Calcium metabolism in pregnancy / by Cynthia Morton

Cynthia Morton
University of Nebraska Medical Center

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

Part of the Medical Education Commons

Recommended Citation
https://digitalcommons.unmc.edu/mdtheses/819

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.
CALCIUM METABOLISM IN PREGNANCY

BY

CYNTHIA MORTON

(SENIOR THESIS)

PRESERVED TO THE COLLEGE OF MEDICINE

UNIVERSITY OF NEBRASKA

OMAHA

1940
CALCIUM METABOLISM IN PREGNANCY

Calcium is an indispensable mineral in normal body metabolism. It is found to be a constituent of all animal fluids and soft tissues, and plays an important role in many physiological processes. As examples of those functions may be listed the following: a) coagulation of blood, b) formation of bone, c) cardiac rhythmicity, d) maintenance of normal neuro-muscular excitability, e) membrane permeability, and f) milk production. (12) All of these factors may be considered to be important in the maintenance of a normal pregnancy, followed by a period of lactation. During those periods, pregnancy and lactation, there is increased demand for calcium by the maternal organism, which, in turn, supplies the needs of the growing fetus and child. Because the average American diet does not provide the minimal calcium requirements of a pregnant woman, and because the fetus must be provided with its mineral and vitamin requisites for growth, at the expense of the maternal reserves if she is not provided with additional supplies, the dangers of dietary deficiencies and the values of dietary supplements during pregnancy should be realized. It shall be the purpose of this paper to present the findings of those who have run balance experiments on
pregnant and lactating women, and their conclusions with regard to the necessity for supplementing an average diet during pregnancy. There will be considered reports of cases in which either the mother, child or both have suffered as the result of inadequately supplying the products for adequate calcium metabolism in pregnancy. Much of the experimental work to be reported has been done upon non-gravid individuals, but the principles of the information gained from their work is applicable to pregnant women.

In order to better understand the study of calcium requirements of pregnancy, let us review a few generally accepted facts concerning the normal calcium metabolism of humans. Two per cent of the weight of the adult body represents the weight of calcium found in the body. Ninety-seven per cent of the calcium is found in the skeleton. The calcium level of the blood serum, normally between 9-11.5 mg./%, is an index to calcium metabolism, for it is controlled by the balance between intake and output of the mineral by the body, and the degree of activity of the parathyroid glands. Forty-five per cent of the calcium in the blood is non-diffusible because it is in a complex relationship with serum protein, chiefly albumin. However, 55% of the calcium is diffusible, and nearly all of this is in the ionized
forms of calcium carbonate and calcium phosphate. (12) The ionization of calcium in the body fluids is determined chiefly by the protein content of the fluids. The relationship between calcium and protein can be described by a simple mass law equation yielding the ionization constant of calcium proteinate. Protein-containing fluid may be thought of as a solution of calcium proteinate, which ionizes as a weak electrolyte into calcium and protein ions, with a residue of un-ionized compound. With the total calcium and total protein known, the calcium ions may be readily calculated. Variables influencing the ionization of calcium are not of too great importance: pH, temperature, albumin:globulin ratio and magnesium content. (80) Mull and Bill (90) found in their investigations upon normal non-pregnant women in Cleveland, that the calcium content of the serum is not effected by age or diet, if the intake is adequate. These authors give as the normal range of serum calcium in healthy, non-pregnant women, 10-11.5 mg.%. 

In a series of studies in 1952 Oberst and Plass (93) found the average serum calcium of non-pregnant women to be 10.4 mg.%. Early in pregnancy there was no consistent change. However, during the eighth and ninth months the average dropped to 9.5 mg.%. During labor
the serum calcium level rose to an average of 9.9 mg.%, and remained at this level during the succeeding 7 to 9 days of observation. Hull and Bill (91) in a study of sixty normal non-pregnant women found the average serum calcium to be 10.4 mg.%, and these authors suggested that the lower limit of the commonly accepted normal range, 9 mg.%, may be too low. At the onset of labor their average finding was 9.8 mg.%, and there was no significant change at delivery or two days postpartum. However, at seven days postpartum the average had risen to 10.3 mg.%, and there was a gradual rise to 10.5 mg.% at twelve to fourteen days postpartum. At about six weeks postpartum, in fifty-two of the sixty cases, most of whom were nursing, the average was 10.4 mg.%. Only eight readings were below 10 mg.%, and the lowest of these was only 9.4 mg.%. In a later study by these same men (89), based upon 900 subjects, there was an average fall of serum calcium of approximately 5%. In comparison with the average for normal, non-pregnant women this was a fall of 11%. The decline was progressive as pregnancy advanced; but the fall was interrupted six or seven weeks before delivery, followed by a slight rise until delivery, followed by a sharper elevation after delivery. Ramsey, et al., (99) in a study of ninety-six women found at the seventh month of pregnancy an
average of 9.34 mg./%, indicating a fall of 13%. Thirty-nine per cent of their cases showed a level of less than 9 mg./%, a level which is too low for good health. In this series there was no evidence to indicate the cause of the fall, for the women had received supplements of vitamin A and D. M. Bodansy (16) reported the percentage of women in his group whose serum calcium fell below the 8.0 mg./% mark at different months of pregnancy:

<table>
<thead>
<tr>
<th>Month</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd to 6th</td>
<td>0.0%</td>
</tr>
<tr>
<td>7th month</td>
<td>12.9%</td>
</tr>
<tr>
<td>8th month</td>
<td>15.4%</td>
</tr>
<tr>
<td>9th month</td>
<td>17.6%</td>
</tr>
<tr>
<td>10th month</td>
<td>14.6%</td>
</tr>
<tr>
<td>At term</td>
<td>23.2%</td>
</tr>
</tbody>
</table>

In the study of Bodansky and Duff (17) the highest incidence of subnormal calcium level, that is, below 9 mg./% occurred in the ninth lunar month in 24% of their patients. This 24% did not all have calcium-deficient diets, and not all with higher concentrations were receiving adequate diets. In Bodansky's recent study (15) entitled "Changes in Serum Calcium, Inorganic Phosphorus and Phosphatase Activity in the Pregnant Woman", he traces the blood levels of these elements during gestation. The following two cases are typical, and show the general trends.
Attention is called in the series to the increased frequency of values below 9 mg.% as pregnancy advanced. An adequate or even superabundant calcium intake does not necessarily assure the maintenance of serum calcium at the normal non-pregnant level. A positive calcium balance during pregnancy is entirely consistent with moderate hypocalcemia. An 8.5 to 9.0 mg.% level in pregnancy may be compatible with an adequate calcium intake and a positive calcium balance. Even lower values in late pregnancy do not necessarily indicate an abnormal metabolism. The majority of values below 8.5 mg.%, however, are due to dietary deficiency. The normal serum calcium of non-gravid women, 10-10.5 mg.% is not necessarily the normal or desired level for pregnancy. Efficiency of calcium utilization, of fundamental importance to the gravid woman, may depend on a serum calcium concentration below the accustomed level. How can this be reconciled with augmented parathyroid activity? Parathyroid hyperplasia is the general response to calcium and vitamin D deficiencies, associated
with rickets, osteomalacia and hyperphosphatemia. In a long-continued calcium deficiency, the parathyroids are incapable of compensation. Parathyroid hyperplasia does not result in an abnormal increase of blood calcium or even in a normal, non-pregnant level. The action of the parathyroids seems to be limited to maintain the serum calcium just above the tetany level. If it can be assumed that parathyroid hyperfunction is normal in pregnancy, the fall in serum calcium in late pregnancy may be considered to be the sign of relative parathyroid insufficiency. Experience indicates that during pregnancy there is an approximately reciprocal relationship between the level of calcium intake and the degree of parathyroid enlargement. With regard to parathyroid control should be mentioned Bodansky's studies on phosphatase levels in the blood. A significant rise in serum phosphatase activity occurs almost invariably during gestation. In case A cited above the level rose from 3.2 Bodansky units at three months to 8.7 units at term. Up to the seventh lunar month, the majority of cases (82%) were within the normal range for adults, i.e., 1.5-4 units. By the tenth lunar month more than 80% were above the normal limit, and at the time of labor 87% showed a level higher than four units. The progressive rise in phos-
Phosphatase during pregnancy is related to the increased lability of bone metabolism of the maternal organism. Bodansky and Jaffe (18) state that serum phosphatase is an expression of the "controlled specific reactivity" to the resorption of bone, whether it be normal or pathologic. The destruction of bone per se, unless accompanied by new bone or osteoid formation, is probably not associated with a marked rise of phosphatase. With regard to phosphatase, Andrews (5) writes that in the bone osteoclasts, hypertrophic cells and certain periosteal cells secrete the enzyme, phosphatase, which is widely distributed, found especially in the mucosa of the small intestine, also in large quantities in active areas of calcification and in fetal and young growing bones. The enzyme splits organic phosphorus compounds, liberating inorganic phosphorus compounds. Sherman (108) states in addition that the enzyme action of phosphatase makes available an increased concentration of phosphorus, which readily combines with the calcium ion to form the major constituent of bone in ossifying centers. Mercante (81) states that the rise in blood phosphatase is coincident with the greatest activity of fetal ossification and presumably with the period of greatest phosphatase need. It may also be considered a compensatory response in the mother, as
the fetus does not elaborate much phosphatase at this time. The elevated blood phosphatase may represent a pathological or potentially pathological state of bone metabolism in the mother or fetus. Cantarow (22) states that the weight of the parathyroid glands is greater in the female than in the male. During the active sexual period of the female there is an increase of weight of the glands of about 22%. After forty-five years of age the size of the parathyroids is diminished. This hyperplasia is not associated with pregnancy, but may represent a response to increased activity of the anterior pituitary gland. In a review of the parathyroid glands, Thompson and Collip (115) state that the hormone acts directly on bone cells resulting in the production of osteoclasts and the release of calcium. If the glands are hyperactive, the calcium-ion concentration of the blood is increased; if the glands are deficient in action, the concentration is lowered. From the blood of pregnant women, Hoffmann (47) is reported to have prepared an extract possessing the pharmacological properties of the parathyroid hormone, most active when extracted during the tenth month of pregnancy. An extract prepared from the blood of non-pregnant women was relatively inactive. Hamilton and coworkers (40) likewise wrote that the blood of pregnant women contains
a substance which behaves like the parathyroid hormone in elevating the calcium level of the blood. Under certain conditions the injection of pregnant blood into rabbits causes a decided elevation in the serum calcium. In their experiments the blood of a seventh-month pregnancy possessed the maximum potency.

Since it is quite apparent that the parathyroid glands alone do not control the calcium level in pregnancy, other factors which may have an influence must be considered. Bočansky (15,16) suggests the possibility of their being a special antihormone checking the rise of calcium by some depressant action, an antagonist to the action of the parathyroid glands. The fact that the serum calcium rises sharply after parturition suggests the abolition at that time of the calcium-depressing effect. This sudden rise occurs postpartum even when the drain on the calcium reserves is undiminished or even increased; also there may be a change from a positive to a negative balance; these factors may point to an intrinsic factor which controls the serum calcium level in the gravid organism. It is logical to consider the placenta as the source of this depressant factor, if the depression is lost after parturition. This idea is presented by Bočansky and Duff. (17) They quote Bonskov and Bremm (20) who reported having
extracted a calcium-raising substance from the placenta.

There have been several reports of investigations made on the effect of estrogentic substances upon the blood calcium level. In 1927 Mirvish and Bosman (85) produced a lowered serum calcium in rabbits and man by the administration of ovarian extracts, and they associate ovarian hormone activity with the fall in blood calcium during pregnancy. In 1930 Franz Mathieu (69) reported that severe tetany can be produced in thyroparathyroidectomized female dogs by the injection of gonadotropic substance, prolan, provided the ovaries are intact, indicating the presence in the ovaries of a calcium-depressing substance. In the same year Mathieu and Barnes (70) reported the lowering of blood calcium in parathyroidectomized dogs, with theelin and theelol, more markedly with the latter. However, the blood calcium of one normal male and one normal female were unaffected by either compound. However, there is discrepancy in the findings of other workers. Dixon (28) wrote that from experimental results it can only be concluded that estrin and corpus luteum hormone cause no gross change in the serum calcium in rabbits, dogs and rats. The injection of anterior pituitary extract into rats, sufficient to cause luteinization of the ovaries, caused no change in their serum calcium.
McCullagh and Kearns (79) were unable to demonstrate any correlation between variations in the amounts of sex hormones in the body and the levels of serum calcium and phosphorus. The sex glands have a pronounced effect upon the neuro-muscular excitability in human parathyroid tetany, but acting through some separate mechanism. Marlow and Koch (67) observed no significant or consistent effect on serum calcium of fowls, rats or rabbits when a purified estrogenic preparation from hogs' ovaries was injected. An extract from pregnant urine also resulted in no definite effects. These authors state that their findings are even suggestive of a rise, although irregular and insignificant. They believe the cause of the fall of blood calcium in pregnancy appears to be the fetus. It is more logical to expect a rise in blood calcium to protect the pregnant mother and aid the fetus, if the ovarian hormone was in control. In the experiments of Huey and Marlow (51) none of the fractions in the stages of purification of estrogenic substance, the purified extract or a combination of these products caused a definite or consistent change in the serum calcium and inorganic phosphorus. Leven and Smith (62) write: "We seriously doubt whether estrin actually has a physiologically significant effect on mammalian blood calcium level. The increase in serum
calcium is great in birds, similar to that occurring with the deposition of the calcium-rich shell. Implications concerning the influence of estrin via the calcium balance on growth, stature, bone formation, etc., seem of doubtful significance." Data from 142 calcium determinations in their experiments indicate very little if any effect of estrin administration or ovariectomy on serum calcium level. A slight elevation noted after estrin therapy appears to be transitory in nature. In a summary of reports of work done on mineral metabolism, Greenberg (37) concludes: "Administration of estrogenic hormones of the gonads is without effect on the blood calcium level."

Assuming, then, that the need for calcium in pregnancy is raised above the normal level, although the serum calcium at the same time is at a lesser normal, let us consider the balance experiments, fetal retention of calcium, dietary requirements of calcium, and the availability of calcium in the diet. Calcium balance is the difference between calcium ingestion and excretion. A positive balance, or retention, is found during growth, pregnancy, acromegaly and in a period following calcium starvation. A negative balance is found in infantile rickets, renal rickets, sprue, osteomalacia, hyperparathyroidism, hyperthyroidism,
starvation, calcium deficiency, and usually during lactation. Best and Taylor (12) Studies on the composition of the human fetus date back to 1877 to Fehling, the German chemist, who determined the ash content of eleven fetuses at different stages of their development. The inconsistent findings of different authors may be accounted for by the difficulty in measuring the age and the difficulty in being sure that the fetus is normal in view of the fact that it is available for analysis. The figures for total ash and calcium content vary widely in different reports. In some newborns the total calcium is thirty-three grams; in others, less than half as much. One wonders if the infants with high calcium, if they had lived, would have been less subject to rickets than those with low calcium. Animal experiments give evidence of the superiority of higher ash content. The lowest figures in any investigation appeared in post-war period in Germany when rickets and osteomalacia were prevalent. Blunt and Cowan (13). The first balance experiments were reported by Hoffström (48), who determined mineral retentions weekly during the last twenty-three weeks of pregnancy. He found much fluctuation; some weeks had negative balances, while some had high positive balances, some of which may have been due to the delayed excretion of feces.
Excess calcium was used for the growth of the placenta, muscles, mammary glands as well as the normal storage in the female. The mother did not give her reserve to the child, for her intake was high, averaging 1.7 grams of calcium per day. Bauer, Albright and Aub (8) believe from experimental date that there is a very appreciable minimal requirement of calcium necessary to keep the body in calcium balance. They found that a certain definite amount of calcium had to be excreted each day regardless of the intake, and only when calcium was furnished in excess of the amount to be excreted was there a positive balance. They made an attempt to see if the large amount of calcium excreted on a low-calcium diet could be used during pregnancy to meet fetal demands for calcium. The excretion of the same amounts of calcium at periods when low-calcium diet was given, both in the fifth month when only a small amount is needed by the fetus and in the eighth month when a large amount is needed, suggests that calcium excreted on a low calcium diet is not available for the fetus. In their balance experiments Coons and Blunt (25) found that calcium retention began to rise in the fourth month, gradually rising to the ninth, followed by a steep rise in retention to the end of the
tenth lunar month, where the retention was the greatest. None of their cases showed storage of excesses. Those with the highest storage corresponded to the fetal requirement; most fell far below the requirement. Where the daily intake was below one gram, storage of calcium was low. Similar findings resulted from the work of Goss and Schmidt (36) in the same year. Sherman's work, Chemistry of Food and Nutrition, (108) has been quoted by many as an authority as to calcium requirements. He states that the average daily excretion of calcium is 0.45 grams, and one-sixth of the diets investigated did not supply even that quantity of the elements. This author sets the fetal requirement as 0.68 grams per day, a total of twenty grams of calcium and nineteen grams of phosphorus being required during fetal life for complete skeletal development and perfectly-formed teeth and jaws. It is misleading to consider the amount of calcium in the urine alone as the measure of the amount which the body absorbed; or the amount in the feces as a measure of the amount which has escaped utilization. After utilization a large part of the phosphorus and a still larger part of the calcium is likely to be eliminated through the intestine rather than through the kidneys. The food supply may appear to be liberal and
varied, and yet unless milk and green-leafed vegetables are well represented it may become calcium-poor. In adults there may be a long-continued loss of calcium without the appearance of symptoms, because the losses from the blood and soft tissues may be replaced by calcium withdrawn from the bones. Sherman (109) reported that the calcium of different foods is not equally absorbed, calcium of milk being well-utilized and that of certain vegetables poorly so. Rose (104), also an authority on nutrition, recommends the intake of one gram of calcium per day; this amount is supplied by one quart of milk. Coons and Schiefelbusch (27) based their work on subjects with normal pregnancies, that is, there was no vomiting or toxemias to deplete chlorides and upset the water balance or the acid-base equilibrium. No negative balance was found for calcium or magnesium. Good storage of the two elements were parallel, indicating that factors favoring retention were common to the two. The data lends no support to the theory that magnesium is a substitute for calcium in a deficiency of the latter. The highest content of calcium in a fetus, thirty-three grams, represented the deposition of 0.22 grams per day for the last half of gestation, when 95% of the total is laid down.
The dietary habits of women do not change to assure the increased intake required in pregnancy. To insure calcium balance in the non-pregnant, non-lactating woman only 0.5-0.6 grams are required per day, whereas in later pregnancy 1.5-2.0 grams are required. Coons, et al. (26). According to Hummell and coworkers (52) 12% of the calcium ingested during the last four months of pregnancy is retained. There is even greater efficiency of utilization in women with less satisfactory nutritional backgrounds when placed on an adequate diet. In Food Health and Income Orr (94) says that diets in common use in large sections of the population do not provide intakes of calcium or phosphorus at the suggested levels of one to two grams per day. An analysis of the diets indicates the shortage of calcium likely to be greater than that of phosphorus. Two-thirds of all dietary calcium is derived from milk and cheese, and it is difficult to see how an adequate amount can be ensured except by greatly increasing the consumption of dairy products. To increase the calcium intake of pregnant women of the poorest section of the community from an average of 0.57 to 1.6 grams per day would require one quart of milk per person per day. According to Leitch (61) a slight retention of calcium
may occur on an intake of only 0.25 to 0.3 grams in one out of six cases. When the requirement of 0.5 to 0.6 grams per day is met, the frequency of daily positive and negative balances is one to one. In a woman not ingesting vitamin D, at or above a daily intake of 0.55 grams calcium, losses of one period are equaled by gains of another, but below this intake, the output usually exceeds the intake. According to Pyle and coworkers (98) the level of calcium in food has little affect on the calcium level of the blood within comparatively wide limits. There is a close correlation between serum and fecal calcium. Presumably a moderate degree of hypocalcemia is advantageous to the gravid woman because it is accompanied by a decreased transfer of calcium from the blood to the bowel. Tisdall and Drake (116) recommend 1.5 grams of calcium per day to insure equilibrium during pregnancy. The inadequacy of the average human diet with regard to calcium supply is demonstrated. Not only is the calcium retention low, but the per cent of calcium retention is less than it would be in a diet containing the same amount of calcium, more of which was taken in the form of milk. Andrews (5) states in his paper on "Calcium Metabolism" that the urinary excretion of calcium varies from 0.1 gram per day on a low-calcium
diet to 0.5 grams per day on a normal diet, and normal adults require one gram calcium per day to furnish 0.7 grams calcium for each day's work.

The presence of a normally sufficient quantity of calcium in the diet does not necessarily mean that it will be absorbed and utilized. There are certain factors which must be in their proper relationships for the most efficient utilization of the available minerals. Among these factors the first to be considered will be vitamin D. In 1925 Miles and Feng (32) experimented with vitamin D on patients suffering with osteomalacia. By supplying calcium and vitamin D, as cod-liver oil, they prevented the drain of calcium, turning the negative balance into a positive one. When olive oil replaced the cod-liver oil, calcium alone without vitamin D was insufficient to change the balance or alleviate the symptoms of the disease. Less encouraging results were reported in 1928 by Hart, Tourtellotte and Heyl (42). Adults on an acidotic, calcium-deficient diet showed no increased tendency to calcium retention as a result of daily irradiation (ultra-violet) for twenty days or by the addition to the diet of cod-liver oil up to the quantity of 12 c.c. per day. They concluded that increased vitamin D ingestion does not decrease the min-
imal requirement for calcium. Macy and coworkers (66) found the daily use of 15 cc. codliver oil and 10 gm. yeast for two months when milk flow was at its highest effectively stimulated better calcium utilization by three lactating women. During the experiment there was a decreased fecal excretion of calcium and phosphorus both absolutely and relatively, which illustrates a marked alteration in metabolism and accounts for a greater assimilation of these elements. The women experienced a more economical utilization of their available food constituents and a greater feeling of well-being after the addition of codliver oil and yeast to their diets. In 1931 Harris and Innes (42), writing on the mode of action of vitamin D state that while the addition of vitamin D to the diet tends to raise the blood calcium, the actual level is the resultant of several factors: increased net absorption, dissolution from certain sites, and, when high levels are reached deposition in other sites and increased urinary excretion. That the increased ingestion of vitamin D does not decrease the minimal requirement for calcium is again emphasized in 1932 by Bauer, Marble and Claflin (10). In their studies the patients retained calcium when the intake was ample and no vitamin D was ingested. There
was no increased retention when thirty to ninety milligrams of irradiated ergosterol was given in addition to the high calcium diet, but there was evidence of increased absorption for the urinary excretion was increased and fecal calcium correspondingly decreased when vitamin D was given. Similar results were reported by Hanscher, Donelson and Erickson (94). Of three young women on a calcium intake usually considered to be ample, and receiving no vitamin D, two lost 0.1 gram per day, and one was approximately in calcium equilibrium. After supplementing with fifteen grams cod liver oil per day for twenty-three days the average calcium losses were not decreased, and there was no significant alteration in the mode of calcium excretion. Because the administration of vitamin D usually leads to a lowering of calcium and phosphorus in the feces, Albright and Sulkowski (2) desired to discover if that is due to an increased absorption or of decreased reexcretion. From their work they concluded: 1) vitamin D therapy led to a decreased fecal excretion of calcium and increased urinary calcium excretion and an elevation of serum calcium, which in turn, led to diminished parathyroid activity, 2) with the giving of intravenous calcium there followed no increase in fecal calcium, whereas
orally administered calcium did increase the fecal calcium; therefore, vitamin D decreased the fecal calcium excretion due to an increased absorption of calcium and not to a decreased reexcretion into the gastrointestinal tract. Jeans and Stearns (57) have summarized the human requirement of vitamin D. The measure of vitamin D required presupposes the ingestion of a diet adequate in all respects, especially ample calcium and phosphorus, and should include the recognition of human requirements including both the quantity necessary to prevent obvious clinico-pathological changes and an amount to promote a condition of normal health and nutrition. Again, the ingestion of vitamin D does not lessen the requirement for calcium; the increase in utilization varies with the person. Vitamin D should help an adult inefficient in the absorption of calcium, but vitamin D ordinarily does not increase the retention of those who have high retention without it, and not if the calcium intake is deficient. It is advisable to give vitamin D during pregnancy and lactation. However the optimal amount is not known. During lactation the requirement may be greater than at any other period of life and a daily dosage of 800 units or more is suggested, together with an abundant intake of
calcium and phosphorus. Vitamin D may also be formed within the body by the action of the ultraviolet rays of the sunlight irradiating the ergosterol of the subcutaneous tissues. Its value was very clear to Hutchison and Sha (72) in 1922. Twenty-five per cent of infants from well-to-do mothers who practiced "purdah", a religious seclusion practiced by high-caste Hindu and Mohammedan women, had definite signs of rickets, whereas only 5% of children of lower-caste Hindus had evidence of the disease. The mothers of this group had an abundance of sunshine. In the balance experiments of Hull and Bill (89) they observed that the calcium in the serum for all stages of gestation was on the average higher during the period from June to December than from January to June. This seemed to be accounted for by the increased amount of ultraviolet in the sunshine and the increased exposure during those months. Likewise, Coons and coworkers (26) found that pregnant women in Chicago (latitude 41.9) required more calcium than pregnant women in Stillwater, Oklahoma (latitude 36.1). The difference in the efficiency of calcium utilization was attributed to the amount of sunshine.

One wonders, as the use of vitamin D preparations becomes more widespread, if there is any danger of its
excessive use. Harris and Innes (42) write that in vitamin D excesses the increased blood calcium is derived first, by increased net absorption, and second, by an increased withdrawal from body stores. In hypervitaminoses produced on diets rich in calcium with moderate overdoses of vitamin D the first factor is of special consequence; however, with calcium deficient diets and larger excesses of the vitamin, withdrawal from the bone shaft is the main source. Taylor, et. al. (112) studied the action of irradiated ergosterol and its relation to parathyroid function. They believe that there is a direct stimulation of parathyroid function by the vitamin when its concentration is sufficiently great, and that this represents a compensatory mechanism to withdraw calcium from the bones to increase the excretion of calcium when abnormal amounts of the vitamin enters the body. Aub (4) also states that in excess vitamin D mimics hyperparathyroidism. Reed (101) writes that the calcium excretion may be increased without abnormal blood levels as the result of large doses of vitamin D. He has given the vitamin in enormous dosage to adults with apparently few untoward effects. The limit of tolerance varies with the individual, but seems to be 150,000 units or more, even when given in
a very concentrated product. The tolerance to vitamin D is relatively high whether adults utilize the concentrated doses effectively or not.

One of the important factors influencing the mode of excretion of calcium and phosphorus is the concentration of fatty acid in the intestinal contents. With an increase of fatty acids, there follows an increased formation of calcium soaps, a decrease in the amount of calcium phosphate, followed by excretion of the calcium soaps and an increased absorption of phosphates and increased excretion of phosphates in the urine. Tefler (114). The absorption of calcium is prevented in steatorrhea because of the formation of insoluble calcium salts and soaps. Aub (4).

The influence of the reaction of the diet is more or less of a disputed question. The following will summarize the writings which deal with this factor on absorption and utilization of calcium. In 1922 Bogert and Kirkpatrick (19) wrote that calcium excretion was increased, especially that in the urine by changing the food allowance of potato (basic residue) to rice (acid residue). In basic diets the excretion was mainly in the feces, whereas in acid diets the calcium was excreted in the urine. This would indicate an increased
absorption with acid diets. However, during the period in which acid-forming diets were consumed there was an increased total excretion and increased negative calcium balance, not to be accounted for by calcium deficiency in the diets. Calcium was retained more readily on a basic diet than on a balanced or acid-forming diet, while calcium excretion was greater on an acid-forming diet than on a balanced or base-forming diet. In 1922 Hamilton and Moriarty (41) wrote that basic diets lead to decalcification due to decreased absorption because of increased alkalinity of the intestinal contents. Howe (49) in 1928 wrote that some foods containing only a fair amount of calcium leave an acid residue in the body. The metabolic end-products or ash of such foods, meats and cereals, consist of acid radicals of phosphoric, sulphuric and hydrochloric acids. A part of the calcium intake is utilized to neutralize these strong acids before calcium can be stored, resulting in a lessened efficiency of utilization. Bauer et al. (8) wrote that negative nitrogen balances may decrease calcium utilization by the production of acid radicals by tissue catabolism. On experimental work with rats in 1930 Goss and Schmidt (56) found that young rats from mothers maintained 1) on acid diets and 2) on alkaline
diets, kept for some time after birth on the respective
diets, showed no difference in the storage of calcium
and phosphorus. Bernheim (11) and Best and Taylor (12)
wrote that sugars, especially lactose favor the absorp-
tion of calcium, due to the increased intraintestinal
acidity with the formation of organic acids from the
sugars. In view of the important position held by
fruits in the American diet, investigation was undertaken
by Lindell and coworkers (83) to determine the effect of
typical fruits on calcium retention. Experimenting on
rats they found that calcium retention was increased
8 to 11% with the addition of fruits to an adequate diet.
The calcium carbonate of the diet reacted with the acid
of the fruit to form the benzoate, citrate or malate,
salts which are more soluble than the carbonate. That
the increased retention was due to an increase of the
acidity of the intestinal tract with the addition of the
fruits, was also suggested by Esselen (51). In exper-
imental work on growing children Chaney and Blunt (24)
found that the addition of orange juice to a normal diet
caused an increase in the calcium retention, amounting
to 11.2% on one child and 10.5% in another, considerably
more than the little excess calcium in the diet would
indicate. They discuss several factors which may be
involved: 1) the additional vitamins promoting an economical use of elements already present but not effectively used; 2) the additional calcium and phosphorus inducing the retention of these and possibly other elements in excess of the amount added; 3) factors stimulating greater flow of hydrochloric acid in the stomach, increasing the acidity of the upper intestine and facilitating greater absorption of the minerals; 4) a basic residue favoring normal activities in the growing body.

Because there is such a close relationship between the metabolism of calcium and phosphorus, the influence of the calcium:phosphorus ratio in the diet is worthy of discussion. Robison (102), in his discussion of ossification, shows the close relationship of these two elements in that function. Hexose monophosphate ester in the intestine forms soluble salts with calcium, which are absorbed and carried in the blood stream to the site of ossification. Under the action of an enzyme present in ossifying cartilage, this calcium salt is hydrolyzed, and calcium phosphate and a certain amount of carbonate is precipitated in the organic matrix around the osteoblasts. Orr et. al. (95) found in their metabolism studies that excess calcium in the diet increases the total absorption and retention of calcium, but impairs
the phosphorus retention. Excess phosphorus in the diet exercises an unfavorable influence on calcium metabolism, accompanied by an increased calcium loss in the feces. The retention of one element in the intestine by an excess of the other element in the diet is best explained by the formation of insoluble phosphates of calcium which cannot be absorbed. Bauer, Albright and Aub (8) state that calcium metabolism is inseparably linked with phosphorus metabolism. Most of the calcium retained in the body is usually assumed to be in the form of tertiary calcium phosphate deposited in the bones. Farquharson, Salter and Aub (22) found that wide differences in the intake ratio of calcium and phosphorus apparently has less effect on retention of these elements by adults than by children. They found little effect on the excretion of calcium in either the urine or feces or on the calcium balance. Even when the phosphorus intake was increased five-fold, the only effect noted was a slight lowering of the calcium of the urine in one case. In one patient on a higher calcium intake, the effect of more than doubling the phosphorus intake was negative. La Mer (60) wrote: "Calcium is efficiently absorbed only when it is ingested in a balanced combination consisting of three parts calcium and two parts phosphorus."
Calcium is absorbed in the intestine and deposited in tissues only when in this ratio." According to Tisdall and Drake (116) with an adequate phosphorus and low calcium diet, retention of calcium and phosphorus is increased in the ratio of two to one when extra calcium retention is brought about by the addition of calcium to the diet. In a diet adequate in phosphorus, the amount of phosphorus retained is dependent upon the amount of calcium retained. Andrews' (2) statement may be used as a summary of the work done upon the calcium:phosphorus ratio: "There is an intimate relation between calcium and phosphorus, each requiring the other for its metabolism, although the quantitative relations are not constant."

Other endocrine factors than the parathyroids influence calcium metabolism. Of these the thyroid is mentioned most frequently. Its actions, briefly, as given by Aub and coworkers (5,6) are these. Hyperfunctioning of the thyroid glands favors calcium excretion in excess of normal, serum calcium remaining within normal limits in most cases, a few cases showing a decrease. They report a case in which the calcium excretion is increased 251% in a patient with a basal metabolism rate of plus 55%. Excretion is also increased
with thyroid therapy, and decreased in myxedema. This increase of calcium excretion is not dependent upon elevation of the metabolism alone, for in three-fourths of the cases with high metabolism due to leukemia or fever there was found normal calcium elimination. The thyroid hormone, which raises only slightly the serum calcium and phosphorus of otherwise normal individuals, elevates appreciably the low serum calcium of patients with parathyroid tetany by drawing calcium from the bones.

Macy and coworkers (65) report in their balance experiments that the greatest negative calcium balance of one of the subjects of their series was during the twenty-sixth week of gestation. The only factor differing from her ordinary routine was psychic, there being some situation at that time producing great worry and stress.

Having considered the requirements for balanced calcium metabolism of pregnancy, and the factors which may influence its absorption and utilization, let us turn to the consideration of some of the results of inadequately meeting that requirement. With regard to the fetus there are the developing bones and teeth to consider. Only negligible amounts of calcium are de-
Posited in the skeleton before the fifth month of intra-uterine life, and over 60% of the skeletal calcium of the newborn is the result of deposits during the last two months of prenatal life. Best and Taylor (12).

The following graph readily shows the rapid increment of calcium by the fetus during the last of its intra-uterine life. Graph after Hess (46).

<table>
<thead>
<tr>
<th>Duration of the pregnancy in months</th>
<th>Calcium content of fetus in gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>3</td>
<td>7.3</td>
</tr>
<tr>
<td>4</td>
<td>10.0</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>15.0</td>
</tr>
<tr>
<td>7</td>
<td>17.5</td>
</tr>
<tr>
<td>8</td>
<td>20.0</td>
</tr>
<tr>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td>10</td>
<td>25.0</td>
</tr>
<tr>
<td>11</td>
<td>27.5</td>
</tr>
<tr>
<td>12</td>
<td>30.0</td>
</tr>
</tbody>
</table>
Givens and Macy (35) have made analyses of human fetuses. They write that calcium stored through the first four months of growth averages little more than 0.1 gm. Thirteen to thirty-three grams are fixed in the fetal tissues during the succeeding months, the greatest calcium deposition being in the last three months. The following chart shows the monthly increments of calcium as computed by them.

<table>
<thead>
<tr>
<th>Lunar month</th>
<th>Grams, calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd</td>
<td>0.01</td>
</tr>
<tr>
<td>4th</td>
<td>0.11</td>
</tr>
<tr>
<td>5th</td>
<td>0.83</td>
</tr>
<tr>
<td>6th</td>
<td>1.71</td>
</tr>
<tr>
<td>7th</td>
<td>0.98</td>
</tr>
<tr>
<td>8th</td>
<td>3.16</td>
</tr>
<tr>
<td>9th</td>
<td>5.54</td>
</tr>
<tr>
<td>10th</td>
<td>12.10</td>
</tr>
</tbody>
</table>

In *The Natural History of the Human Teeth*, by John Hunter (55), we find: "In the fifth or seventh month, the edges or tips of these five substances are begin to ossify.....so at this age in both Jaws, there are in all twenty Teeth begin to ossify, and the stamina of twenty-four." Coons and Blunt (25) concluded from x-ray examinations of bones of normal infants from well-fed mothers that the calcification was best where retention of calcium and phosphorus by the mother during pregnancy was the highest. When the calcium intake was low, prerachitic changes in the newborn were evident,
definite cupping of the distal end of the ulna, flaring and fringing of the ends of the long bones, poor outlining of the ends of the diaphyses by calcium. Maxwell and Turnbull (75) reported two cases of fetal rickets, with roentgenographic evidence of the children who were born of osteomalacic mothers. The report of dental structure was as follows: calcification of the border of the dentine was irregular in outline, the odontogenic zone was wider than normal and the decalcified enamel showed some abnormality of staining. Booher and Hansmann (21) found no difference in the degree of calcification of tibiae of newborn infants from mothers whose calcium intake had varied within fairly wide limits as judged by their milk consumption. When the age of the mothers was such that active calcification of their own bones should have been taking place simultaneously, this had no appreciable effect on the calcification of the skeletons of the full-term fetuses borne by them. With respect to the deposition of inorganic constituents of its bones, the normal human fetus may be regarded as entirely parasitic upon the maternal organism. This fact is substantuated by experiments which show the serum calcium level to be higher in the fetus than in the mater-
nal organism. The averages of the cases of Hull and Bill (91) were 11.7 mg.% in the blood of the umbilical cord and 9.8 mg.% in the maternal blood at the time of delivery. The same investigators (89) wrote that the calcium concentration in the fetal (cord) blood was uniformly higher than the corresponding concentration in the maternal blood, with a one to three milligram variance. Maxwell, Hu and Turnbull (73) established beyond a doubt that rickets may occur in utero. They write of a Chinese woman, 38 years of age, who had been on a starvation diet (two meals per day with no meat or animal fat) for three years, with pains of osteomalacia for two years. At the time of delivery she was in hypocalcemia (7.88 mg.%), and the infant showed a marked rosary and Harrison's groove. X-rays showed rachitic-like changes in the long bones, which were later verified by histological examination. To bring the condition closer home, Rector (100) cites the case of congenital rickets in the state of Massachusetts. The mother was 32 years of age, had very poor nutrition throughout her pregnancy, vomited severely for weeks, retained little food, and developed hypertension, albuminuria and marked secondary anemia at the time of delivery. The child was full-term.
delivered by breech extraction, and weighed 7½40z. After eight hours bleeding occurred from the nose and mouth. Twenty-five c.c. of whole blood were injected immediately without effect. After repeated hematemesis, respiratory irregularity developed and death followed on the second day. X-rays of the costochondral junctions showed marked flaring and irregular metaphyseal cupping. Necropsy findings showed a well-nourished, well-developed child, whose general appearance was not unusual except for a marked rachitic rosary. There were gross and petechial hemorrhages. The bones showed thick costochondral junctions, irregular and thickened zones of primary ossification, pallor and density of the trabeculae, much thickened, widened and very cellular preparatory zones of cartilage. The junctions of bone with cartilage were convex toward the diaphysis. Diagnosis: Hemorrhagic disease of the newborn, and fetal rickets. Wolfe (118) reports the case of a Chinese child borne by a primipara of 19 years. During the month preceding labor, the mother had several attacks of carpopedal spasm daily, lasting for a few minutes. At admission she had positive Chvostek and Trousseau signs. The blood calcium was 5.4 mg.%, phosphorus, 2.9 mg.%. X-ray showed no evidence of osteo-
malacia. X-rays of the infant showed mild but definite rachitic changes of the epiphyseal ends of the long bones. Its blood calcium was 8.1 mg. and phosphorus, 4.2 mg. Its diet was supplemented with cod-liver oil and the child was kept in the sun. The child was seen again at twenty months of age when it was brought in with bronchopneumonia. At that time there was a suggestion of Harrison's groove, but there was no enlargement of the costochondral junctions. X-ray showed no evidence of rickets. An upper incisor was extracted for study. Normal enamel was found on the incisal third of the incisor teeth and absence or extreme hypoplasia of enamel on the incisal tip of the canines and occlusal third of the first decidual molar. The author inferred that calcification began normally at the seventeenth week of fetal life and proceeded until the twenty-third week. Calcification from then on was extremely poor, as seen by the marked hypoplasia of the enamel and absence of enamel from the lingual surfaces of the incisors. Normal calcification was resumed at a period corresponding approximately to the first week of extrauterine life when the rachitic condition was recognized and treatment given. While the bony changes may disappear so that no evidence of previous rickets may be
found, changes in the teeth are permanent and remain as evidence of the disease process. Hull (88) wrote that the lower values of cord blood, resulting from lowered maternal values usually found in pregnancy, may represent an inadequate available supply of calcium and phosphorus for fetal metabolism with impairment of bone and tooth growth in utero. The value of maintaining calcium and phosphorus levels of the blood during pregnancy is possibly more important to the development of the fetus than to the health of the patient herself. From experimentation with rats Lyons (64) concludes that calcium:phosphorus deficiencies in the diet of pregnant and lactating female rats may cause the death of the litter, may produce smaller rats, and may have some effect on the production of dental decay. The deficiency may not disturb the pregnancy owing to the reserve in the mother rat, but may prevent the raising of the litter. If this is applicable to humans, the pregnant woman has only a definite amount of tidal calcium and phosphorus available for the fetus, and if the demand is too great and the diet is not supplemented, the fetus may be deficient in size or may be unable to maintain life. Finola and coworkers (34) found a significant increase in density of bone and decreased size
of the fontanel of babies whose mothers received a good diet, supplemented with approximately 1.5 gm calcium as dicalcium phosphate and 7,000 units of vitamin D as viosterol, in comparison with infants whose mothers received a good diet without the addition of calcium and vitamin D. A poor diet in the mother during pregnancy is one of the chief predisposing factors in the development of rickets and dental caries in children. McCall and Krasnow (76) wrote that in deciduous dentition the crowns are fully formed and very largely calcified in utero, hence hypoplastic enamel in these teeth is chargeable to prenatal systemic disturbance. The hypoplastic deciduous tooth is smooth when erupted but lacks density. Caries attacks large areas of the hypoplastic deciduous tooth which may decay with rapid loss of enamel en masse. In permanent dentition, crown formation and calcification of even the first teeth to erupt, the central incisors and first molars, begins at about the time of birth, hence hypoplasia of enamel is traced to systemic disturbance at and following birth. Hypoplastic enamel of permanent teeth is pitted and grooved, but calcification of the deformed structures is usually normal in its density. It is not prone to decay unless the grooves and pits are of such a depth as to make self-cleansing
and cleaning by a brush difficult.

There has been much impressional controversy in the past over the occurrence of decalcification with resulting caries formation in the teeth of pregnant women. However, this assumption is not borne out by scientific studies. John Hunter (55) in 1778 wrote that experiments pointed to a vital difference between bone and dentin and that bone can be resorbed and its calcium withdrawn while dentin does not show such capacity. The absence of vascular paths by which calcium might be withdrawn from the dentin was noted. He was never able to inject teeth in such a way as to be able to trace vessels from the pulp into the substance of the newformed tooth...

"It is to be observed that affections of the whole body have less influence upon the Teeth than any other part of the body. Thus, in children affected with the rickets, the Teeth grow equally well as in health, although all the other bones are much affected; and hence their Teeth being of a larger size in proportion to the other parts, their mouths are protuberant." In 1895 Peterson (97) wrote that extreme tooth decay in pregnancy may be due partly to the lack of oral hygiene, partly to a change in the hydrogen-ion concentration of the blood toward the acid side. It is probably true that dental

41.

arter formation and are very like human molars, he found that with calcium-deficient diets the molars

42.
showed reduction of total ash with a small decrease in calcium and phosphorus and a small increase in magnesium. "It is seen from these studies that it is possible to produce chemical changes in an already formed tooth by changing the diet. There are greater changes in bones than in teeth because the circulation in bones is better than in teeth, consequently changes are more rapid."

In experiments by Ziskin (119), Mull, Bill and Kinney (92) and Klein (59) the conclusion is drawn that the occurrence of dental caries is no more frequent in women who have borne children than in women of a corresponding age who have never borne children. The curves of incidence of carious teeth according to age and number of pregnancies are very similar in the two groups, tending to show that age is the determining factor in the increase of caries rather than pregnancy. Sorrin (110) writes that when the nutritional requirements are neglected in gravid women, a gingivitis, followed by loss of bone is observed, often caries, extreme sensitiveness and local acidity develops." Stern (111) writes that there seems to be no apparent relationship between dental caries and acidity of the mouth. In discussing the role of the endocrines in producing dental caries, Rony (103) supports the idea that hypo-or hyperfunction of glands may
influence the quality of the teeth during the formative period, but after they have attained their final size and structure the enamel and probably the dentin, too, is not thus affected. With regard to hyperparathyroidism, Albright, Aub and Bauer (1) write, "The teeth do not take part in the generalized decalcification. They may fall out because of disease of the jaws, but they themselves remain well calcified. Well-calcified teeth stand out sharply against the poorly-calcified jaws by x-ray. There is strong evidence against their being a reserve supply of calcium." In a personal communication of K. S. Strock (112) discussing parathyroid disease, "...at first I thought that lack of caries was purely incidental, but later, as case after case, both in the young and in older ones, showed a lack of caries, it began to seem an important finding." A patient with hyperparathyroidism for three years went through a pregnancy, developing only two new cavities. Ziskin and Hotelling (120) wrote that in poor hygiene bacterial action on debris formed lactic acid, but the acid formed was not sufficient to produce caries. The same is true in the increased acidity accompanying nausea and vomiting of pregnancy. Impaction of course particles of fermentable foods, in their opinion, is the chief factor.
the daily loss becomes very small, and a balance can be maintained on this very low level for a time before death. In mild cases McRudden advises good hygienic measures. He advises concerning the dangers of rapidly-recurring pregnancies. In cases in which sterilization seemed advisable, he recommended artificial menopause by x-rays rather than by surgery.

Maxwell and coworkers have written several articles about osteomalacia in China. Maxwell and Miles (74) wrote that the incidence of osteomalacia in certain districts of China showed diets of mothers afflicted with the disease to be deficient in calcium, phosphorus and vitamin D. The symptoms of the disease are pain in the lumbar region and thighs, aching in character, coming and going, better some days than others, worse in winter than summer; bone tenderness, especially over the lower ribs and pelvic girdle; alterations in long bones, resulting in coxa vara or irregular curvatures. Fractures were not a marked feature of their cases. Osteomalacic pelves are, if very severe, very distorted with great narrowing of the birth canal, the sacrum becoming convex backward, the acetabula carried inward, the symphysis outward, the descending rami of the pubis and the ascending rami of the ischii tending to
approximate. The chest tends to become barrel-shaped. There is inflammation about the alveolar edge of the gums, not due to pyorrhea. Although the teeth are not directly affected, they become loose and drop out due to the involvement of the jaw bones. Tetany is very common. In the history of an osteomalacic patient the clinical course of the disease may be found to be more or less similar to the following: first pregnancy, normal; second, pain during the last few months, but normal labor; third, pain as early as the third month, labor requiring craniotomy or forceps delivery; fourth, pain more severe during pregnancy, labor requiring a difficult craniotomy or caesarian section at the time of parturition. After treating patients with the disease Miles and Feng (82) concluded that the deficiency producing the disease was primarily one of vitamin D although there was often an associated calcium deficiency. In a discussion of "Osteomalacia and Diet" Maxwell (71) stated that the daily intake of calcium of the poorer Chinese was often only 0.1 to 0.2 grams, and early in pregnancy the calcium concentration was only about 8 mg.%. In these patients tetany regularly developed at term, the calcium concentration decreasing to an average of 3.5 mg.%. Calcium deficiency in the
mother was conducive to the development of fetal rickets. Maxwell stated that the low serum calcium illustrates the breakdown of the parathyroid compensatory mechanism. A summary of cases gave the impression that the etiology was primarily a deficiency of dietary calcium, for the patients had all been living in the sunshine. A rapid improvement on the addition of vitamin D is only observed if vitamins A and C are included in the diet, while excess cereal appears to exert an adverse influence. In a report from the Peiping University Medical College Hospital the osteomalacic patients improved somewhat with the administration of large quantities of calcium, but it was only when vitamin D was added that real improvement began, both in blood figures and condition of the patient. Maxwell doubts if the calcium, phosphorus imbalance has any relation to the parathyroid gland. The administration of parathormone to these patients damages rather than improves them, although the blood calcium may rise to high figures. Moehlig (87) writes that the clinical symptoms of osteoporosis are severe pains in the extremities, backache and frequent headaches. Weakness with lack of power as well as pain often incapacitates the patient. Advanced cases usually have swelling of the extremities. Symptoms
are present four or five years before x-ray demonstrates the osseous changes; this fact often leads to the diagnosis of neurosis. In the case of the patient cited by Moehlig there was a high incidence of familial diabetes, obesity, tallness and cardio-vascular-renal disease. It is suggested that pituitary gland function could explain the metabolic factors present in the disease. Evidence shows that carbohydrate metabolism affects calcium metabolism and deposition of calcium in the tissues. Carbohydrate metabolism disturbances lead to calcium metabolism disturbances with consequent skeletal changes, and deposits in soft tissues associated with diabetes and atherosclerosis may be understood to be due in part to a calcium disturbance associated with a disorder of carbohydrate metabolism.

There are several references in the literature to the relationship of calcium deficiency in pregnancy to the occurrence of toxemias of pregnancy. Among the first to propose the theory that eclampsia is due to calcium deficiency was Mitchell (86) in 1910. He states that eclampsia occurs once in 500 pregnancies. He describes the symptoms of eclampsia to be the symptoms of tetany plus coma. He noted that in Fort Worth, Texas, where eclampsia is prevalent, the city water supply con-
tains no calcium salts. Drennan (2) wrote that the pathological changes in the liver in eclamptics may be due to the abstraction of calcium from the maternal organism by the fetus, that calcium which would normally unite with neutral fat in the liver cells to form lipoids and be removed to natural deposits. Linot and Cutler (84) noted the resemblance between the clinical pictures of eclampsia and toxemia of acute hepatic injury in dogs, and studied the guanidine content of the blood of eight patients with pre-eclamptic toxemia and four with true eclampsia. Granidine was found to be increased in every case. This observation, and the association of hepatic lesions with eclampsia, suggested the employment of calcium therapy, which has been found to act in an essentially specific manner in the prevention and control of symptoms and biochemical manifestations of acute hepatic injury. These authors found prompt and striking relief from the urgent symptoms in eclampsia and pre-eclamptic patients following the intravenous injection of 10 c.c. of 10% solution of calcium gluc- onate, repeated if necessary. The guanidine concentration was unaffected, but the blood sugar which had been previously low, rose to normal. The pharmacological calcium effect usually occurred within 15 to 20 minutes.
after the intravenous injection of calcium salts. In fulminating cases, in addition to the above dosage, 10 to 20 c.c. of 10% calcium gluconate were given intramuscularly with 20 to 30 units of parathormone. The intravenous injections were repeated at four to six hour intervals if necessary, the intramuscular injection at six to eight hour intervals, and the parathormone injections at eighteen to twenty-four hour intervals. There was little or no danger of hypercalcemia from parathormone in this dosage, but the serum was checked daily. Oral administration of calcium is usually impossible in severe cases. Lopez (63) found that the administration of parathormone in eclamptic and pre-eclamptic patients produced excellent results within a few hours, complete cessation of convulsions, relief from headache and dizziness, improvement in eyesight, loss of muscle cramps and drop in blood pressure. The pharmacological calcium effect is ordinarily produced in four to ten hours after the administration of parathormone, but in these cases the calcium in the blood did not show an appreciable increase after the use of the parathyroid extract. Guthmann and Schol (39) recommended the routine use of systematic ultra-violet irradiation during pregnancy, believing that the develop-
ment of osteomalacia and tetany is prevented and the incidence and severity of eclampsia may be diminished. Ross and coworkers (105) noted patients with eclampsia to be in a poor state of nutrition. In the same areas in which eclampsia occurred most frequently, they also found a large percentage of pellagra and similar diseases. Diets deficient grossly in vitamins and minerals were common. They observed that toxemias are most frequent in the uninformed, improperly-nourished, medically-inarticulate group. Hartley (44) wrote an article, entitled, "The Tetanoid Syndrome in Obstetrics." He states that maternal tetany is rare as a frank tetany, but tetanoid manifestations are commonly observed: nervous hyperexcitability, cramp-like pains in the legs, irritability of disposition, insomnia, transitory edema and paresthesias of the extremities. He has observed striking relief following the administration of parathormone, thirty to fifty units at three to five-day intervals in combination with calcium salts orally or intravenously. He did not find that the blood calcium level consistently corresponded to the clinical findings; however, in the more severe cases it was definitely below normal. Symptoms occurred in some in whom the blood calcium was normal.
Clinical improvement lagged behind the speedy adjustment of calcium, and he concluded that the serum calcium estimation does little more than form a partial criterion for judging the state of the mineral metabolism.

Throughout this paper there have been occasional references to various author's opinions concerning calcium prophylaxis and therapy in pregnancy and in its complications based on calcium deficiency. Other views on calcium therapy will follow. In 1923 Park (96) wrote: "Personally, I believe that if pregnant women received ample, well-balanced diets, in which green vegetables were abundantly supplied and cow's milk was regularly taken, and they were kept a sufficient part of their time in the open air and sun, and their infants were placed in the direct rays of the sun for a part of each day and were fed codliver oil for the first two or three years of life, more could be accomplished with regard to the eradication of caries of the teeth than in all other ways put together, and that rickets would be abolished from the earth." The next year Jansen (56) studied blood calcium changes in the normal human subject after feeding various calcium salts and noted an increase which varied with the salt employed. He found that calcium bicarbonate was the
most serviceable of the calcium salts for inducing an increase in the serum calcium in man. By experimenting with varying sizes of oral dosage of calcium lactate in ten patients, Kahn and Roe (58) concluded that the five-gram dose produced the optimal retention. They declared their disagreement with many authors that blood calcium cannot be increased by the oral administration of calcium salts. Cantarow (28) found that the solubility of calcium is favored by high-acid reaction of the gastric contents, and advised that calcium salts should be administered one to one-and-one-half hours before meals. Greenberg and Gunther (38) found no difference in the efficiency of inducing increases in serum calcium with any of the soluble calcium salts. The rise was proportional to the calcium content of the dose, so on the weight basis, there was an advantage in compounds of lower molecular weight. A two-gram dose of calcium corresponded to seven grams of the chloride, eight grams acetate, eleven grams lactate, and twenty-two grams gluconate. The two grams of calcium increased serum calcium 1.5 mg%, an augmentation of 15%. Bernheim (11) advised the use of one quart of milk or one-fourth pound of cheese per day to supply from 0.7 to 1.0 gram of calcium. The same supply
could be derived from the use of five grams of calcium lactate or ten grams of calcium gluconate. Schmidt and Greenberg (107) advised the use of two grams of calcium per day in the diet plus viosterol to reduce the incidence of dental caries during lactation. Orr (94), considering the financial aspect of calcium prophylaxis, contended that to supply calcium as the lactate is much more expensive than milk without providing any of the additional nutritional value. According to Aub (4) one gram of calcium is yielded from one quart of milk, 11.2 grams of the gluconate and 7.7 grams of the lactate. When the absorption of large quantities is desired, an adequate intake of vitamin D facilitates calcium absorption. Best and Taylor (12) write that it is impossible to maintain the calcium level above normal by the administration of calcium salts. After ingestion of large doses of soluble calcium salts, the serum calcium level rises to its maximum in two hours, and is normal again three hours later. In Martin's (68) series of forty cases in which he supplemented diets with minerals and vitamins in comparison with a control group, he felt that he could draw no positive conclusions. However, his findings did indicate the value of adequate minerals and vitamins in the prevention of antepartum
SUMMARY

1. A positive calcium balance during pregnancy is entirely consistent with moderate hypocalcemia. The efficiency of calcium utilization in pregnant women may depend on a serum calcium concentration below the accustomed level.

2. Hyperplasia of the parathyroid glands accompanies pregnancy, coincident in many cases with a lowered serum calcium. There may be an anti-hormone present during pregnancy which limits overactivity of the parathyroids.

3. The calcium requirement of gravid women is greater than in the non-gravid, especially during the last three months of gestation when the fetal increment is the greatest.

4. Adequate calcium in the diet, or a diet supplemented with inorganic calcium compounds are beneficial in maintaining calcium balance.

5. Vitamin D increases the absorption and utilization of calcium to the extent of the requirements, but does not promote the retention of any marked excess.

6. An acid reaction in the upper intestinal tract increases absorption of calcium, but diets with basic residues seem to facilitate better utilization of
calcium in the tissues.
7. There is an intimate relationship between calcium and phosphorus in metabolism, but definite quantitative ratios of the two in the diet are not necessary for favorable absorption.
8. Deficiencies of calcium supply to the fetus during the formative period of the deciduous teeth in utero produce hypoplastic enamel, subject to decay.
9. Fetal rickets develops most frequently in children of osteomalacic mothers on calcium-deficient diets.
10. Pregnancy per se cannot be considered to be the cause of dental caries in women. Metabolic conditions may be a factor.
11. Frequent, rapidly-repeated pregnancies without adequate calcium intake produces osteomalacia in the mother.
12. Calcium salts and parathormone may be used with advantage in the treatment of toxemias of pregnancy.
13. High-calcium diets during pregnancy, supplemented with calcium salts and vitamin D are desirable, for they increase the general well-being of the patient and prevent losses from her calcium reserves.
BIBLIOGRAPHY


20. Bomskov, C., and Bremm, H., quoted by Bodansky and Duff (17).


60. La Mer, V.K., Proc. Am. Assoc. for Adv. of Science, Syracuse University, June 23, 1932. Quoted by Cantarow (23).


