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COMPARATIVE PLACENTAL TRANSFER, LOCALIZATION, AND EFFECTS OF RADIONUCLIDES IN EXPERIMENTAL ANIMAL AND HUMAN PREGNANCIES

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Estimating radiation doses to the human embryo/fetus from radionuclides and predicting effects requires extrapolation of data from studies of laboratory species, with scaling for species-specific developmental stage and gestational time relationships and maturities at birth. Combinations of fetal-to-maternal ratios of concentrations, patterns of deposition, transfer kinetics, and compartmental and physiologic models are used to predict radioactivity levels and radiation doses to the conceptus. There is agreement between values expressing fractional transfer across the placenta (θ) with tabulated values for fractional absorption (f_1) from gastrointestinal (GI) tract or lung for most substances commonly involved in metabolic processes. A tendency toward disagreement for some other materials is thought to involve explanations based on their physicochemistry, toxicity, or the influence of target tissue development on placental transfer kinetics.

Information about three well-documented elements that are absorbed from the GI tract and cross the placenta - cesium, strontium, and iodine - serve to present comparative behavior patterns in experimental animal and human pregnancies and illustrate approaches to predicting radiation dose and effect. Cesium is readily diffusible, and its transfer patterns are reasonably independent of species and stage of gestation. Concentrations are similar throughout tissues of the woman and the conceptus, there are no major preferential sites of localization; radiation doses are uniform so that effects are similar to those from external irradiation. The biological behavior of strontium and calcium is similar; both are primarily deposited in bone. Stage-dependent differences in skeletal elements development and their relative masses among species interact to influence concentrations of radioactivity in blood and in the conceptus, deposition throughout the skeleton, and placental transfer dynamics. Perinatal exposure of experimental animals to strontium can adversely affect skeletal development and increase tumor incidence in bone and adjacent soft tissues. Iodine is primarily localized to the thyroid gland, which does not become functional until the fetal stage. Consequently, placental transfer, fetal deposition, and metabolic details are strongly influenced by stage- and species-dependent differences in thyroid development, as are long-term consequences, including thyroid neoplasia. Thus, many reported among-species differences in radionuclide disposition and effect can be reconciled on the basis of comparative developmental chronologies, especially preferential deposition sites and other histogenic conditions. Dosimetric approaches depend on the intended use of the radiation dose calculations, and range from absorbed doses in target tissues to doses to the entire embryo or fetus.

INTRODUCTION

There are several reasons for the continuing interest that is directed toward evaluating both the early and the delayed effects of prenatal exposure to ionizing radiation. One aspect evolves from the general usefulness that is associated with the many attributes that have allowed x- or γ-radiation from external sources to serve as the archetypical or prototypic teratogen. External irradiation contrasts with chemical teratogen exposure; it is among the few agents that does not require absorption by the woman, metabolic activation, or transfer across the placenta. The radiation doses can be readily measured, and dose distribution is usually uniform throughout the uterus, embryo, and fetus.

Studies with radiobiological, as well as teratological objectives have provided information about the relationships between radiation doses and several responses that are characteristic of developmental stage. This knowledge is being used by advisory and regulatory bodies to establish dose limits for occupational and general populations. Current dose limits for external radiation exposures of the human embryo/fetus and recommendations for conservative use of radiological procedures in medical practice during pregnancy have required the use of certain reasonable elements of extrapolation of data regarding dose-dependence of effects in laboratory species. Extrapolations of data from high-dose exposures of pregnant woman or animals for predicting effects at low doses are of greater uncertainty, as are extrapolations from acute to chronic exposures.

Ionizing radiation is probably the first teratogen for which quantitative cause and effect relationships and patterns were demonstrated. It is of more than academic interest that the sequence of processes during its teratogenic actions have not been determined unequivocally. Moreover, the fundamental lesions leading to these changes, as well as to other types of effect that remain latent until after birth or during adulthood, have not been explored in detail. It is only recently that the unique characteristics of irradiation are being exploited to provide systems for investigating basic teratogenic processes, including fundamental alterations that may occur at the molecular level. Results from initial reports suggest that mechanistic information may evolve from such studies, and that such knowledge will facilitate defining dose- response relationships and provide a more rational basis for extrapolations.

Obvious uncertainties currently involved with extrapolations make complete dose and effect analyses especially difficult with radionuclides – the primary concern of this paper and the workshop. In addition to the extrapolations indicated above, evaluations of internal exposure involve utilizing information about effects of uniform exposures for predicting those that would derive from localized doses. This situation poses greater needs for extrapolations to estimate prenatal radiation doses and to predict effects of the internally deposited radioactive substances in the human fetus.

SOURCES OF DATA

For some radionuclides, there are data that are based on analyses of materials derived from humans, such as umbilical cord blood, placentas, miscarried or aborted conceptuses, and deciduous teeth, but these are relatively limited in number. Some of these data derive from reports of exposure situations involving natural radionuclides; examples include deposition of inhaled radon progeny and medical or occupational exposures to radium salts. There are reports of tissue radioanalyses from pregnant women or infants who had been exposed to man-made isotopes of elements such as cesium, strontium, iodides, and transuranics resulting from environmental releases. Perhaps the largest body of data on radionuclides is that which has been obtained for radiopharmaceuticals and for metabolites that were used for some clinical evaluations and earlier clinical experiments. Accidental exposures of human populations in the Marshall Islands have provided additional information concerning radioiodines and data about placental transfer of mixtures of radionuclides may be forthcoming from people who were exposed in the Chernobyl accident.

Many of these studies and their results are described in representative comprehensive reviews that include data from evaluations of prenatal radiation and radionuclide exposures of humans, such as IAEA (1976, 1979) and UNSCEAR (1977, 1986). As exemplified by studies considered in these compilations, experimental approaches to radionuclide exposures of intrauterine animals are of even more disparate nature. This wider range is further indicated by reviews and symposium volumes that will provide a broad spectrum of information and references (CEC, 1984; Gerber, Metivier, and Smith, 1987; Sikov, 1981, 1989; Sikov and Mahlum, 1969). These sources also contain several synoptic and research papers; only a few will be cited to identify additional aspects.

Perhaps most commonly, the reported data were derived from radioanalytic or autoradiographic determination of radioactivity and distribution in fetoplacental and maternal structures at the conclusion of acute or subchronic developmental toxicity and teratology studies (Fig. 1). Typically, radionuclides were administered to rodents at representative stages of timed pregnancies; intravenous injection was the most frequent route but oral, inhalation, parenteral, and percutaneous administrations have been used (Fig. 1 A). Most early reports are of experiments that were performed to determine intrauterine and postnatal effects; maternal and fetoplacental tissues were collected and analyzed at the termination of the study. More recent investigations have included determinations of transfer, fetoplacental content and distribution, as well as biological changes at intermediate times.

Fewer studies have been performed in which information was obtained during the course of more prolonged experiments, using external counting procedures to determine whole body or organ content. Perhaps the most useful types of data are those that were obtained through deliberate sequences of measurements of dynamic processes in

multiple structures; these provide the most accurate and convenient basis to calculate kinetic parameters (Fig. 2 A). Experiments of this type have included repeated measurements of maternal and fetal blood concentrations and periodic sampling of placental structures and tissues of the dam and conceptus at sequential times after exposure.

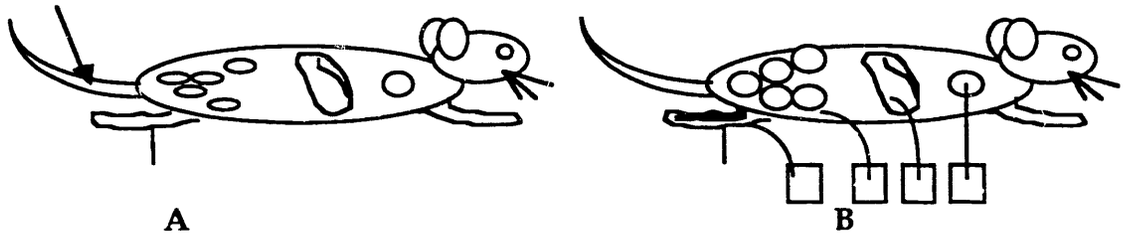

Figure 1. Diagrammatic representation of typical experimental approaches to study of radiotoxicity, placental transfer, and distribution. (A) Radionuclide is injected, or otherwise administered, at selected times of gestation. (B) Animals are sacrificed at one or more subsequent times to evaluate effects and obtain maternal and fetoplacental tissues for radioanalytic and/or autoradiograpic determination of radioactivity content and distribution.

Numerous studies of placental and fetal physiology have investigated transport processes and mechanisms and have examined factors that affect or modify placental transfer and fetoplacental distribution (Battaglia and Meschia, 1986). Many of such studies were not primarily directed toward determining radionuclide disposition per se, but they have provided metabolic and other types of information that has been useful for extending the conclusions of more directed dosimetric investigations. Experiments of these types cover a wide range, and include biochemical experiments using placental tissue homogenates. Substantial information has been derived from studies in whole-animal preparations where sequential blood samples were collected from indwelling catheters that were inserted into maternal and fetal blood vessels prior to exposure (Fig. 2 B). Such investigations have yielded empirical data of the type from which kinetics can be derived as well as much of our understanding of mechanism and the basic information that provides a basis for interpretation of less detailed studies (Battaglia and Meschia, 1986; Meznarich et al., 1989).

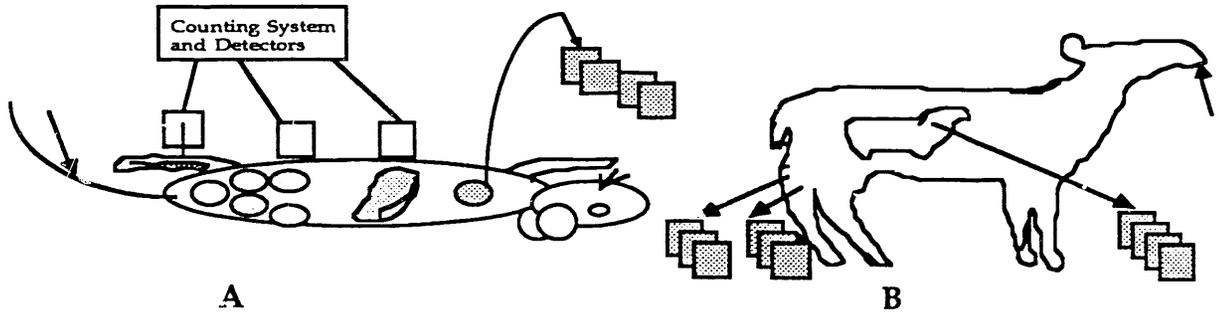

Figure 2. Diagrammatic representation of approaches to repeated measurement. (A) External counting of organ radioactivity and serial collections of maternal blood for radioanalysis. (B) Serial collection of maternal and fetal blood samples through indwelling cannulas during or after exposure.

Data sets with multiple uses for dosimetric purposes are also provided by studies in which placentas were used to determine the physiologic parameter known as clearance (Kelman and Walter, 1977). The technical approach, diagramed in Fig. 3, has been applied to isolated human placentas obtained at term, as well as studies that employ animal placentas in situ for a similar approach. The fetus is not included in the system in either situation, so that the measurements quantify placental transfer capacities and limitations for specific materials under selected conditions. Clearance (C) is calculated as the minute volume of maternal plasma that would contain an amount of radioactivity equal to that entering the perfusate and is expressed in ml/min. It is calculated as:

$$C = P/M \cdot R,$$

where the nuclide and tritium concentrations (Bq/ml) in perfusing solution and maternal blood are denoted as P and M, respectively. Perfusate flow rate (R), expressed in ml/min, is considered equivalent to umbilical flow rate (Kelman and Walter, 1977). Combining results from studies of animal and human placentas has been used to provide a basis to develop estimates of relative degree of transfer among materials while obtaining comparative results among species that allow for evaluation and validation of extrapolations.

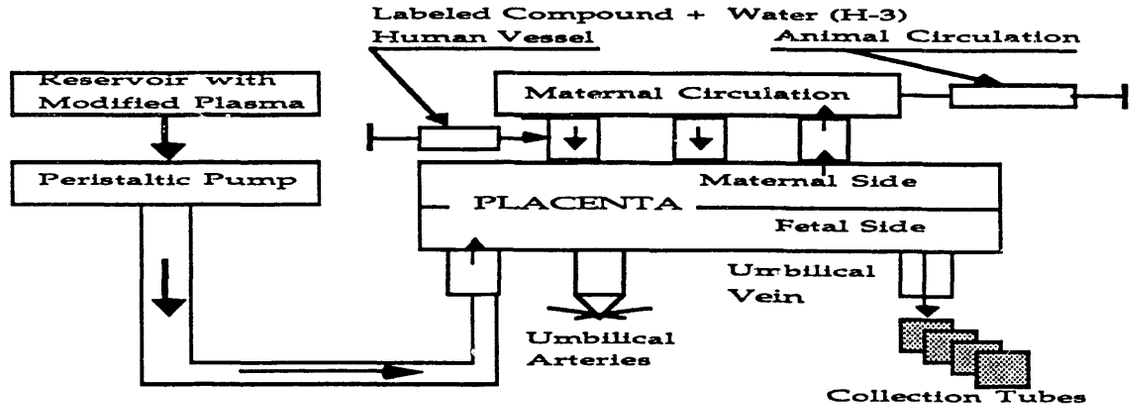

Figure. 3. Schematic diagram of perfusion system for measurement of clearance by the placenta

ESTIMATION OF RADIATION DOSES TO THE EMBRYO/FETUS

A few relevant generalities will be briefly noted here to provide a basis to understand concepts that follow; these concepts will be amplified by other papers in this volume. As may be inferred from the description of perfusion techniques, in order for materials to be transferred from the pregnant woman or animal to the fetal circulation they must first be present in her circulating blood. The two circulations are physically separated within the placenta, while their arrangement and the number of layers of cells or membranes that intervene between them are dependent on species. As has been considered in detail by Battaglia and Meschia (1986), the directional flow patterns vary among species and range between being predominantly concurrent and countercurrent

(Fig. 4), and the patterns have a pronounced influence on relative concentrations and exchange between maternal and fetal circulations.

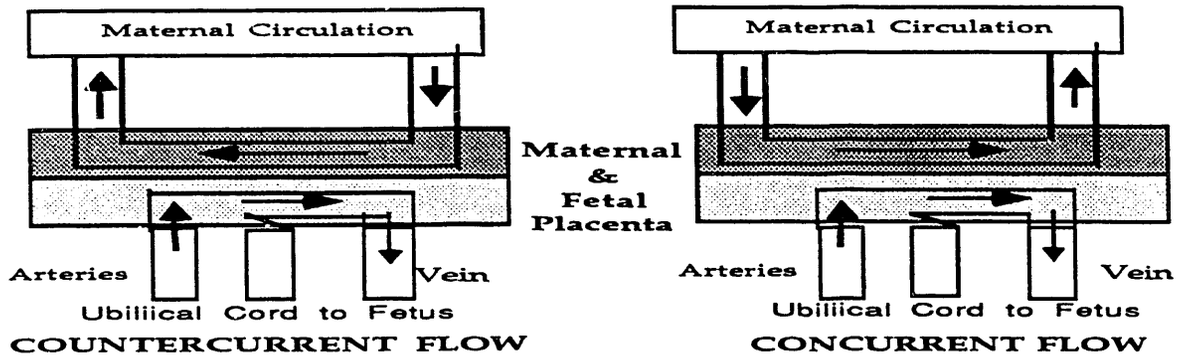

Figure 4. Diagrammatic representation of the maternal and fetal blood circulations to and within the placenta, showing relative location and arrangements of blood flows.

As detailed in the cited text, and others, diffusion is the most common process involved in placental transfer. Because diffusion is directly related to concentration differences, the magnitude of transfer may be limited by blood flow rates (Battaglia and Meschia, 1986). There are other important transfer processes such as active transport, pinocytosis, and leakage as exemplified by the role of Rh factor and the presence of fetal cells in the maternal circulation. Transfer of many materials involves diffusion in combination with another process. For example, many amino acids are actively transported but measurements have demonstrated that diffusion alone may be sufficient to provide for fetal requirements under physiological conditions (Kelman and Sikov, 1983)

Several approaches and methodologies have been developed for estimating radiation doses in the embryo/fetus through the use of relative radionuclide concentrations and activities. Fetal to maternal concentration ratios have been used as the basis for calculations and for predicting the resulting effects and their correlations with dose. The values used for quantitative estimates of radioactivity and effect may be based, in part, on data from human materials and by comparisons and extrapolations of animal data. These processes may involve assumptions and estimations that should be noted to provide an appreciation of the magnitude of the inherent uncertainties.

Scaling for Extrapolation

Independent of similarities and differences of transfer processes among species per se, there are other recurrent factors underlie considerations of extrapolation of dose and effect in the embryo/fetus (Hayton, 1989). A major confounding factor is that human pregnancies, as well as those of most other primates, tend to be monotocous, i.e., there is a single conceptus. In contrast, many of the animal species from which transfer data are obtained have multiple offspring, a situation known as polytocous. The uterus is

bicornuate in many of these species, with associated differences in the location and flow patterns of the uterine vasculature. It has never been completely resolved whether the basis for extrapolation should be the individual fetus or fetoplacental unit or if the total mass is the controlling factor. The few available data suggest that it will be found that some intermediate approach is the most appropriate.

Another important factor is that placental transfer and fetoplacental distribution and retention are stage dependent and that these conditions must be scaled to species characteristics. In particular, there is a general sequence of developmental stages that pertain across mammalian species, but the stages differ in their relative length and relationships to chronological times of gestation. The degree of maturity at birth differs, even among related species, so that expression of age relative to fraction of gestation does not completely resolve these difficulties. Nevertheless, appropriate consideration of relative maturities and times that major structures develop can help to provide a reasonable basis for comparisons and extrapolations.

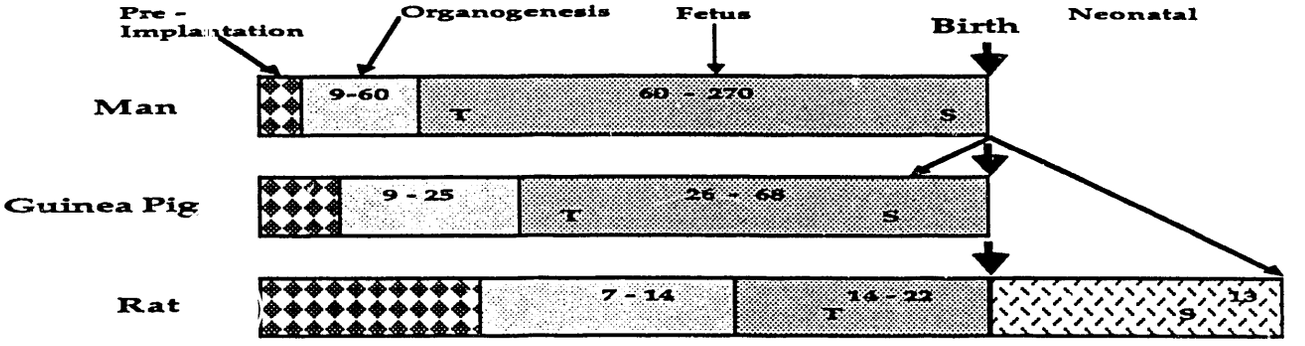

Figure 5. Comparison of length of major developmental periods relative to their overall gestational periods (days) in humans, guinea pigs, and rats. Maturities relative to the newborn human and the times of beginning functional development of the thyroid gland (T) and of major skeletal calcification (S) are indicated.

It is generally accepted that developmental stage at the time of irradiation is an important factor in determining effect and, to this end, Fig. 5 provides a simplified modification of a diagrammatic representation that was presented by UNSCEAR (1986). Absolute and relative lengths of the period of organogenesis, which is the stage that is most susceptible to teratogenic effects, varies among species and so influences the observed spectrum of malformations that are commonly detected. The fetal guinea pig attains an overall degree of development comparable to the newborn human at a time prior to birth, but the rat does not reach a stage generally comparable to the newborn human until during its second week of postnatal life. Moreover, the times of attaining equivalent measures of development of many major tissues, including thyroid function and skeletal ossification, do not have identical temporal relationships to these developmental landmarks. These differences are of concern relative to specific

comparisons and extrapolations; a satisfactory approach has not yet been developed to completely integrate this important consideration into analyses.

Approaches to Estimation

Irrespective of how the data are obtained and integrated, the most direct methods for estimating radiation dose are based on ratios of fetal-to-maternal concentration – total, organ, or in combination with deposition patterns. Although this approach may be considered naive in its simplest form, it often provides the same final result as is obtained by more complex analyses. Moreover, its direct reliance on empirical data helps to circumvent the need to make assumptions about unknown placental transfer processes for specific materials. This calculation benefits from providing the ability to directly estimate relative radiation doses, even though organ doses may not be routinely determined after radionuclide exposures of women in occupational or medical settings (Roedler, 87; Stather, 87; other papers in Gerber, Metivier, and Smith, 1987).

In situations where adequate information is available, empirical data of the same sorts (including those from many of the same studies) may be used for calculating or estimating transfer kinetics across the placenta. Knowledge of the normal physiology of some of these materials often may be used to supplement these calculations, and may make it possible to incorporate the effects of stage-dependant metabolic considerations as well as growth and body composition. These kinetic values can then be used in combination with compartmental models to calculate concentrations and total content of radioactivity. In their most rudimentary form, these models might consist of two compartments and an overall, or inferred, transfer coefficient.

More complex models range to those involving multiple compartments with an associated series of gestational-stage-related coefficients (Sikov and Kelman, 1989). Predictions of tissue or organ levels of exogenous agents, including radionuclides, have been determined through what has been termed as physiologically based modeling (Clewell and Anderson, 1989). Several estimates and assumptions are currently required for their use for adults in most practical situations, but current attempts are being made to extend this approach to include the placenta, conceptus, and fetal organs.

Appropriate variations of these several approaches, together with estimates of retention and dilution, are used to provide estimates of radioactivity in the conceptus and its component structures. These values are then used for calculation of radiation absorbed dose using traditional approaches or, more appropriately, through extension of the MIRD schema. This system incorporates contributions of energy from both self and maternal sources, sizes of the woman and embryo/fetus, and nuclide-specific half lives, emissions, and energies. This approach may be used in combination with evolving mathematical descriptions of the pregnant woman at characteristic stages, as described in

the paper by Watson in this volume. A similar approach has been proposed in which more general descriptions of dimensions, shape, and mass are used to implement the MIRD system (NRC, 1990).

Our current state must be characterized as one of relative ignorance. In this situation, it seems most appropriate to employ an eclectic approach, using all available combinations of data to estimate the content and localization of radioactivity from animal studies, whether expressed as concentrations or activities. This process is enhanced by adjustment of the resulting estimated values following comparisons with any parallel data from human materials.

GENERAL CONCEPTS AND APPROACHES

It was recognized that the availability of generalized placental transfer values would have broad utility for radionuclide dosimetry. This led us to attempt to derive such values and examine the reasonableness of correlations between these tentative values and other factors that may have common features. In the hope of obtaining results with acceptable levels of validity, these efforts have involved multiple iterations of two parallel approaches that are based on several types of empirical and derived composite parameters. One pathway has involved estimating generalized factors that could be used to represent fractional transfer across the placenta. Clearly, this approach was stimulated by the concepts underlying f_1 values for fractional absorption from the gastrointestinal (GI) tract or lung. These numerical estimates have been of general and well-recognized utility in several aspects related to radiation protection. We are tentatively denoting this factor by the Greek letter theta ,θ, because it phonetically starts with 'T' for transfer and does not seem to be widely used for signifying any dosimetric value. Attempts are being made to obtain values that would be generally applicable to all or most stages of gestation. Comparisons show a good general correlation between θ and the corresponding tabulated values of f_1 for the GI tract, and lung, but a substantial number of outlying points are evident (Fig. 6).

Attempts to determine reasons for exceptions, based on comparisons of actual values, indicated that correlations were closest for materials that are commonly involved in metabolic processes. The contrary pertained and there tended to be disagreement for substances that are not ordinarily involved in metabolism as well as many, but not all, materials that are generally considered as toxic, which has led to help direct the search (Hackett and Kelman, 1983). Possibilities include altered blood flow, the role of transport processes and proteins, and the impact of differences in chemical form of materials in the site of entry (gut or lung) and after they enter blood. Relationships between placental transfer kinetics and the development of specific target tissues are also implicated, and these factors are of concern relative to effects. On the other hand, a satisfactory explanation has not been determined for other discrepancies, including the marked difference between clearance values calculated from human and guinea pig placental perfusion measurements of cadmium transfer.

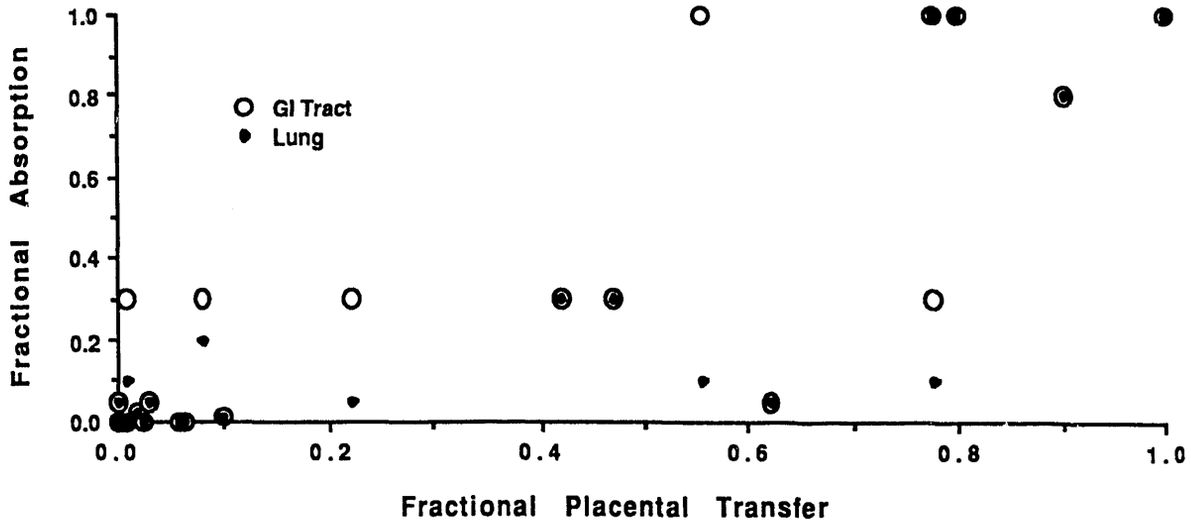

Figure 6. General correlation between corresponding values of fractional placental transfer, denoted θ, and values for fractional absorption, f_1, from the gastrointestinal tract or lung. Identical f_1 values from the two intake locations are indicated by overlapping symbols, but there are several instances of multiple occurences that are not identified.

It will facilitate amplifying on these potential explanations to first describe our other approach, which is directed toward physicochemical and metabolic correlates of transfer. This approach was stimulated by the accomplishments of early attempts by Sternberg (1968) in which he related transfer, deposition, and kinetics to these factors. In our initial attempts, we plotted measured values of fetal concentration (percent dose per gram fetal weight) for several heavy elements at 24 hours after intravenous injection in pregnant rats against a number of tabulated values for physicochemical parameters. The results yielded an encouraging pattern (Fig. 7) and led to extending the range of relationships. Estimating additional values for fractional transfer across the placenta provides a wider range of materials than our initial array of concentration values for these heavy elements. To determine comparability, these fractional transfer values were superimposed onto the concentration relationships and reasonable agreement between the two is evident (Fig. 7). We are using data in the literature to estimate additional values of placental transfer coefficients andfetal concentrations to compare biological behaviors with physicochemical characteristics. The ultimate hope is to establish a system that will facilitate interpretation or provide prediction concepts and techniques.

The underlying basis for the various sets of values that were examined for extent of correlation in the two approaches are not necessarily comparable in all details, and some may illustrate the multiple complications involved in extrapolation from animal to human. Placental transfer tends to be more bidirectional in character than gastrointestinal absorption. Other aspects of the processes seem to be more complex and affected by variations in biological conditions, but it is recognized that this may be only perception. Parenthetically, it might be noted that there are useful similarities, as well as important differences between approaches that are appropriate for intrauterine dosimetry of toxic chemicals as contrasted and for radionuclide dosimetry.

Table 1. Examples of materials for which tabulated values of fractional absorption into the transfer compartment (f_1) from the GI tract or the lung differ among themselves or from estimates (θ) of fractional placental transfer.

Material	f_1 - GI Tract	f_1 - Lung	θ – Placenta
Americium	0.001	0.0005	0.006
Cadmium	0.05	0.05	0.6 Guinea Pig
Cadmium	0.05	0.05	0.06 Human
Cerium	0.0003	0.0003	0.06
Cobalt	0.3	0.05	0.2
Einsteinium	0.001	0.0004	0.02
Mercury (Inorganic)	0.02	0.02	0.02
Mercury (Methyl)	1.0	1.0	0.8
Neptunium	0.001	0.01	0.06
Plutonium	0.001	0.0001	0.063
Polonium	0.3	0.1	0.01
Thorium	0.001	0.0004	≤ 0.001
Uranium	0.05	0.05	0.03
Vanadium	0.01	0.01	0.1

Analyses are often facilitated by the knowledge and ability to distinguish between transfer, equilibrium, and steady state conditions. The situation involved in absorption of relatively insoluble or poorly absorbed materials is relatively simple, but considerations may differ for the placenta and GI tract or lung, including extent of involvement of different transport proteins and their roles. To illustrate, consider a material that is a mixture of (physic)ochemical forms such that 20 % of the total in the gut or lung is in absorbable form and enters blood within hours after intake; this affects the composition of the mixture that is available for placental transfer (Fig. 8).

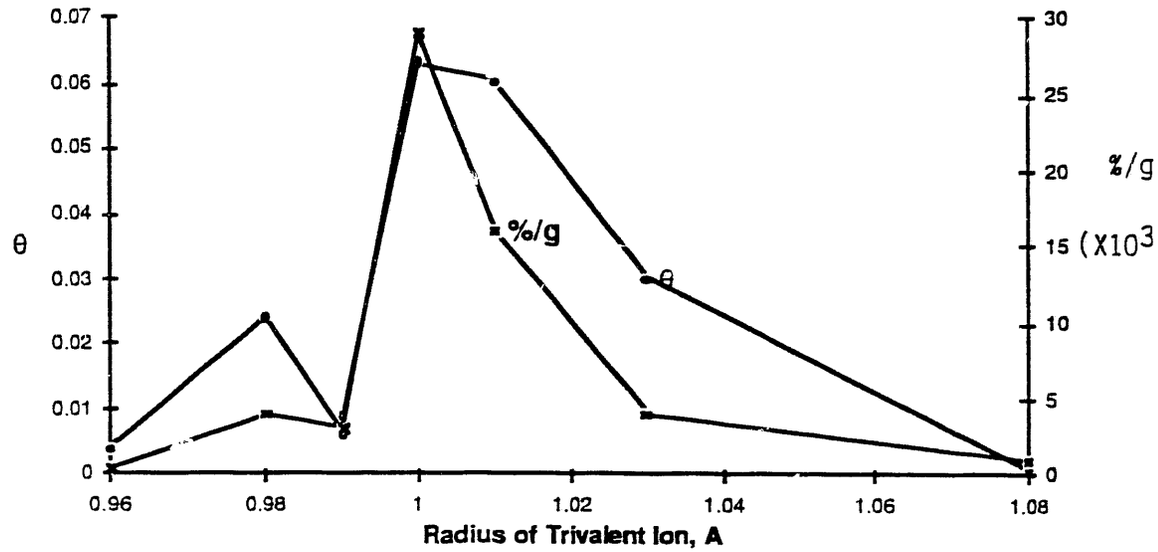

Figure 7. Similarities between the relationships of fetal concentrations (% dose/g) at 24 hr after intravenous injection of rats with transuranic elements and the corresponding placental transfer coefficients (θ) with the radius of the trivalent ion.

A greater fraction of the materials that is in the blood may expected to be in this absorbable form than it was in gut or lung. In this case, calculations of placental transfer are based on the absorbed fraction, which may be involved with transport protein or chelate. Accordingly, binding and transport processes, metabolic specificities, and concentration gradients must be examined for understanding both similarities and differences.

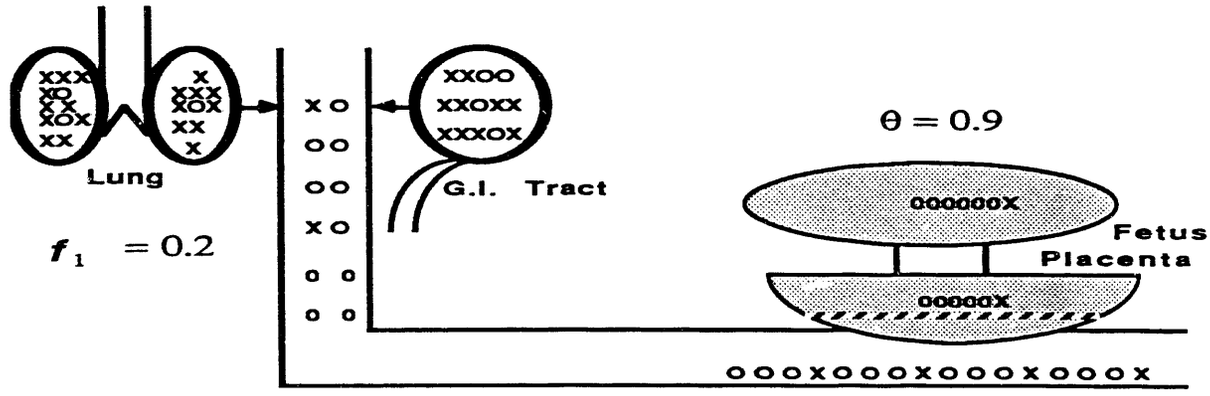

Figure 8. Diagrammatic representation of an explanation for differences between coefficients for fractional gastrointestinal or pulmonary absorption and placental transfer. As described in the text, this is based on greater fractions of readily absorbable (o) than poorly absorbed material (x) in blood than originally present in gut or lung.

This line of investigation raises additional questions relative to radiation doses to fetoplacental structures. The answers tend to be relatively straightforward when considering the identity of specific target tissues for prenatal or early postnatal effects. The targets are more difficult to identify when addressing delayed lesions, e.g., carcinogenesis, where the structure in which the tumor develops or is detected may not exist at the time of exposure. From a long-range standpoint, this subject assumes important mechanistic implications, but also illustrates a need for further development of concepts and for more sophisticated dosimetry.

Biological effects that result from the insult may alter the temporal relationships between placental transfer kinetics and concentrations. The transfer patterns often further implicate the role played by the development of target tissues. Formal consideration of these intuitively obvious relationships will be deferred for presentation in conjunction with examination of models. In addition to the influence of such progressive changes in tissue mass and differentiation, studies with elements such as radiozinc have illustrated that developmentally related differences in tissue binding and the availability of competing stable elements may have a marked effect on effective residence times (Erdman et al., 1969). Nevertheless, these factor should be recognized while reading the following descriptions of the database material that will form the basis for formally examining these interactions.

ILLUSTRATIONS OF APPROACH

The scenario for illustrating factors in placental transfer patterns, approaches to predicting radiation dose and effect, and modeling their implications ideally would be based on materials with relatively uncomplicated transfer and availability of adequate numerical databases. A reasonable knowledge of their species-related characteristics in anatomical and physiological development and corresponding estimates of stage-dependent kinetics should be available. A suitable spectrum for such an illustration is provided by consideration of three elements - cesium, strontium, and iodine. Extensive data concerning their comparative behavior in humans and in experimental animals are available in the compendia cited above, especially reviews and analyses in Gerber et al. (1987), while long-term effects, especially carcinogenesis, have been reviewed by Sikov (1981,1989); accordingly, only limited citations will be provided. Their radioisotopes are absorbed from the gastrointestinal tract, can cross the placenta and they are close homologs of natural metabolites. At the same time, there are differences among them in extent of dependence of transfer and fetoplacental distribution on stage of development, which will form the basis for demonstrating the role of progressive development of preferential deposition sites. The temporal and stage relationships of the development of these target tissues differ among species and give rise to reported differences and models describing their distribution patterns.

Cesium is chemically similar to potassium and, in its most common or ionic forms, it displays much the same metabolic behaviors in biological tissues and fluids. The generalized distribution of cesium is the same in adult women as in animals and initial concentrations are essentially identical among comparable soft tissues of the dam and conceptus. Some reports state that pregnancy does not have an appreciable effect on its absorption, distribution, or excretion, although it is more commonly accepted that turnover rates are increased in pregnant women. (NCRP, 1977). There are theoretical reasons to expect that concentration in the embryo/fetus might be greater than the dam, but a difference has not been reliably detectable by empirical measurement.

Except for metabolic alterations associated with pregnancy, transfer patterns seem to be essentially independent of species and stage of gestation, including early stages, and there are not major sites of preferential localization. Thus, the resulting radiation doses tend to be uniform so that the patterns of effect are similar to those produced by external irradiation when due allowance is made for protraction of exposure across several developmental stages.

Strontium is an alkaline earth, with a metabolic behavior that is similar to that of calcium in most respects. There are quantitative differences in the net transfer of the two elements between metabolic compartments, however, which is usually expressed quantitatively in terms of OR (observed ratio) values between biological compartments. These ratios have been the subject of measurement and publication throughout the

years. Calcium is an important component of bone and it serves as a membrane component and intracellular messenger. It is not clear to what extent these secondary functions may be assumed by strontium. However, they do not seem to represent a major fraction of body content, and any dependence on time of postnatal or prenatal life or stage of gestation probably would not be quantitatively important.

Pregnancy is known to affect calcium metabolism, and presumably the strontium metabolism of a woman's bone changes throughout pregnancy. The embryo does not contain actual bone during the earlier stages of gestation, and skeletal elements do not begin to assume definitive shape or form until during the fetal period. The development and calcification of bone matrix become progressively more important through later gestation and postnatal life, so that the rate and extent of deposition increase as the human fetus approaches term. In turn, these factors influence total radioactivity in blood and in the conceptus, concentration throughout the skeleton, and the dynamics of placental transfer. These considerations, which will be discussed later, are especially pertinent in extrapolations because prenatal bone maturation is substantially greater in the human fetus than in some common laboratory rodent species, such as the mouse and rat, in which calcification occurs predominantly in the postnatal period. These stage-dependent species developmental differences and relative masses of skeletal elements interact to introduce complications into analysis, although they are amenable to interpretation.

Perinatal exposure of experimental animals to radiostrontium can produce deleterious effects on intrauterine development as well as changes that are not detectable until later in life. Administration of high levels of some strontium isotopes to rodents during organogenesis are embryotoxic and teratogenic. Dosimetry varies with physical characteristics of the specific isotope, but there is reasonable compatibility between these effects and those associated with external photon exposure after allowing for differences in partition of dose among tissues, as well as dose rates and protraction. Specific sites for localization of the element may have marked influences on the effects it produces after the target tissues have developed. For example, incorporation of radiostrontium, and of radiophosphorus to implicate the metabolic parallel, has been shown to result in malformations of the skeletal system. It has been reported that exposure of pregnant rodents to these nuclides (Sr-90 or P-32) results in an increased incidence of bone tumors in the offspring. In addition to such relatively straightforward relationships, prenatal Sr-90 pituitary tumors that presumably result from high radiation doses from strontium that localized in the sella turcica (Schmahl and Kollmer, 1981).

Iodine has several radioactive isotopes, with a range of half lives and decay schemes. There are numerous routes through which members of the population may receive exposure. The circumstances involving a potential for exposure during pregnancy range from inadvertent administration for medical procedures, intakes of materials during their preparation or administration as radiopharmaceuticals, and depositions via accidental releases or contamination in the general environment. Availability is

usually as iodides, which are readily absorbed into blood from the GI tract, lung, and other sites; most iodine in the body is localized to the thyroid gland. Prenatally, the thyroid must undergo substantial morphologic and physiologic development before it has a capacity to trap and metabolize iodine, but as was noted, it does not develop until well into the fetal period, nominally 17 days in the rat and 13 weeks in the human fetus. The relative degree of fetal and maternal function is also related to species, maturity at birth, and stage of gestation, but both are affected by stable iodine content of the diet. Consequently, descriptions of placental transfer, fetal deposition, and other details of iodine metabolism are strongly influenced by stage- and species-dependent differences in the morphologic and functional development of the thyroid.

Under pituitary control, inorganic iodine is rapidly removed from circulating blood by thyroid follicular cells and incorporated into molecules of thyroid hormone. These are stored as colloid in the follicular lumens, gradually released into blood, and so is in the circulation while being transported to tissues. Inorganic iodine in the blood, and iodine-containing hormone to a lesser extent, readily crosses the placenta and is assessable to the embryo or fetus. When factors such as gestational stage are considered, animal findings are remarkably consistent with most human data and the ratio of concentration in the human fetal to maternal thyroid is often accepted to being greatest toward term. Depending on half lives of the radioisotopes, and whether exposure is chronic or acute, the fetal thyroid concentration and radiation doses in the last months of pregnancy has been estimated to be as much as 3- to 9-fold greater than that in the adult woman (Book, 1969). A similar relationship pertains in laboratory animals although maximum concentrations may not occur until the neonatal period in some species.

This situation also illustrates the influence that localization has on radiation dose and resulting effects after the specific target tissues have developed. As examples, animal experiments have demonstrated acute, subacute, and long-term changes in morphology and physiology of the rodent thyroid after late prenatal or neonatal exposure. There are results suggesting that perinatal photon irradiation, but especially radioiodine exposure, may increase thyroid tumor development in humans. Comparable relationships have been more clearly documented in perinatal rodents (Walinder and Ronnback, 1984).

The foregoing are among several examples that illustrate that, even though physical interactions with tissue are the same, there are quantitative differences in the apparent responsiveness of exposure from internal radionuclides relative to acute exposures from external photon beams (Sikov, 1981. The underlying factors include inhomogeneities of tissue radiation doses, differing effectiveness of some particulate radiations, and protraction effects that may lead to exposures extending over several stages of gestation. Radiation doses to perinatal animals and to their individual tissues relative to administered activity are often less than the corresponding doses to their dams or to older animals. As a result of these differences, perinatal animals may appear to be less sensitive to induction of late effects than are adults when responses are compared on the basis of amount of radionuclide administered.

When responses are expressed relative to radiation absorbed doses, however, perinatal animals are often found to be more susceptible than adults to tumorigenesis by exposure to internal radionuclides, as well as to other long-term consequences. As a further broad generalization, exposure to many radionuclides may involve age-related differences in predominant type of tumor and/or in the sites at which tumors develop (Sikov, 1989). This difference and the existence of nuclide-specific organs or tissues of tumor development partially involve interactions of dosimetric and developmental factors. As we have previously suggested, involvement of oncodevelopmental genes and other aspects of the molecular mileau remain as relevant, but incompletely explored, possibilities.

MODELING PLACENTAL TRANSFER AND RADIONUCLIDE DISTRIBUTION

As was indicated in the foregoing sections, many of the reported differences in fetoplacental radionuclide disposition among species can be reconciled on the basis of comparative developmental chronologies. This implicates differing temporal relationships for the development of target tissues for preferential deposition, which together with histogenesis, are involved in placental transfer kinetics and in the generation of models for evaluation and prediction. These models and utilization of the resulting extrapolations must be based on an understanding of the comparative aspects of placental transfer. Other factors such as distribution and retention must be considered and it may be necessary to include the modifications associated with dose-effect patterns in the embryo/fetus The morphological basis may differ from the physiological, and their relationships will depend on stage of gestation.

Thus, all information must be scaled to the species-specific developmental- stage and gestational-time relationships and maturities at birth that were presented above. As was indicated, many reported differences in fetoplacental disposition among species can be reconciled on the basis of the comparative chronology of developmental and structural factors. This implicates a different set of relationships for the development of target tissues. especially those that become preferential sites of deposition. Histogenic differences that affect localization will involve placental transfer kinetics and affect the construction of the models for evaluation.

Compartmental Models

The two compartment closed model is the simplest form. A third compartment can be introduced between maternal and fetal compartments, to represent placenta, but it will be essentially transparent in many situations. Some models, such as those used by the ICRP, involve two subcompartments on either side (Fig. 9). These general models may be made more biologically relevant and conceptually useful by formally dividing the compartments on both sides of the placenta into transfer (blood) and tissue compartments, with an undefined degree of exchangeability between them (Fig. 10).

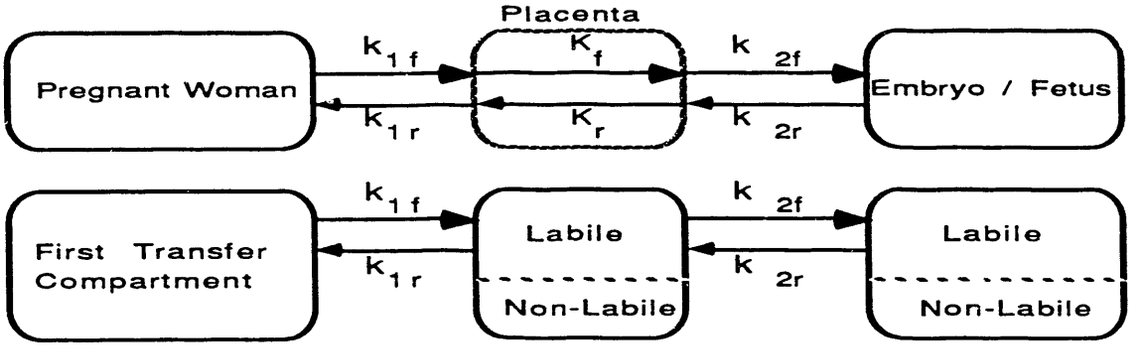

Figure 9. The upper diagram shows the generalized two compartment model with potentially transparent placental compartment interposed. The equivalent model, as used by the ICRP, is shown below.

Even in the absence of quantitative values, qualitative considerations intuitively suggest that greater transfer into fetal tissue would reduce fetal blood concentration and, in the absence of other alterations in the system, would be expected to increase rate and amount of transfer to the fetus.

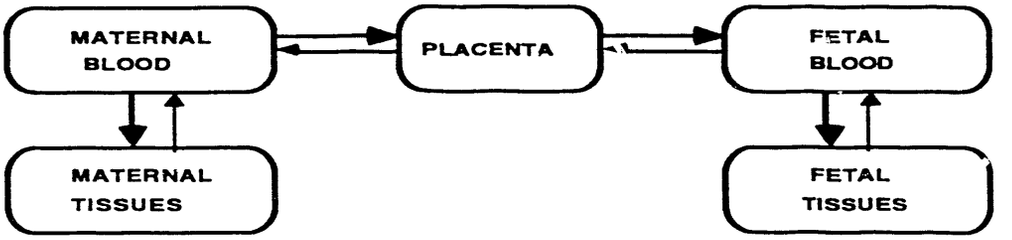

Figure 10. Expanded version of the model shown in Fig. 9; compartments have been formally divided to form a model with five compartments

Similarities and dissimilarities between prenatal development, placental structure and function, and radiation responses of the laboratory animal and the human conceptus must be included in derivation of models. There is a loss of radioactivity from maternal blood to her other compartments, but the same finite fractional transfer value to the fetus or fetal circulation may pertain through all increments of time. As was described above, approximations of this fraction are provided by the comparable values relating to clearance. Predictions of tissue or organ levels of exogenous agents, including radionuclides, are being determined from so-called physiologically based or biologically motivated models (Clewell and Anderson, 1989). These represent the opposite end of the spectrum of sophistication and provide a basis for examining relationships and alternative blood flow pathways. As was mentioned above, this approach is desirable as an ultimate goal but estimated values and assumptions are currently required for its use in most practical situations, which could affect conclusions. Efforts have been made to introduce fetoplacental components and their blood flows into this model, and formalized efforts at expansions currently are being undertaken.

More complex models, involving multiple compartments with associated series of stage-related coefficients, represent other possible approaches. Numerous organs can be included in the model, they can grouped into organ systems, and specific target organs can be introduced into the compartmental models. In some regards, these then begin to resemble physiologically based models, while representing closed models as open systems would provide a further basis for generalizations (Fig. 11).

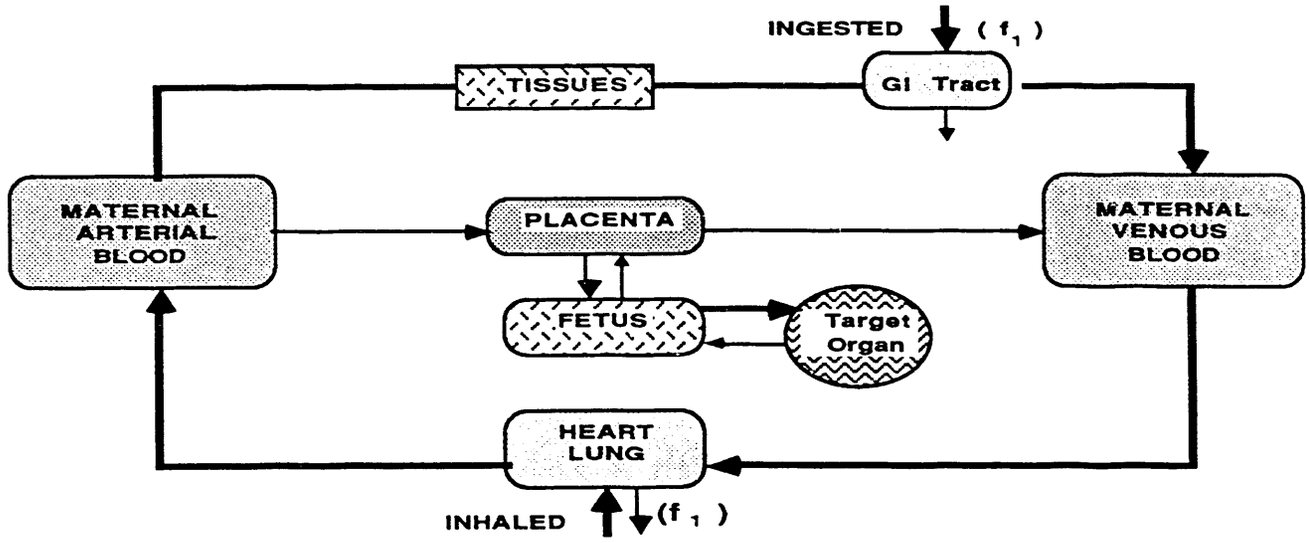

Figure 11. Open compartmental model expanded from closed model of Fig. 10, to show alternative blood circulations and provide for consideration of role of fetal target organ.

In simplified, nonmathematical form, Fick's law may be stated as:

Net Transfer = Diffusion Coefficient · Area/Thickness · Concentration Difference

Examination of Fig. 11 suggests that deposition of increasing fractional amounts of radioactivity in the target organ would lead to a decreased relative concentration in the remainder of the fetus, including its blood. In turn, this would lead to an increased concentration gradient relative to the maternal blood in the placenta. Because rate of transfer is related to this concentration difference, increased deposition in a progressively developing target organ or system should result in increased fetal content, even when transfer occurs only by diffusion.

We have published a comparison that illustrates the relationships between clearance and other expressions (Sikov and Kelman, 1989). Placental clearance values and the 5-compartment model (Fig. 10) were used to predict fetal concentrations at 24 hr after intravenous injection in near-term guinea pigs. This calculation used clearance values that were measured independently for Pu-239 and for Am-241, and assumed that all placental transfer was to the fetus, even though it was not in the perfusion system when clearance was measured. Kinetic coefficients of removal rate from maternal blood were estimated from data published by others, and were combined with measured values for

rate of loss from the maternal blood. Actual values of fetal radioactivity had been measured during an independent experiment with these nuclides at the same stages of gestation. It was found that there was remarkably good agreement between predicted and measured values for the two nuclides. The open compartmental model (Fig. 11) may allow calculation of clearance values or kinetic coefficients from a series of measurements in experimental systems such as illustrated in Fig. 2B, which also provide relative concentrations in the fetus and dam and their tissues.

Dosimetric Implications

Dosimetric consequences differ relative to the intended use of radiation doses calculated from activity levels. Approaches range between radiation absorbed doses rates and doses to the embryo/fetus, on one hand, and dose rates and dose to target tissues on the other. Compliance with current regulations and dose limits requires different dosimetric approaches than might be appropriate for other use for different purposes with various isotopes of these elements. As was discussed above, most of the fetal strontium content is in bone, but current dose limits in the United States and many other countries are stated in terms of the embryo/fetus. Consequently, the conceptus would be the appropriate structure to use for this purpose, with calculation of self-dose based on its activity and relevant S-values. In the other sense, however, it would be more appropriate for specific purposes to calculate average concentration to skeleton or skeletal elements from determinations of their activity or concentration. Examination of the situation with Sr-90 provides a basis to compare these considerations as they relate to dosimetry and interpretation. The above discussion and the earlier evaluations described by Roedler (1987) are both based on analyses of the same general literature, and lead to generally compatible estimates of concentration ratios, dose rates, and dose.

From reports on biological materials from individuals exposed via fallout, Roedler calculated that the fetus to adult concentration ratios were in the range of 0.5 - 1 for wet bone, which increased to 2 - 4 when based on specific activity relative to calcium. As was indicated, the distinction between average bone dose and average fetal dose could lead to major differences in the numerical value for the conceptus to maternal ratio. Another major consideration is that Roedler's analyses were expressed as 'dose commitment' so that calculations extended into the period beyond the time of birth. The consequences of this difference in approach illustrate the unresolved implications associated with expressions of lifetime doses and those that state the dose to the embryo/fetus during specific gestation periods.

This dichotomy between recognized biological realities and pragmatic needs is even more prominently illustrated by the radioiodines, as was discussed in preceding sections. As an accommodation to regulatory requirements, it is necessary to estimate activity and calculate doses to the total embryo and fetus. This approach is the most correct for the embryo - the stage for which the greatest concern for certain types of

deleterious effects has been expressed. It is clear, however, that it may be inappropriate for use during the fetal period, when the primary dose from iodine radioisotopes will be to the thyroid gland, which may display significant effects. Because most current dose limits are restricted to the embryo/fetus, potential future modifications may suggest inclusion of calculated dose to the fetal thyroid.

Limitations and Needs

The explicit and implicit limitations inherent in the forgoing considerations identify needs that must be met for full utilization of approaches. Diversities among animal data relate to experimental differences and expression of results. Stage affects placental structure and function, growth, and body composition; the metabolism of both the pregnant animal and the embryo/fetus is influenced by dietary and general environmental factors. The comparable relations for the human and human data are not monolithic but display similar progressions when they are expressed relative to stage. Thus, it will not be possible to define a"universal" value to would express embryo/fetal concentration or activity throughout gestation for most, if not all, elements and their isotopes. As a consequence, a single fetal to maternal concentration ratio may not be determinable, and probably does not exist except as a broad approximation, but a series of stage-dependent values might be obtained by conservative extrapolation. For most elements and their isotopes, it appears that the error associated with relative dose rates may be less than with doses. Irrespective of approach, therefore, it seems prudent to accept that dosimetric statements must be restricted to specific materials and stages.

A realization is implicit that we should specify the structure to which dose is calculated and the purpose for which it is determined. With present information, this usually might be restricted to the embryo/fetus for protection relative to induction of congenital effects. These limitations serve to illustrate a need to further develop concepts and approaches that allow for doses and effects to specific structures in which localization occurs, understanding to allow combining prenatal and postnatal doses, and providing for progressive changes in constituent structures and their sensitivities. Other needs are determination of appropriate values that would consider protraction of exposure over multiple developmental stages, beyond DREF, and ascertaining that values for relative effectiveness of particulate radiations are the same for the conceptus as for the adult.

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