, B. W., Poppers, P. J., Finster, M., and Conney, A. H.: Stimulatory Effect of Cigarette Smoking on the Hydroxylation of 3,4-Benzpyrene and the N-Demethylation of 3-Methyl-4-Monomethylaminoazobenzene by Enzymes in Human Placenta. *Clin. Pharmacol. Therap.*, 10, (1969): 100-109.
56. Wimsatt, W. A.: Some Aspects of the Comparative Anatomy of the Mammalian Placenta. *Am. J. Obstet. and Gynecol.*, 84, (1962): 1568-1594.
57. Yaffer, S. J.: Some Aspects of Perinatal Pharmacology. *Annual Review of Medicine*, 17, (1966): 213-234.

India's Approach to Cattle Development: Heifer Project As Catalyst In India's White Revolution

by Liam O'Dea
HPI India Representative
Edited by Dan E. Woodle*

India—1970	
Human Population	550 million
Cattle Population	250 million
Annual Milk Production	25 million tons
Daily per capita availability of milk	140 ml.
Per capita income per year	\$78

Statistics can be misleading and these are not 100% accurate, but even allowing for such limitations, it is clear that:

- a. There is scarcely half enough milk to meet the recommended minimum requirement of 250 ml. per person per day.

- b. The income of millions of India's people are below the subsistence level.

Background

These are two basic facts of present day India. It was not always so. Two hundred years ago India's population was probably not more that 20% of its present level. Apart from periodic and regional famines, there was probably sufficient food for everyone. Cattle have always been one of India's great assets, providing draft power, transport, fuel, fertilizer and milk. It is

* Mr. Woodle is a third year student in the College of Veterinary Medicine, Iowa State University.