RECEIVED BY DTIE OCT 9 1969

COO-1339-24

MASTER

Animal Metabolic Studies of Strontium and Calcium with Specific

Reference to Fallout Radionuclides

Second Comprehensive Report

for the Period August 16, 1966 - August 15, 1969

Submitted by the

Department of Animal Science

College of Agriculture

and the

Department of Veterinary Physiology and Pharmacology

College of Veterinary Medicine

University of Illinois

Urbana, Illinois 61801

Contract No. AT (11-1)-1339

Supported by: Division of Biology and Medicine

United States Atomic Energy Commission

Washington, D. C. 20545

LEGAL NOTICE

This report was prepared as an account of Government sponsored work. Neither the United States, nor the Commission, nor any person acting on behalf of the Commission:
A. Makes any warranty or representation, expressed or implied, with respect to the accuracy, completeness, or usefulness of the information contained in this report, or that the use of any information, apparatus, method, or process disclosed in this report may not infringe privately owned rights; or
B. Assumes any liabilities with respect to the use of, or for damages resulting from the use of any information, apparatus, method, or process disclosed in this report.
As used in the above, "person acting on behalf of the Commission" includes any employee or contractor of the Commission, or employee of such contractor, to the extent that such employee or contractor of the Commission, or employee of such contractor prepares, disseminates, or provides access to, any information pursuant to his employment or contract with the Commission, or his employment with such contractor.

RESTRICTION OF THIS DOCUMENT IS UNLIMITED

DISCLAIMER

This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency Thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.

DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.

TABLE OF CONTENTS

	<u>Page</u>
1. MAJOR RESEARCH ACCOMPLISHMENTS	1
2. PLANS FOR CONTINUATION OF PRESENT OBJECTIVES AND NEW OBJECTIVES PROPOSED ON THE BASIS OF PAST RESULTS	8
3. GRADUATE STUDENTS AND POST-DOCTORATES TRAINED UNDER PROJECT	9
4. BIBLIOGRAPHY OF PUBLICATIONS	10
5. COMMENT ON STATE OF KNOWLEDGE IN THIS RESEARCH AREA AND NEED FOR FUTURE INVESTIGATION	16
6. FEDERAL SUPPORT FOR OVER-ALL RESEARCH PROGRAM	18

1. MAJOR RESEARCH ACCOMPLISHMENTS

A brief synopsis of the originally stated objectives for the period December 1, 1966 to November 30, 1969 is presented, so that our research accomplishments may be considered with respect to them. The objectives were:

A. Calcium-47 Kinetic studies in goats

1. To evaluate methods for studying Ca-47 Kinetics
2. To determine the parameters of the readily exchangeable Ca pool (RECaP) in normal non-lactating goats
3. To determine the parameters as a function of
 - a. dietary Ca and phosphorus (P) intake
 - b. dietary Ca:P ratio
 - c. carbohydrate content of diet
 - d. lactation
 - e. pregnancy
 - f. thyroid and parathyroid status
4. To determine the effects of these same phenomena on the parameters of the RECaP in cattle and other species

B. Retention of Strontium-85 in swine

1. To determine the retention of Sr-85 in swine as a function of age, two levels of dietary Ca and P intake, and breed (standard vs. miniature)
2. To measure urinary hydroxyproline excretion in swine as a function of age, two levels of dietary Ca and P intake, and breed (standard vs. miniature)

3. To relate the patterns of radiostrontium removal and hydroxyproline excretion in swine to patterns in man.
4. To examine the effects of hypophysectomy, thyroidectomy and parathyroidectomy followed by hormonal replacement on the retention of Sr-85 in swine and dogs.
5. To investigate the influence of specific hormones on the incorporation of Sr-85 into bone (crystal) in swine and dogs and to extrapolate these findings to man.

To a large measure most of these objectives were completed, particularly for Part A, "Calcium-47 Kinetic Studies in Goats." The method used for measuring the size (E), half-life ($T_{1/2}$) and transfer rate (TR) of the RECaP is repeated in the current progress report (COO-1339-23) and it is published as part of the proceedings, entitled Parturient Hypocalcemia which resulted from The Conference on Parturient Paresis in Dairy Animals. Many data on the parameters of E, $T_{1/2}$, and TR of the RECaP were obtained from non-lactating, non-pregnant goats on normal rations and, as expected, an age-dependence was found. Younger animals had larger E, shorter $T_{1/2}$, and larger TR values. Similar results were obtained from cattle. These and other data on pregnant and lactating goats have been published as abstracts and are in manuscript or have been submitted for publication (COO-1339-18, 26, 35 and 36). During the course of gestation E enlarges slightly and $T_{1/2}$ decreases in somewhat reciprocal fashion until parturition, at which time no measurements have been obtained. In lactation larger E and shorter $T_{1/2}$ is maintained than during periods of non-lactation in the same animal serving as its own control. Further work remains, in particular the changes in calcium metabolism just before, during, and just after parturition.

Studies on the influence of dietary intake of Ca and P on the RECaP of goats are still in progress. Some of this work has been published (COO-1339-28) or is in the form of a manuscript (COO-1339-30). There is no question that the levels of dietary Ca and P have an influence on the RECaP in non-lactating, non-pregnant goats. Although the magnitude of the dietary effect on TR was not great, significant differences in TR from the goats on the control ration were detected. What was surprising was that both low Ca and high Ca rations produced a decrease in the TR of the RECaP. The role of dietary P per se on the blood Ca and P values in goats on the two experimental rations is being further investigated in a small sample of animals. In addition further dietary studies of a similar design are being conducted on a larger group of goats over a short experimental period to determine any histopathological changes in bone, kidney, parathyroid and other tissues as well as to examine the kinetic parameters of the RECaP and to sample blood for Ca and Pi determinations. A big question still remains as to the influence of parathyroid hormone, whether direct or indirect, on the RECaP of animals on different intakes of Ca and P. Future experiments are planned to examine the role of PTH.

In a study designed to test whether insulin had an effect on Ca and P metabolism several goats were alloxanized and blood Ca and Pi concentrations as well as those of other parameters were measured with time. No changes were observed in Ca concentration whereas Pi concentration was elevated for as long as 40 days post-alloxan treatment (See COO-1339-39).

No work has been done to determine what effect the carbohydrate content of the diet may have on the parameters of the RECaP and on calcium

homeostasis in general. Although energy intake is an important consideration, our experiments have not examined and, because of the more pressing urgency of other aspects of the general problem, probably will not examine the interplay of carbohydrate intake and calcium metabolism.

No experiments have been conducted the role of thyroid hormone per se in calcium metabolism for the same reason. Thyroid hormone is known to stimulate bone resorption and it has been used only in replacement therapy for two thyroparathyroidectomized goats whose RECaP was examined both pre- and post-thyroparathyroidectomy. Thus, the effect of thyroid hormone itself has not been explored. However, much more work remains to be conducted on thyroparathyroidectomized animals receiving replacement therapy to determine changes occurring in the RECaP of goats on different dietary Ca and P intakes and also of goats during pregnancy and lactation.

Whether or not the goat is a good model for the cow in the study of parturient paresis remains to be seen. However, our findings from preliminary experiments using dairy cows indicates that the goat and cow are very similar with respect to the decrease in E and increase in $T_{\frac{1}{2}}$ of the RECaP as a function of age. In addition, values of E in the mature goat (about 4 grams) and mature cow (about 40 grams) are comparable when it is considered that the body weight of the cow is about 10 times greater than the goat. For further comparison the size of the RECaP in an adult man of body weight roughly equivalent to that of a mature goat is estimated to be about 5 grams. From a comparative point of view, then, our data indicate that our analytical method is sufficiently sensitive to detect meaningful differences in the RECaP due to various perturbations. Experiments using pregnant Jersey cows that are designed to test the

effects of pregnancy, parturition and lactation on the parameters of the RECaP are in progress.

The objectives listed under Part B, "Retention of Strontium-85 in Swine," are only partially completed, but an estimated one to one and a half more years are required to complete most of those objectives before this part of the project would profitably be phased out. The necessary information should be obtained by then. The reasoning behind this statement is that, unlike in dogs, there appears to be no single period of maximal Sr-85 retention as measured 200 days post-injection (P.I.) in pigs injected at one time only between birth and six months of age. Both Decker, Kaspar and Norris (Rad. Research 23: 475, 1964) and Anderson and Comar (Rad. Research 34:153, 1968) found that beagles retain Sr-85 maximally when injected at 5 or 6 months of age, whereas in the swine, growing at a nearly linear rate between birth and six months, retention as measured 200 days P.I. remains at a similar value, about 28% (See C00-1339-37). This value is not significantly changed by a dietary Ca and P intake (1.2%:0.8%) that is higher than recommended by the National Research Council (0.8%:0.6%). Although all of our standard pig litters have not been of the same breed, there appears to be no difference in retention of standard pigs injected at the same age. However, miniature swine of our limited sampling, perhaps because of a difference in growth rate, retain Sr-85 differently from standard swine. Many more miniature swine need to be examined before any meaningful comparisons can be drawn.

Urinary hydroxyproline measurements have been made in a number of different swine from birth to one year of age, using during the first month a specially designed collection apparatus (C00-1339-12). Although

wide daily fluctuations in output and individual variations exist, an overall age-related pattern emerges, which is somewhat similar to man when comparison is made on an output per body weight basis. In addition, exercise was shown to have a very definite inhibiting effect on hydroxyproline excretion as well as a small but significant enhancing effect on Sr-85 retention. Either an inhibition of bone resorption or stimulation of bone accretion could explain these findings, but from an examination of other reports in the literature on collagen metabolism (see J. F. Woessner, Jr. in Collagen Metabolism, Volume 2B, Academic Press, 1968) the former mechanism would appear more likely. For more detailed accounts of these experiments see documents C00-1339-19, -20 and -38. Comparison of urinary hydroxyproline excretion and Sr-85 removed from the skeleton of young growing swine as a function of age has been made and both were found to correlate with growth rate (also see C00-1339-38).

Eight swine at six months of age were injected with a 15 μ Ci dose of Sr-85 to determine distribution and specific activity (Sr-85/gm Ca) of the radionuclide in selected bones of the skeleton at times one day to six months P.I. The expected decline in specific activity as a function of time was found, but also uncovered was the different way in which the long bones, vertebrae and skull lay down bone Ca and retain Sr-85. A hypothesis of the way in which these three different types of bone turn over their mineral relative to one another is discussed (see C00-1339-32). A similar study of two pigs injected near birth revealed interesting changes in skeletal turnover of different bones (see C00-1339-17).

Whole body retention of orally administered Sr-85 in swine given sodium alginate or barium and sodium sulfates was no different 10 days post-administration from control animals, but earlier retention was significantly depressed by the sulfates. Alginate at the high concentrations used appeared to have little effect on retention, perhaps because of its low palatability for swine (see C00-1339-21).

Experiments to examine the effects of hypophysectomy using yttrium-90 on Sr-85 retention in swine have been delayed for the past year because the University of Illinois nuclear reactor was not in operation. However, the experiments are about to be renewed and hypophysectomies should be completed by the end of the current contract year. The effects of thyroidectomy and parathyroidectomy on Sr-85 retention in swine have not been started due to lack of adequate facilities. Furthermore, in a strong effort not to let the project become too diffuse, this work will not be proposed for future investigations.

Future research will be pointed toward a thorough investigation of calcium metabolism in cattle. The goat will be used as a model for the cow when advisable and small laboratory animals will be employed when short preliminary experiments warrant large numbers of animals, such as rat (C00-1339-33, 42) and dog (C00-1339-34) experiments we have conducted recently. Thus, Sr-85 retention experiments with swine will be phased out unless the Division of Biology and Medicine considers further experiments desirable.

Whereas meaningful research findings have been obtained in the two different lines of investigations with dairy animals and swine over the past three-year period, it is considered that even more significant results will be garnered from a more intensive attack on the problem of disturbed calcium homeostasis in cows suffering from parturient paresis.

2. PLANS FOR CONTINUATION OF PRESENT OBJECTIVES AND NEW OBJECTIVE
PROPOSED ON THE BASIS OF PAST RESULTS.

As indicated in the first section of this report, continuation of the previously proposed objectives for goats is also planned for studying Ca-47 kinetics in pregnant cattle. In addition some ideas or hypotheses that bear testing in cows and goats have resulted from our investigations of the RECaP in pregnant and lactating goats and from the work of others, namely:

1. That there may be a relationship between estrogen and total and ionic calcium concentrations (and probably phosphorus) in the blood as a function of time of gestation;
2. That there may be a peripheral block or antagonism of parathyroid action, i.e., lack of bone end-organ response, caused by increasing titers of estrogen, especially in the last week or two prior to parturition in the cow;
3. That the antagonistic effect on parathyroid hormone action by estrogen may not be directly on the bone resorptive mechanism but may be an indirect effect resulting from the known nuclear binding capacity for estrogen which is postulated to be released in high amounts within 24-hours post-parturition;
4. That the turnover of the RECaP may not be affected, or only slightly so, by the estrogenic inhibition of parathyroid hormone;
5. That estrogen may also have an inhibitory effect on intestinal calcium absorption in late pregnancy; and
6. That an unbalanced dietary calcium and phosphorus intake may only slightly perturb, but significantly so in some cases,

the already exaggerated calcium homeostatic mechanism of dairy cows during late pregnancy and early lactation.

In the next three-year period, it is planned to begin investigations to test all of these hypotheses, using normal and thyroparathyroidectomized goats and cows which are pregnant. (Two pregnant Jersey cows already are under investigation.) It would be ideal to use cows entirely, but large numbers of cows are not available and the cost of maintaining and conducting Ca-47 experiments with them would be prohibitive. It may be necessary to use rats in some preliminary experiments, such as in investigations of intestinal calcium absorption. At the level of bone and to some extent at the gut, only a very few experiments on the effects of estrogen have been reported in the literature. Thus, this relatively untouched area of investigations promises to be very rewarding. (See Proposed Technical Program, 1969-1972, for a more detailed discussion.)

Plans for completing the objective of measuring Sr-85 retention in standard miniature swine as a function of age from six months to one year have been stated previously. This study will be terminated when a specific age of maximal retention has been found.

3. GRADUATE STUDENTS AND POST-DOCTORATES TRAINED UNDER PROJECT

The following individuals trained under this project, either wholly or in part, are listed according to the type of program under which they worked.

1. Y. H. Kuo, Ph.D. in Veterinary Physiology: research and thesis completed; degree to be awarded February 1970.

2. G. E. Shaw, Ph.D. in Veterinary Physiology: research completed and thesis in progress; degree to be awarded February 1970.
3. P. R. Ribisl, Ph.D. in Physical Education, 1968.
4. T. G. Lohman, Ph.D. in Animal Science, 1967.
5. L. Milin, M.S. in Veterinary Physiology, 1968.
6. J. R. Posada, Post-Doctorate (NAS-NRC Support), 1967-1968; Colombian Veterinarian.
7. S. Bautista, Post-Doctorate (NAS-NRC Support), 1968 (4 months); Filipino Veterinarian of the Philippines Atomic Energy Commission.

R. F. Bevill, DVM, is joining our group as a Ph.D. candidate in Veterinary Physiology.

In addition several veterinary medical students have worked under this project at various times and have contributed significantly.

These individuals are listed as follows:

1. L. D. Baker, D.V.M.
2. M. W. Balk, D.V.M.
3. R. A. McMullen, D.V.M.
4. J. D. McKean, 4th year veterinary student.
5. J. W. Greenfield, 3rd year veterinary student.

4. BIBLIOGRAPHY OF PUBLICATIONS

Of the following documents submitted to the AEC in the past three-year period, those that have been published are followed by an asterisk (*).

Documents Submitted to AEC for Period

December 1, 1966 Through November 30, 1969

COO-1339-12	Aug. 15, 1967	An Inexpensive Metabolic Unit for Baby Pigs from Birth to Four Weeks. J. J. B. Anderson, L. D. Baker and A. R. Twardock. Lab. Anim. Care., <u>17</u> :569-572, 1967.*
-13	"	Distribution of Radiostrontium in the Skeleton of the Young Pig with Age (Abstract). J. J. B. Anderson and L. D. Baker. Am. Zool. <u>7</u> :204, 1967.*
-14	"	Cesium-137 retention in cattle, sheep and swine. A. R. Twardock and W. C. Crackel. Health Physics <u>16</u> :315-323, 1969.*
-15	"	Note: Stepwise regression. T. G. Lohman, P. R. Ribisl and H. W. Norton.
-16	"	Fourth Progress Report (December 1, 1966 - November 30, 1967).
-17	Aug. 15, 1968	Effect of Time on Distribution of Injected Radiostrontium in the Skeleton of Young Pigs. J. J. B. Anderson. Health Physics <u>15</u> :237-241, 1969.*
-18	"	Calcium-47 Kinetics in Dairy Goats (Abstract). Y. H. Kuo, A. R. Twardock, W. C. Crackel, J. J. B. Anderson and T. G. Lohman. Fed. Proc. <u>27</u> :311, 1968.*

- COO-1339-19 Aug. 15, 1968 Urinary Hydroxyproline, Excretion in Swine as a Function of Age (Abstract). J. J. B. Anderson. Fed. Proc. 27:728, 1968.*
- 20 " MS. Effect of Exercise on Mineral and Organic Bone Turnover in Swine. J. J. B. Anderson and L. Milin.
- 21 " Whole-body Retention of Strontium-85 in Swine Given Sodium Alginate or Barium and Sodium Sulfates. L. Milin and J. J. B. Anderson. J. Nutr. 97:181-184, 1969.*
- 22 " Fifth Progress Report (December 1, 1967-November 30, 1968).
- 23 Aug. 15, 1969 Sixth Progress Report (December 1, 1968-November 30, 1969).
- 24 " Second Comprehensive Progress Report (December 2, 1966-November 30, 1969)
- 25 " Effect of Growth Hormone on Bone Mineral Turnover in Hypophysectomized and Normal Rats (Abstract). J. J. B. Anderson and J. D. McKean. Fed. Proc. 28 (No.2): 373, 1969.*
- 26 " Calcium-47 Kinetics in Cattle (Abstract). W. C. Crackel, J. J. B. Anderson and A. R. Twardock. Fed. Proc. 28 (No. 2): 760, 1969.*

- C00-1339-27 Aug. 15, 1969 Measurement of Calcium Kinetics in Dairy Goats. A. R. Twardock, Y. H. Kuo, W. C. Crackel and J. J. B. Anderson. In: Parturient Hypocalcemia. J. J. B. Anderson, ed. New York: Academic Press (in press).*
- 28 " Effects of High and Low Dietary Calcium on the Size and Half-Life of the Readily Exchangeable Calcium Pool in Female Goats Under Two Different Feeding Conditions. J. J. B. Anderson, Y. H. Kuo, W. C. Crackel, and A. R. Twardock. In: Parturient Hypocalcemia. J. J. B. Anderson, ed. New York: Academic Press (in press).*
- 29 " Strontium-85 Retention in Neonatal Swine: Effect of Rearing on the Sow Versus Separation from the Sow. J. J. B. Anderson and W. C. Crackel. In: Radiation Biology of the Fetal and Juvenile Mammal, M. R. Sikov, ed. Oak Ridge: Div. of Technical Information, USAEC (in press).*
- 30 " MS. Long Term Effects of High and Low Calcium Diets on Calcium Kinetics in Dairy Goats. J. J. B. Anderson, W. C. Crackel, Y. H. Kuo, A. R. Twardock and H. W. Norton.

COO-1339-31

Aug. 15, 1969

Effect of Two Different Dietary Calcium and Phosphorus Levels on ^{85}Sr Retention in Swine (Abstract). J. J. B. Anderson and W. C. Crackel. Radiat. Res. Soc. 17th Annual Meeting, May 18, 1969.*

-32

"

MS. Effect of Time on Distribution of Injected Radiostrontium in the Skeleton of Six-Month-Old Swine and Its Relation to Calcium Accretion and Bone Growth. J. J. B. Anderson, J. W. Greenfield, J. R. Posada, M. Cupp and W. C. Crackel.

-33

"

MS. Effects of Growth Hormone on Bone Mineral Turnover in Hypophysectomized and Normal Rats. J. J. B. Anderson.

-34

"

MS. Long Term Effects of Calcitonin on Plasma Calcium and Phosphorus Concentrations in Thyroparathyroidectomized and Normal Mature Beagles. J. J. B. Anderson, M. W. Balk, W. C. Crackel, M. K. Austin and E. C. Bollmeier.

-35

"

MS. Calcium-47 Kinetics in Cattle. J. J. B. Anderson, W. C. Crackel and A. R. Twardock.

-36

"

MS. Calcium-47 Kinetics in Goats During Pregnancy and Lactation. J. J. B. Anderson, Y. H. Kuo, W. C. Crackel and A. R. Twardock.

COO-1339-37

Aug. 15, 1969

-38

"

MS. Strontium-85 Retention in Swine as a Function of Age and Dietary Calcium and Phosphorus Intake. J. J. B. Anderson and W. C. Crackel.

-39

"

MS. The Effect of Age and Urinary Hydroxyproline Excretion in Swine and Its Relation to Strontium-85 Removal. J. J. B. Anderson and W. C. Crackel.

-40

"

Effects of Alloxan Diabetes on the Clinical Chemistry and Calcium Metabolism of Dairy Goats. Y. H. Kuo. Ph.D. Thesis, University of Illinois.

-41

"

MS. Calibration of Liquid-Scintillation Counter for Measuring Human Whole-Body Potassium. T. G. Lohman, P. R. Ribisl, J. J. B. Anderson, A. R. Twardock and H. W. Norton.

Effect and Lack of Estrogen on Bone Retention of Sr-85 in Normal and Castrate Female Rats (Abstract). J. J. B. Anderson, J. Greenfield, J. R. Posada and W. C. Crackel. Proceedings of International Union of Physiological Sciences, VII: 12, 1968 (24th International Congress).*

-42

"

MS. Estrogen Inhibitory Action on Bone Mineral Turnover in Mature Female Rats. J. J. B. Anderson, J. W. Greenfield, J. R. Posada and W. C. Crackel.

5. COMMENT ON STATE OF KNOWLEDGE IN THIS RESEARCH AREA AND NEED FOR FUTURE INVESTIGATION

Three research groups are presently very active in attempting to elucidate the etiology of parturient paresis in dairy cattle from a physiological approach. These groups are represented by G. P. Mayer, C. F. Ramberg, Jr. and D. S. Kronfeld at the University of Pennsylvania, J. M. Payne and co-workers at the ARC Institute for Research on Animal Diseases at Compton, England, and our own group. Another investigator, C. C. Capen at Ohio State University, has been examining the ultra-structural changes occurring in the parathyroid and thyroid glands in parturient cows. E. T. Littledike at the USDA Animal Disease Laboratory at Ames has been investigating the functional role of the adrenal and B-cells of the pancreas with respect to their hormonal output in parturient hypocalcemic cows. Still other groups have attacked the problem from a nutritional point of view. Much recent work is collected in the proceedings of a conference entitled, "Parturient Paresis in Dairy Animals" held at the University of Illinois in November, 1968. "Parturient Hypocalcemia" is the title of the volume published by Academic Press.

The current state of knowledge in this area may be summarized as follows: Intestinal calcium absorption decreases while the availability of calcium from the so-called exchangeable pool of the skeleton also decreases as a function of age. In addition the output of calcium and phosphorus into colostrum per lactation increases as a function of the number of pregnancies of a given cow, which in effect is a function of age. The increase in the total calcium drain to the fetus and colostrum is not adequately met by calcium inflow from the gut and from exchangeable

bone into blood in cows at parturition beginning about their fourth or fifth pregnancy, or even earlier, resulting in parturient hypocalcemia of a severe nature. Jersey cows are particularly prone to paresis that may result from too severe a hypocalcemia, but other breeds of larger body size, such as Holsteins, are increasingly susceptible to parturient paresis as milk production of the breed increases. A big question remains as to why parathyroid hormone, shown by radioimmunoassay to be present at greater than normal concentration in parturient cows, is unable to stimulate the resorption of a sufficient amount of the so-called deep bone and hence restore blood calcium concentration to a more nearly normal level. The breakdown in the calcium homeostatic mechanism has been suggested to result from a depressed end-organ responsiveness, i.e., bone cells, to parathyroid hormone. Why bone cells are unable to respond to the hormone is not known, but from work with rats by two different groups parathyroid hormone action was shown to be antagonized by estrogens. It is possible that, in pregnant cows which have increasing levels of blood estrogen the last couple of weeks of gestation and a surge of estrogen output prior to parturition, estrogen blocks the bone resorption induced by parathyroid hormone. The mechanism of this postulated antagonism is not known, but it is known that estrogen is strongly bound by the nuclear fraction of cells. Indirect support of the postulated role of estrogen in calcium metabolism has come from a recent report by Bach and Messervy (Vet. Rec. 84:210, 1969) who demonstrated that not only did ionic calcium fall abruptly 24-hours after estrus but also after parturition and after the administration of stilbesterol to ovariectomized cows. These findings suggest a distinct and important role for estrogen in the regulation of blood calcium at

parturition. Estrogen may oppose the action of parathyroid hormone at any of its target tissues, bone, gut and kidney.

Thus, it would appear worthwhile to investigate the effect of estrogen in parturient cows and goats, both normal and thyroparathyroidectomized animals receiving thyroxine replacement therapy. A more detailed approach to these investigations is presented in the research proposal for the 1969 to 1972 period.

6. FEDERAL SUPPORT FOR OVER-ALL RESEARCH PROGRAM

No other federal support for the research findings presented in these reports has been obtained. Neither has any private support been received other than from the University of Illinois. Dr. H. F. Downey has received a small sum of GRS monies through the College of Veterinary Medicine to support his research. Dr. J. J. B. Anderson also obtained from GRS funds a couple of thousand dollars toward partial payment for small animal whole-body counting equipment, whereas the remaining amount came from the University of Illinois. No AEC funds were used toward the purchase of this equipment.

A. R. Twardock has been receiving an NIH grant for several years in support of work on placental transfer of minerals in the guinea pig.

JJBA:mrmm
9/5/69