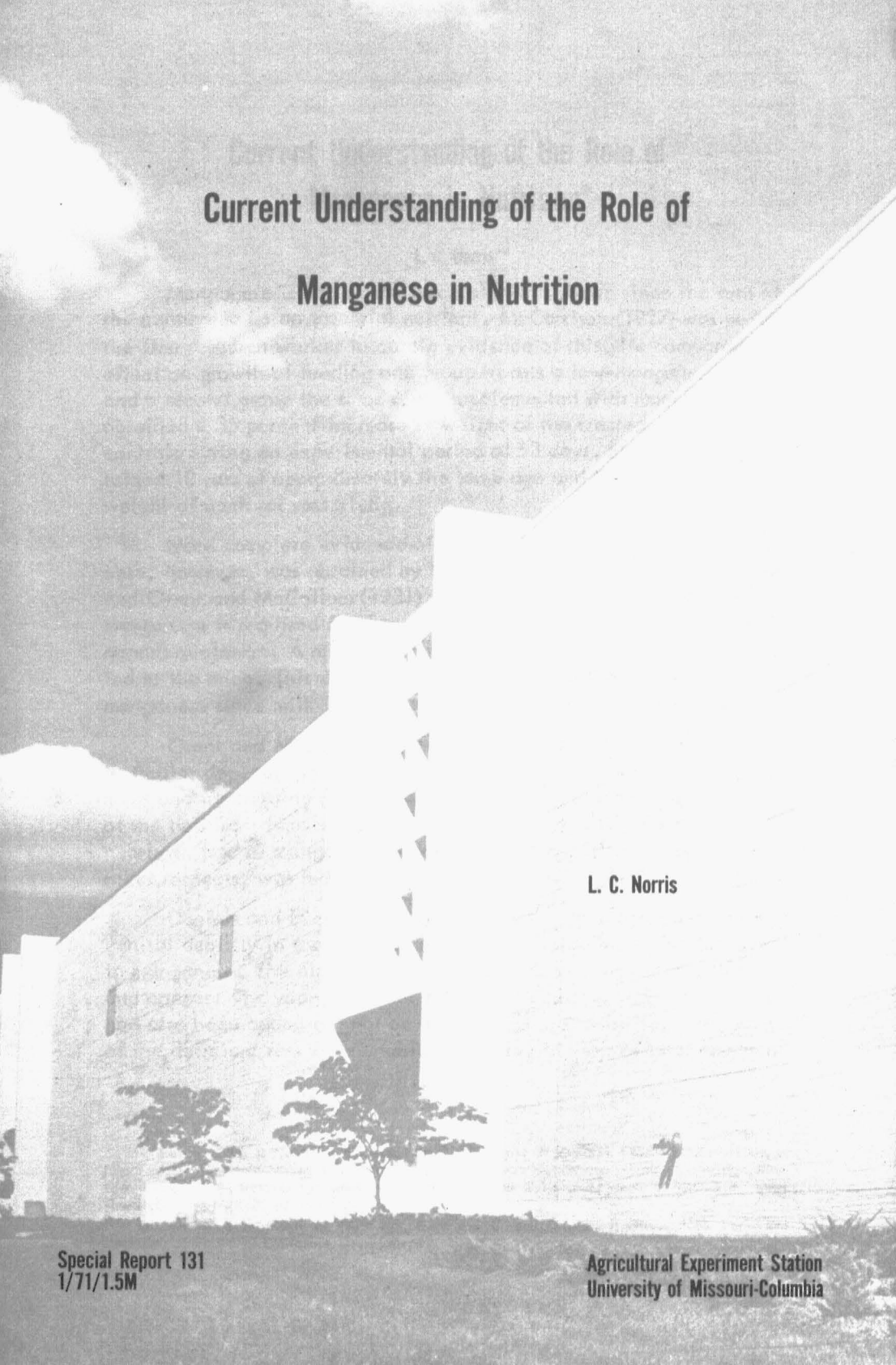
Current Understanding of the Role of Manganese in Nutrition



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Special Report 131
1/71/1.5M

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Manganese is one of the trace elements shown since the turn of the century to be an essential nutrient. McCarrison (1927) was perhaps the first research worker to obtain evidence of this. He compared the effect on growth of feeding one group of rats a low-manganese diet and a second group the same diet, supplemented with manganese, and obtained a 35 percent increase in weight of the treated rats over the controls during an experimental period of 53 days. Each group contained 10 rats of approximately the same age and the average initial weight of each rat was 51.5g.

More complete evidence of the nutritive essentiality of manganese, however, was obtained by Kemmerer, Elvehjem, and Hart (1931) and Orent and McCollum (1931). The former investigators showed that manganese is required for the growth of mice and the maintenance of normal ovulation. A milk diet supplemented with iron and copper was fed to the mice. This diet was ideal for studying the requirement for manganese since milk is greatly deficient in this trace element.

Orent and McCollum (1931) found that manganese prevents testicular degeneration in male rats and promotes the normal development and functioning of mammary tissue. Without manganese the young of the deficient female rats failed to suckle. A purified diet, made nearly as free of manganese as possible, but nutritionally complete in other respects, was fed the rats.

Daniels and Everson (1935) reported the development of congenital debility in the newborn rats of dams supplied a diet deficient in manganese. The diet fed the rats was milk supplemented with iron and copper. The young of other rats fed the milk to which manganese had also been added did not develop congenital debility. The young of the deficient rats were unable to suckle. In view of later research

* A lecture given at Nutrition Emphasis Week, University of Missouri, February 19-21, 1969, in honor of Dr. Albert G. Hogan, the University's great research worker and pioneer in nutrition, longtime friend of the lecturer and associate in activities of the National Academy of Sciences-National Research in the field of nutrition.

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work, this was perhaps due to imperfect bone formation during uterine development.

The results of these investigators, while they demonstrate that manganese is an essential nutrient, do not agree in many respects as to the symptoms caused by a deficiency of the mineral. This may have been caused by differences in species of experimental animals, strain of rats, storage of manganese in the tissues of the dams, composition of experimental diets and perhaps also environmental conditions.

By a fortunate train of circumstances, Wilgus, Norris, and Heuser (1936, 1937b) showed that perosis in chicks is caused by manganese deficiency. The gross symptoms of perosis were curvature and lateral rotation of the leg bones at the hock joint with slipping of the Archilles tendon from the condyles of the tibiotarsus in one or both legs (Plates 1, 2 and 3). Because of the latter symptom perosis was frequently called "slipped tendon." The deformity was described first by Payne (1930) and was the cause at the time of serious losses in the expanding broiler industry. It was designated perosis by Titus (1932) because of the crippling nature of the leg bone deformity.

Payne, Hughes, and Lienhardt (1932) reported that the general use in chick diets of feedstuffs containing large quantities of calcium and phosphorus from bone, was the major factor in the development of perosis. In attempting to find means of preventing perosis, Wilgus, Norris, and Heuser (1937a, 1937b) studied the effect of different phosphate sources and various calcium compounds on the development of perosis. In the course of this work they found that a supply of technical mono-calcium phosphate significantly reduced the incidence of perosis, whereas, reagent-grade mono-calcium phosphate was completely ineffective, and in addition confirmed the observations of Payne, Hughes, and Leinhardt (1932).

On subjecting the technical mono-calcium phosphate to spectographic analysis for contamination with other minerals, Wilgus, Norris, and Heuser (1936, 1937b) found that it contained traces of manganese, zinc, aluminum, and iron. The basal diet used in the previous research was then supplemented with these minerals but only manganese had any marked effect in reducing the incidence and severity of perosis. Moreover, the addition of manganese to the reagent grade mono-calcium phosphate made it as effective as the technical grade in preventing perosis. In all comparable treatments the diet contained the same quantities of calcium and phosphorus. Some of the results, showing the effectiveness of manganese in reducing the incidence and severity of perosis are given in Table 1. The results of Wilgus, Norris, and Heuser (1936, 1937b) were confirmed by Wiese and co-workers (1938).

Lyons and Insko (1937) observed that manganese prevented the development of chondrodystrophy in chick embryos. The chondrodystrophy was characterized chiefly by shortened and thickened legs, shortened wings, and globular contour of the head. This type of chondrodystrophy was found by Byerly and associates (1935) to be prevented by including either wheat germ and liver or wheat germ and whey in the diet of hens. The findings of Wilgus, Norris, and Heuser (1936, 1937b) and those of Lyons and Insko (1937) provide the first evidence that manganese is needed for normal bone formation. Evidence that manganese is needed for reproduction in chickens is also revealed by the research of Lyons and Insko (1937) and by that of Gallup and Norris (1937).

More precise evidence of the need for manganese in bone formation was obtained by Gallup and Norris (1938) and Caskey, Gallup, and Norris (1939). These research workers measured the length of the tibiae, metatarsi, and femura of chicks of comparable weight, fed diets adequate and deficient in manganese, from day-old to six weeks of age and found that a significant reduction in bone length resulted from manganese deficiency. A lack of manganese, therefore, causes a type of micromelia. Illustrations of the reduction in bone length, caused by manganese deficiency are presented in plate 4 and results of measurements of the tibiae and metatarsi of day-old chicks and of the femura of chicks 2, 3, and 4 weeks of age are given in Tables 2 and 3. Significant reduction in the ash of fat-free dry femura was also obtained by Caskey, Gallup, and Norris (1939). These results are given in Table 4.

The effect of manganese deficiency on the skeletal development of the chicks of hens fed a diet deficient in this mineral was found by Caskey and Norris (1940) to be incurable. These research workers fed the micromelic chicks of these hens a diet adequate in manganese from day-old until maturity and compared the dissected bones of these hens with those of normal hens of the same weight and breed. All of the bones of the micromelic hens except the metacarpus and the sternum were found to be significantly reduced in length. The sternum, presumably because little or no calcification occurs during embryonic development, is not affected by manganese deficiency during this phase of growth. The effects of manganese deficiency in the maternal diet on bone development in chicks at day-old and at maturity are illustrated in plates 5 and 6 and the results of the bone measurements are presented in Table 5.

Wiese and co-workers (1939) reported that the blood and bone alkaline phosphatase of chicks was reduced in manganese deficiency. The following year Wiese and co-workers (1940) presented evidence

that maximum alkaline phosphatase activity was located in the extreme ends of the bones of chicks where growth in length is most rapid. The proximal ends of the bones had a higher phsophatase activity than the distal ends. The results of Wiese and co-workers (1939) were confirmed by Combs, Norris, and Heuser (1942) who showed in addition that the reduced bone alkaline phosphatase activity in manganese deficiency in chicks was correlated with a reduction in ash of fat-free, dry tibiotarsi. The results of the latter investigators are presented in Table 6.

Manganese also has been found by Boyer, Shaw, and Phillips (1942) and Shils and McCollum (1943) to be required for the activity of arginase. These investigators showed liver arginase was lower in the livers of manganese-deficient rats than in the livers of normal rats. More recently Leach (1969) has found that manganese is required for the activation of two other enzyme systems in the bones of chicks. One is concerned in the synthesis and polymerization of chondroitin sulfate, an important mucopolysaccharide in bone, and the other in the formation of the bridge linking bone mucopolysaccharides with the serine groups of bone collagen.

The need for manganese in bone formation, reported by Gallup and Norris (1938) and Caskey, Gallup, and Norris (1939), was confirmed by Shils and McCollum (1943) using the rat as the experimental subject. Also in research with rats paired as to growth, Amdur, Norris and Heuser (1945) obtained reduced length of tibiae, bone density, breaking strength of femurs and bone alkaline phosphatase on feeding a manganese deficient diet. No difference in percentage ash in fat-free dry bone, however, was observed. The results of this research are presented in Table 7.

Hurley and associates (1961) have shown likewise that manganese deficiency promotes decreased length of long bones in rats. In this research male and female rats were paired in length rather than in weight. The results are given in Table 8.

In the rabbit, Smith, Medlicott and Ellis (1944) reported that manganese deficiency caused the development of greatly deformed front legs, testicular degeneration and decreased density, length and ash content of humeri and reduced breaking strength of ulnae. The results of these observations are presented in Table 9. In later research using the paired feeding technique Ellis, Smith, and Gates (1947) found that the manganese content and arginase activity of the liver and the alkaline phosphatase activity of the ulnae were reduced in manganese deficiency in the rabbit. The diet fed the rabbits in the research of these investigators was cows' milk enriched with 10 percent

whole milk powder.

Miller and associates (1940) observed a characteristic stiffness in swine, first revealed by a slightly halting gait but which progressed in severity until the pigs could not rise to their feet. Gross symptoms in addition to the stiffness were enlarged hock joints and crooked legs. This occurred in some pigs which never became stiff. The pigs were fed individually indoors but had direct access to sunlight in outdoor paved pens. The stiffness was first observed in pigs fed diets containing 6 to 9 percent minerals. Supplementing the diet with manganese prevented the development of the stiffness but in later work by Keith and associates (1942) manganese was found to be ineffective in curing stiffness which had already developed.

The results of these research workers were not confirmed until those of Plumlee and associates (1956) were reported. These research workers fed weaned female pigs throughout the growing, gestation, and lactation periods on diets containing either 0.5 mg of manganese per kg or 40 mg per kg. The low manganese pigs at the termination of the experiment showed reduced skeletal growth, muscular weakness, and irregular estrual cycles, with complete absence of estrus in some animals. Resorption of fetuses or birth of small, weak pigs which could not stand or walk normally was observed.

In a later report Neher and associates (1956) presented further evidence of the effects on manganese deficiency in swine. They obtained lameness in manganese deficiency, as previously observed, and emphasized, in particular, decrease in bone length in the forelegs and the hindlegs, thickening of bone in the carpal and tarsal areas, and marked bowing of the legs in many animals, even when at maturity the lameness had disappeared. The lipotropic action of manganese observed earlier in rats by Amdur, Norris and Heuser (1946) was demonstrated by the excessive obestity in the manganese-deficient pigs and by the increased fat deposition in the bones.

Evidence of manganese deficiency in cattle is not as striking as that for the other species already discussed. Bentley and Phillips (1951) found, however, that heifers grown on a low-manganese ration grew normally but were slower to exhibit estrus, slightly and persistently slower to conceive, and had a greater number of calves born with weak legs and pasterns at first calving. A picture of a calf, showing typical weak pasterns, is presented in plate 8. On certain sandy and peat soils in the Netherlands, Grashuis and associates (1953) showed that manganese supplementation of the ration or treatment of the pastures with manganese corrected poor growth and body development in calves, leg deformities with

overknuckling, poor fertility, and frequent abortion. Hair coat was also improved.

Hawkins and coworkers (1955), on feeding calves experimental diets containing 1.0 to 1.17 mg manganese per kg, found that by supplementing with manganese the growth depression obtained with mono-calcium phosphate and the reduced blood alkaline phosphatase were partially counteracted. Manganese supplementation also increased life span but mortality on the experimental diet was 100 percent at 244 to 327 days.

A form of ataxia, characterized by head retractions and other head movements in chickens and somewhat similar spasms in mammals, accompanied by failure of the righting mechanisms, is frequently observed in manganese deficiency. The ataxic condition was first observed by Caskey and Norris (1938, 1940) in newly hatched chicks of hens fed a manganese-deficient diet. The ataxic chicks showed opisthotonic and emprosthotonic spasms. Pleurothotonic spasms were also observed. Although the ataxia was limited to the chicks of the manganese deficient hens, the incidence was not entirely convincing, since Knowlton (1929) had observed a similar ataxic condition in chicks assumed to be caused by a simple Mendelian recessive. Therefore, Caskey, Norris, and Heuser (1944) studied the hatchability of the eggs of manganese-deficient and normal hens during a three-year period and determined the percentage incidence of ataxia in the chicks of both groups of hens and the hatching rate. Results of these experiments are presented in Table 10. In the second year's experiment only one chick of the hens supplied a diet adequate in manganese out of a total of approximately 1260 chicks hatched showed any signs of ataxia. Other than this, all of the taxic chicks were observed in the chicks of the manganese deficient hens.

Caskey, Norris, and Heuser (1944) reared some of the ataxic chicks to maturity and mated them to normally-fed males. From the 81 normal eggs incubated, 57 chicks were obtained, none of which showed any symptoms of ataxia. The results of this study are given in Table 11. The ataxia in chicks, first observed by Caskey and Norris (1938, 1940) was thus demonstrated to be caused by manganese deficiency.

Following the research showing that manganese deficiency is the cause of ataxia in chicks, Shils and McCollum (1943) reported the development of loss of equilibrium, loss of righting reaction, rotational movements, incoordination, and ataxia in newborn rats as a consequence of manganese deficiency in the maternal diet. The observation that manganese deficiency in the maternal diet causes the development of ataxia in the newborn young was confirmed by Hill and associates (1950). These research workers raised rats through four generations on

a diet supplying only 0.03 mg of manganese per day and observed ataxia and disturbance of equilibrium that appeared earlier in each successive generation. Hurley, Everson, and Geiger (1958) also showed that ataxia developed in the viable young of manganese deficient rats. Some of the results of these investigators are given in Table 12.

Plumlee and associates (1956) observed ataxia in newborn pigs of dams fed a low-manganese diet. This was manifested by incoordination, turning in circles, poor balance, and carrying the head sidewise. A picture of piglets showing the ataxic condition is presented in plate 8. Everson, Hurley, and Geiger (1959) fed guinea pigs a pelleted, low-manganese diet throughout growth and first, second, and third gestations. Litter size as a consequence was reduced, a high percentage of the young were born dead or prematurely, and all the living young showed ataxia which still persisted after three months. The results of the experimental work are presented in Table 13.

With the exception of the chick, the ataxic condition in the experimental animals was accompanied by an upset in the "righting mechanism" or sense of balance. The first evidence of the cause of this was obtained by Hurley and associates (1960). Later Erway, Hurley, and Fraser (1966) showed the offspring of manganese-deficient mice also developed ataxia and that the ataxic condition was caused by defective development of the otoliths which are necessary for the maintenance of the righting mechanism. Otoliths are sensitive, gelatinous areas with an external single layer of calcium carbonate crystals, located on the walls of the vestibule of the inner ear adjacent to the terminus of the vestibular nerve. Sections of the inner ear of a mouse showing normal otoliths in the left vestibule of the inner ear and otoliths lacking in the right are presented in plate 9. Shrader and Everson (1967) have also found that manganese deficiency in guinea pigs causes defective otolith formation and defective otoliths have been found in manganese deficient chicks by Hurley, Grau, and Erway (1969).

The histopathology of the malformed bones that develop in chicks, fed a diet deficient in manganese has been studied by Nielsen (1942). He concluded that the epiphyseal cartilage is the seat of the changes which cause the retarded growth of bones in length and for the bone deformity observed in perosis in chicks. Wolbach and Hegsted (1953) reported that perosis is the result of retardation of the normal growth sequences of epiphyseal cartilage and the retardation or suppression of endochondral bone growth but that osteogenesis was not affected. They concluded that the changes in epiphyseal cartilage in manganese and choline deficiencies were almost exactly alike.

Leach (1968) observed that in the manganese deficient chick the width of the epiphyseal plate and metaphysis was greatly reduced. This appeared to be caused by impairment of matrix formation rather than cell proliferation. He concluded that the changes in the epiphyseal plate are specific for manganese deficiency since deficiencies of choline, niacin, folic acid, biotin, and zinc do not cause the severe reduction in the formation of extracellular matrix that occurs in manganese deficiency. Leach, therefore, differed with Wolbach and Hegsted (1953) in regard to the similarity of the histopathology of manganese and choline deficiency. Sections of the epiphyseal growth plate of the tibiotarsus of normal and manganese deficient chicks, stained with hematoxylineosin, are presented in plate 10.

The biochemistry of the effect of manganese deficiency on bone development has been studied by Leach and Muenster (1962). The investigators found that a deficiency of manganese results in a marked reduction in the mucopolysaccharide content of chick epiphyses. Most of the reduction occurred in the mucopolysaccharide containing galactosamine. Similar effects were observed in other portions of bone. The effects were not related to food intake or choline content of the diet. Some of the results of Leach and Muenster (1962) are given in Table 14. The findings of these research workers have been confirmed by Tsai and Everson (1967) who reported that in manganese deficiency in guinea pigs the hyaluronic acid, chondroitin sulfate A and C, and the heparin content of dry, fat-free epiphyseal cartilage were reduced. A summary of their results is given in Table 15. Hurley (1967) also obtained evidence in studies with manganese deficient rats of a significant reduction in the hexuronic acid, glucosamine and galactosamine content of the dry, epiphyseal cartilage of rat bones. The results of these studies are given in Table 16.

The requirement of man for manganese has not yet been demonstrated by direct experimentation. It is obviously essential, however, in view of the number of animal species whose nutritive requirements are similar to those of man. These species have been shown to require manganese for growth and reproduction and in particular for normal bone development, for the prevention of ataxia, caused by defective otolith formation, for the activation of certain essential enzymes, and for other metabolic functions.

The most definite evidence that human beings require manganese is perhaps that of Comens (1956, 1960). He treated two patients afflicted with disseminated lupus erythematosis and three patients with hydralizine disease, an ailment similar to disseminated lupus erythematosis, and obtained apparent symptomatic improvement by administering manganous ion. The administration of hydralazine was continued

in the patients suffering from hydralazine disease during treatment with manganese. Comens (1956, 1960) also found that hydralazine caused the development of perosis in 10 day-old cockerels by giving them 10 mg of the drug per day. No perosis developed in another group of cockerels supplied the drug together with 5 mg of manganese citrate per day. Comens (1956, 1960) suggested that hydralazine, since it is a chelating agent, bound manganous ion, thus possibly blocking its functions in essential enzyme systems.

Borg and Colzias (1958) presented evidence that manganese is present in human erythrocytes, presumably as a manganese porphyrin. This presumption was based on the inability following intravenous injection of ^{54}Mn to obtain a fall in the radioactivity per unit weight of hemin after successive recrystallizations. Because of these results Borg and Cotzias (1958) suggested that manganese may have a role in the porphyrin metabolism of cells. Cotzias and Bertinchamps (1960) concluded that manganese is carried in human plasma by a B_1-globulin, designated transmanganin, which does not bind iron but which is specific for manganese.

Another intriguing development which suggests another role of manganese in nutrition, including human nutrition, has recently been reported by Everson and Shrader (1968) and Shrader and Everson (1968). These research workers found that young adult guinea pigs subjected to manganese deficiency during pre-natal and post-natal growth showed decreased utilization of glucose and in consequence had a diabetic-like glucose tolerance curve in response to glucose loading. The glucose tolerance curve obtained by these research workers is given in Figure 1. Histopathological examination of the pancreas of deficient guinea pigs, both newborn and young adult, revealed a marked hypoplasia in some instances. Where this occurred, islet population was reduced and the islets contained fewer and less granulated beta cells. Supplementation of newborn manganese-deficient guinea pigs with manganese for two months promoted normal responses to glucose loading and an increased number of more heavily granulated beta cells than observed in the islets of the pancreas of deficient guinea pigs.

The effects of manganese deficiency on glucose utilization in guinea pigs and on pancreatic development are similar in many respects to diabetis mellitus in human beings. No conclusion, however, can be made, that manganese deficiency is involved in the development of diabetes mellitus, on the basis of similarity of symptoms, but this does indicate, along with the results of the other work on the possible role of manganese on the well-being of mankind, the great need for an enhanced research program on the requirement of human beings for manganese.

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APPENDIX

Table 1 - Discovery of Perosis-Preventing Property of Manganese

Treatment	Ca %	P %	Wt. at 6 wk., g	Perosis %	Severity %
	* Low Ca-P diet				
Basal diet[1]	0.97	0.78	487	87	21
150 mg Mn/kg	0.97	0.78	501	27	6
25 mg Mn/kg	0.97	0.78	503	19	2
	High Ca-P diet				
$Ca(H_2PO_4)_2 \cdot H_2O$, cp	1.21	1.17	442	94	32
$Ca(H_2PO_4)_2 \cdot H_2O$, tech	1.21	1.18	455	40	7
$Ca(H_2PO_4)_2 \cdot H_2O$, cp + 25 mg Mn/kg	1.21	1.17	440	25	6

[1] Contained 9-12 mg Mn/kg

Wilgus, Norris and Heuser 1936, 1937b

Table 2 - Effect of Manganese Content of Maternal Diet on Embryonic Bone Development

Mn in diet, mg/kg	Chicks[1], no/group	Tibia length, mm	Difference, %	Metatarsus length, mm	Difference, %
13	16	26.0		18.7	
			12.5		14.2
53	6	29.7		21.8	
13	12	27.4		19.7	
			13.1		15.1
200	25	31.5		23.2	

[1] New Hampshire, day-old

Caskey, Gallup and Norris 1939

Table 3 - Effect of Manganese on Development of Chick Femurs

Mn in diet mg/kg	Chicks,[1] no./group	Average weight g	Femur length, mm	Difference %	P<
		Age 2 weeks			
5.5	11	120	33.8	1.8	0.1
100	11	119	34.4		
		Age 3 weeks			
5.5	11	173	38.0	7.5	0.01
100	11	173	41.1		
		Age 4 weeks			
5.5	9	223	42.3	8.7	0.001
100	9	222	46.4		

[1] Rhode Island Red

Caskey, Gallup and Norris, 1939

Table 4 - Effect of Manganese on Ash Content of Chick Femurs

Mn in diet mg/kg	Chicks,[1] no./group	Average wt g	Femur wt, g	Ash %	P<
		Age 3 weeks			
5.5	15	167	1.30	42.8	NS
100	15	180	1.37	43.4	
		Age 5 weeks			
5.5	15	268	2.10	41.7	0.01
100	15	381	2.85	44.8	
		Age 6 weeks			
5.5	15	301	2.74	40.5	0.01
100	15	448	3.77	44.4	

[1] Rhode Island Red

Caskey, Gallup and Norris, 1939

Table 5 - Effect of Embryonic Manganese Deficiency on Subsequent Bone Development of Chickens

Bone	Length, cm		Reduction in length, %	P<
	Normal[1]	Micromelic[2]		
Sternum	13.7	13.6	0.7	NS
Femur	9.14	8.15	10.8	0.01
Tibiotarsus	12.9	11.0	15.0	0.001
Tarsometarsus	8.42	6.87	18.4	0.0005
Humerus	7.84	7.30	6.9	0.01
Radius	7.08	6.30	11.0	0.005
Ulna	7.92	7.17	9.5	0.005
Metacarpus	4.24	3.90	8.0	NS

[1]Average wt, 2034 g.

[2]Average wt, 2032 g.

Caskey and Norris, 1940

Table 6 - Effect of Manganese Deficiency on Phosphatase Activity of the Chick Tibiotarsus

Added Mn mg/kg	Chicks,[1] no/group	Weight g	Severity of perosis, %	Ash %	Phosphatase units
		Age 4 weeks			
None	6	251	27.6	42.4	4.02
50	6	262	0.2	43.6	6.58
		Age 6 weeks			
None	8	421	31.5	43.9	2.57
50	8	500	0.0	45.5	6.03
		Age 8 weeks			
None	9	603	27.6	43.4	3.06
50	9	751	0.0	44.8	6.71

[1]Rhode Island Red

Combs, Norris and Heuser, 1942

Table 7 - Effect of Manganese on Bone Development of the Rat

	High Mn	Low Mn	P<
No. rats	18	18	
Final avg wt, g	204	204	
Tibia length, mn[1]	34.5	34.0	0.01
Bone density, g/ml	1.55	1.52	0.05
Strength femur, kg	9.51	7.90	0.001
Phosphatase units/ g fr. bone	15.3	13.9	0.005

[1] Avg 36 tibiae/group

Amdur, Norris and Heuser, 1945

Table 8 - Effect of Manganese on Development of Rat Leg Bones

Age days	Sex	Rats	Body length, mm	Ulna length, mm	Tibia length, mm
			Manganese supplemented		
69-94	M	12	159	26.4	33.4
87-94	F	5	146	24.7	31.4
			Manganese deficient		
200-222	M	6	162	24.8	30.6
200-236	F	9	146	23.3	28.5

Hurley and associates, 1961

Table 9 - Observations on Effect of Manganese Deficiency on Bone Development of Rabbits

Observation	Whole milk powder diet		P<
	Plus Mn	None	
Weight humerus[1], g	1.21	0.92	0.05
Density humerus, g/ml	1.04	0.82	0.01
Length humerus, mm	59.7	52.6	0.01
Ash content humerus, %	61.4	55.7	0.05
Breaking strength ulna, kg	6.16	4.11	0.05

[1] Dry, fat-free

Smith, Medlicott and Ellis, 1944

Table 10 - Incidence of Ataxia in First Generation Chicks of Hens Fed a Low-Manganese Diet

Mn in diet mg/kg	Hens[1] no/group	Fertile eggs incubated, %	Chicks hatched, %	Ataxic chicks, %
		Experiment 1, 1937-38		
6.3	12	684	45.5	8.4
50-100	42	1664	65.0	0.0
		Experiment 2, 1938-39		
6.3	13	359	45.0	11.7
35-100	56	1728	72.7	0.06
		Experiment 3, 1939-40		
6.3	20	592	66.6	2.3
35-100	87	2046	79.5	0.0

[1] Rhode Island Red

Caskey, Norris and Heuser, 1944

Table 11 - Type of Chicks Hatched from Eggs of Ataxic, Micromelic Hens

Ataxic, micromelic hens	8
Egg production, 13 week, %	43.6
Fertile eggs incubated	81
Normal chicks hatched	57
Ataxic chicks hatched	0
Micromelic chicks hatched	0
Average weight of chicks at 8 wk, g	680

Caskey, Norris and Heuser, 1944

Table 12 - Incidence of Ataxia in Normal and Manganese-Deficient Rats

Rat source	Litters no	Young born live, no	Young at 4 wk Live, %	Young at 4 wk Ataxic, %
		Normal		
1st litters	27	199	51.8	0
2nd litters	14	128	67.2	0
2nd generation	8	65	85.9	0
		Manganese-deficient		
1st litters	78	520	13.0	66
2nd litters	19	154	28.4	76
2nd generation	20	120	7.5	100

Hurley, Everson and Geiger, 1958

Table 13 - Incidence of Ataxia in Normal and Manganese Deficient Guinea Pigs

	Stock diet	Synthetic diet	
		+ Mn	- Mn
Live litters, no	19	20	17
Young born, no	63	57	43
Dead at birth, no	13	8	18
Average birth wt, g	99.2	109.7	99.4
Ataxic young, no	0	0	25 (100 %)

Everson, Hurley and Geiger, 1959

Table 14 - Effect of Manganese on Mucopolysaccharide Content of Chick Epipyseal Cartilage

Observations 20 chicks/group	Manganese, mg/kg	
	0	100
Weight, 4 wk, g	294	279
Enlarged hock, %	100	0
Severity index	2.6	0
Hexosamine content[1]		
Total, %	1.36	3.49
Glucosamine, %	0.54	0.95
Galactosamine, %	0.82	2.54
Hexuronic acid, content,[1] %	1.34	3.40

[1] Dry, lipid-free cartilage

Leach and Muenster, 1962

Table 15 - Effect of Manganese on Mucopolysaccharide Content of Guinea Pig Epiphyseal Cartilage

Uronic acid[1] content, %	Manganese, mg/kg 3.0	12.5	P<
Hyaluronic acid	0.146	0.195	0.1
Chondroitin sulfate, total	1.03	1.47	0.05
Chondroitin sulfate C	0.612	0.924	0.1
Chondroitin sulfate A	0.38	0.56	0.1
Heparin	0.07	0.126	0.02

[1] In dry fat-free tissue

Tsai and Everson, 1967

Table 16 - Effect of Manganese on Mucopolysaccharide Content of Rat[1] Epiphyseal Cartilage

Dry cartilage %	- Mn	+ Mn	P
Hexuronic acid	2.37	3.30	0.02
Glucosamine	0.17	0.23	0.02
Galactosamine	1.26	2.18	0.02

[1] Twenty-eight day old

Hurley, 1967

PLATES 1 TO 11

Color prints can be obtained at $2.00 per print from the Agricultural Editors Office, 1-98 Agriculture, University of Missouri-Columbia, Columbia, Missouri 65201.

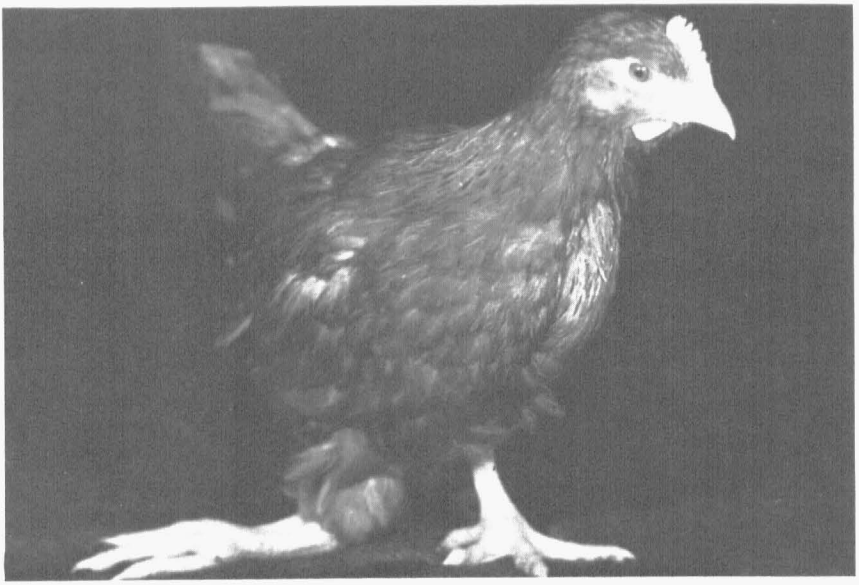


Plate 1. Perosis or "slipped tendon" caused by manganese deficiency. (Courtesy of the Department of Poultry Science, Cornell University.)

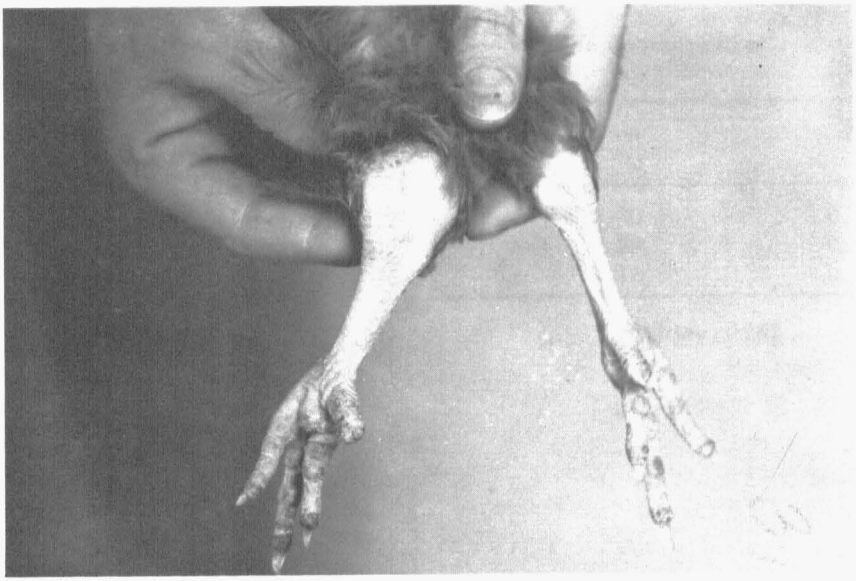


Plate 2. Back of chick leg, showing slipping of the Achilles tendon (caused by manganese deficiency) from the condyles at the distal end of the tibiotarsus. (Courtesy of the Department of Poultry Science, Cornell University.)

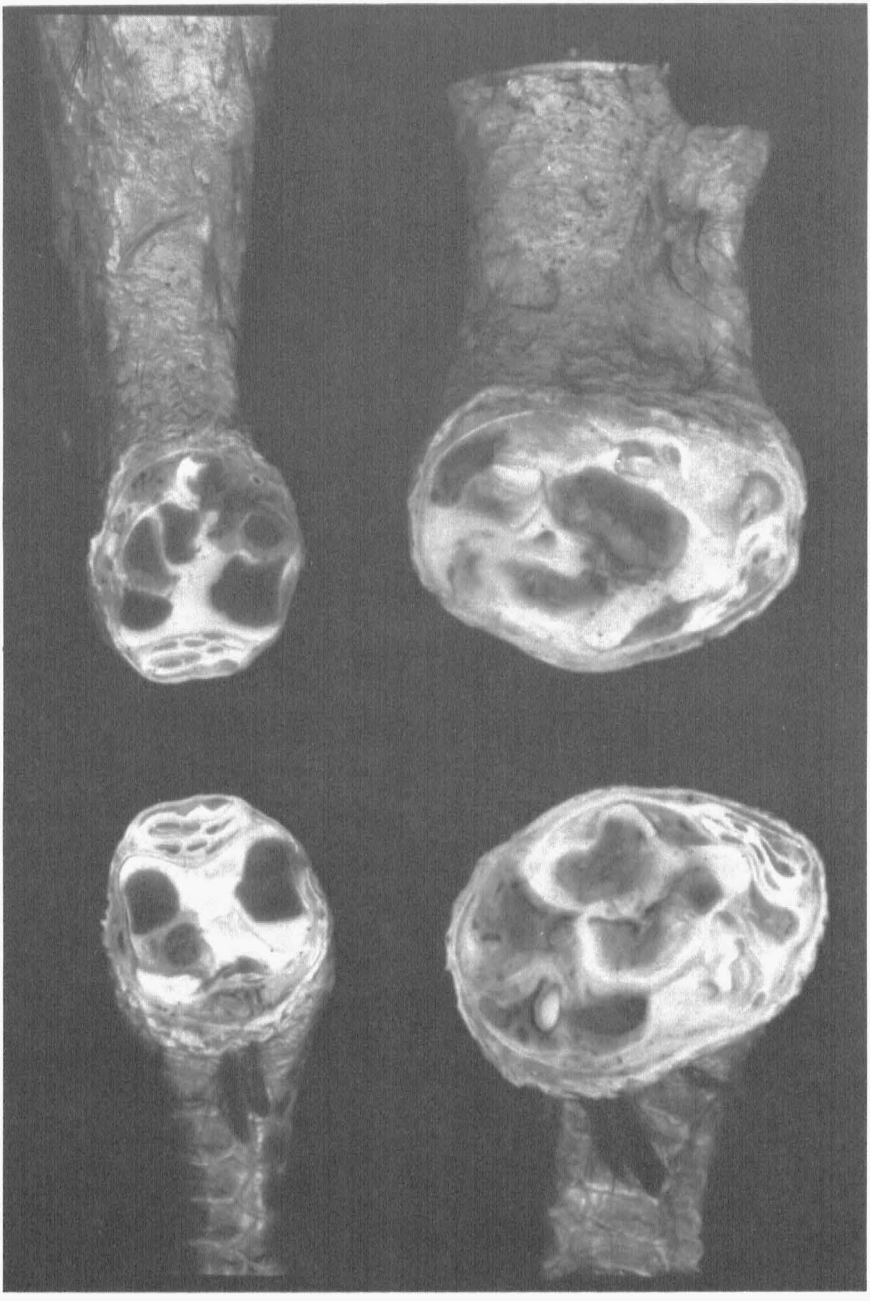


Plate 3. Cross section of a chick hock joint showing lateral rotation of the tibiotarsus at the distal end caused by manganese deficiency. (Courtesy Department of Poultry Science, Cornell University.)

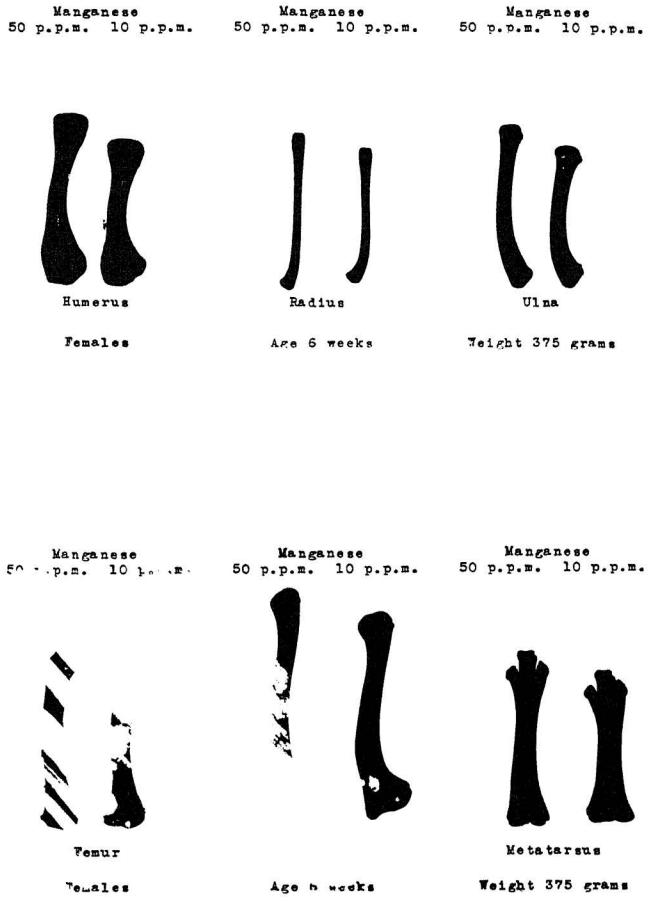


Plate 4. Retardation in the development of chick leg and wing bones due to manganese deficiency. (Caskey, Gallup, and Norris, 1939.)

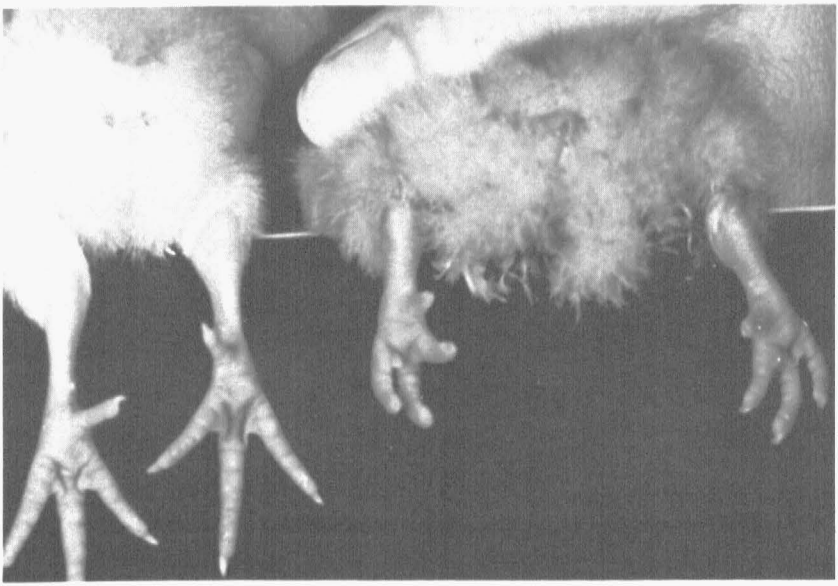
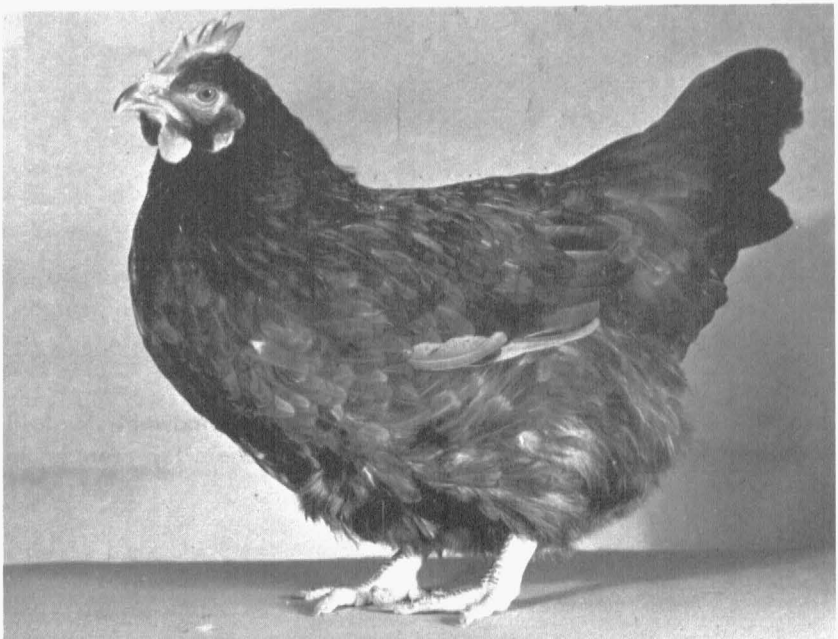


Plate 5. Newly hatched chick (right) showing extreme shortening of the legs due to manganese deficiency in the maternal diet in comparison with a normal chick (left). (Courtesy Department of Poultry Science, Cornell University.)

Plate 6. Newly hatched chick with legs shortened due to manganese deficiency in the maternal diet failed to recover by ingesting a diet adequate in manganese during growth. (Caskey and Norris, 1940.)



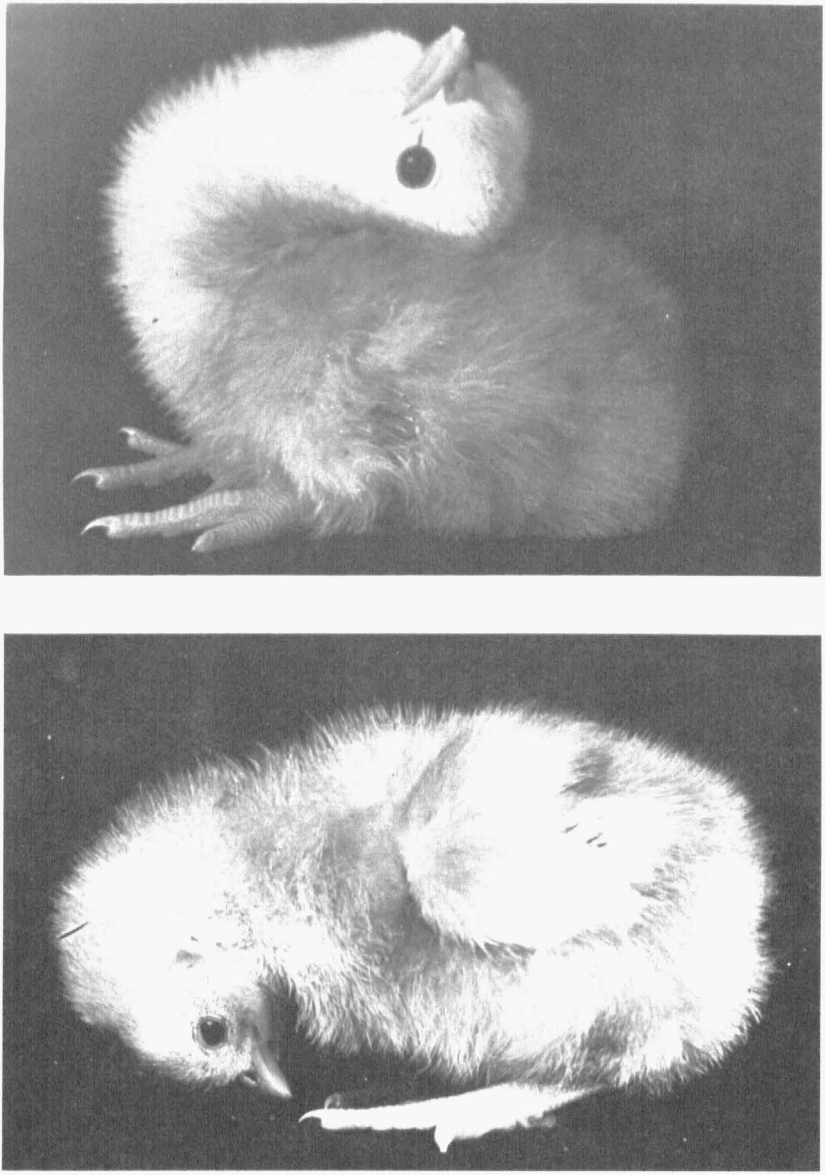


Plate 7. Opisthotonic (top) and emprosthotonic (bottom) spasms in ataxic, newly hatched chicks of hens fed a diet deficient in manganese. (Caskey, Norris and Heuser, 1944.)

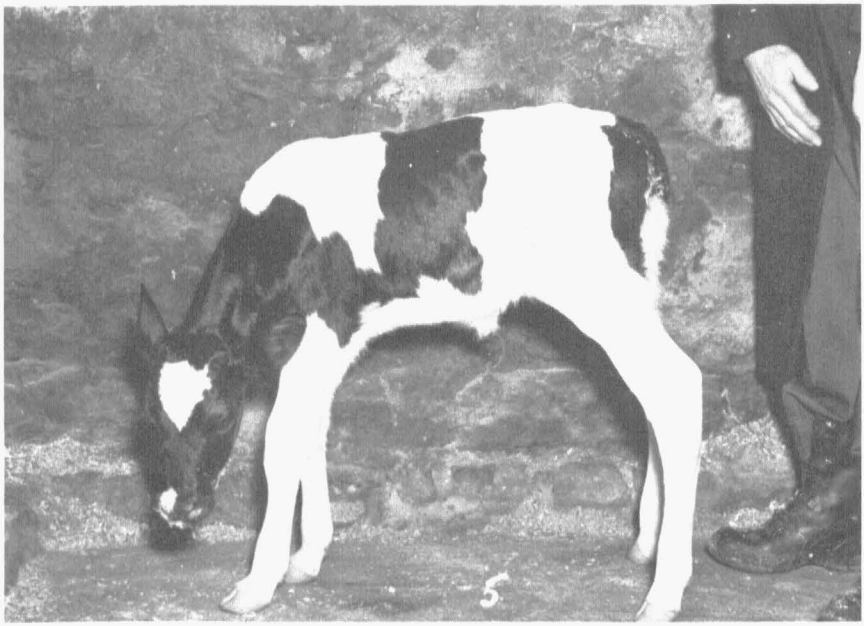


Plate 8. Weak pasterns in a dairy calf caused by manganese deficiency in the diet of the dam. (Bentley and Phillips, 1951.)

Plate 9. Newborn pigs showing loss of equilibrium and ataxia due to manganese deficiency in the maternal diet. (Plumlee and associates, 1956.)

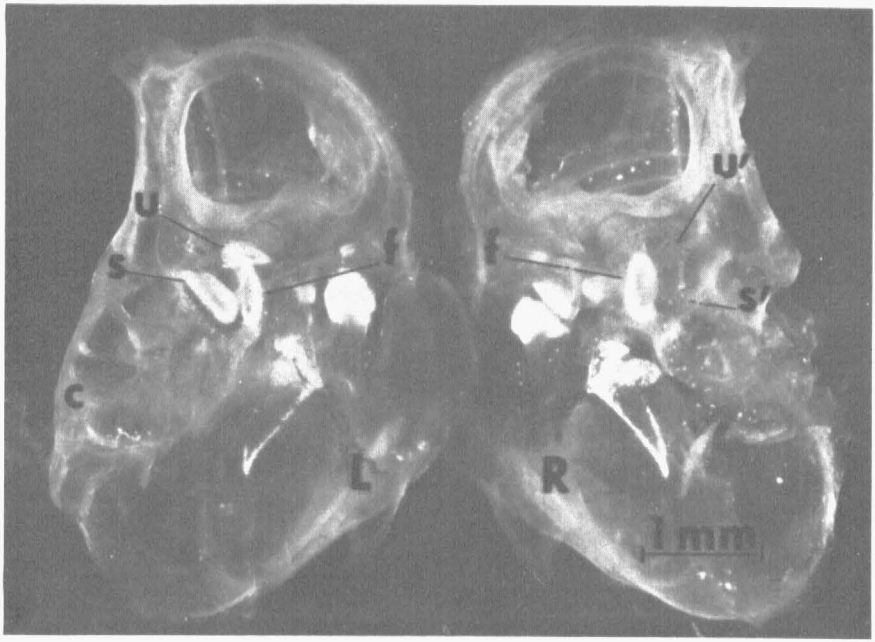


Plate 10. Section of the inner ear of a mouse, showing normal otoliths in the left vestibule and otoliths absent in the right vestibule. Symbols: u, utricular otolith present; s, saccular otolith present; u' and s', otoliths absent, f, fenestra ovalis; c, cochlea; L, left ear; R, right ear. (Erway, Hurley and Fraser, 1966.)

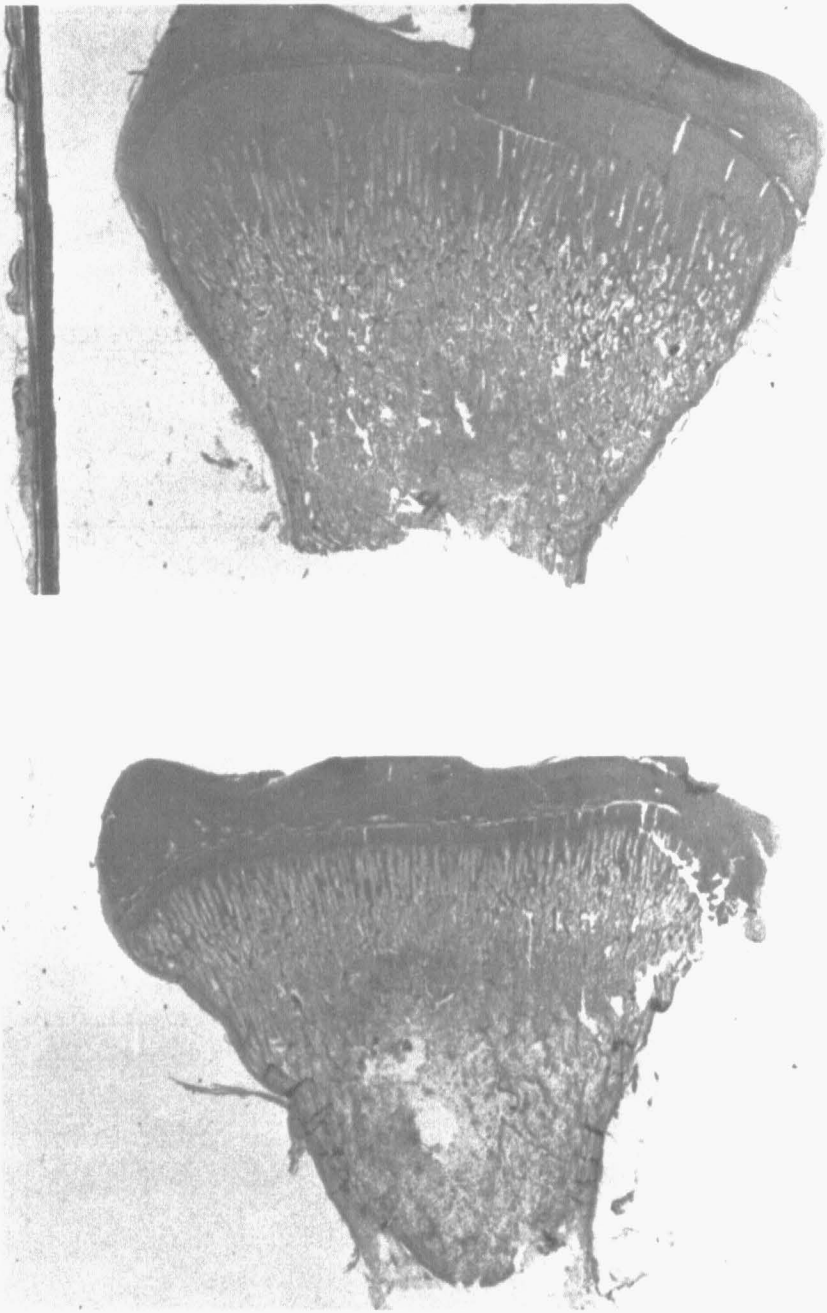


Plate 11. Sections of the epiphyseal growth plate of a normal chick (top) and the narrowed epiphyseal growth plate of a chick fed a diet deficient in manganese (bottom). (Courtesy R. M. Leach, Jr., Pennsylvania State University.)

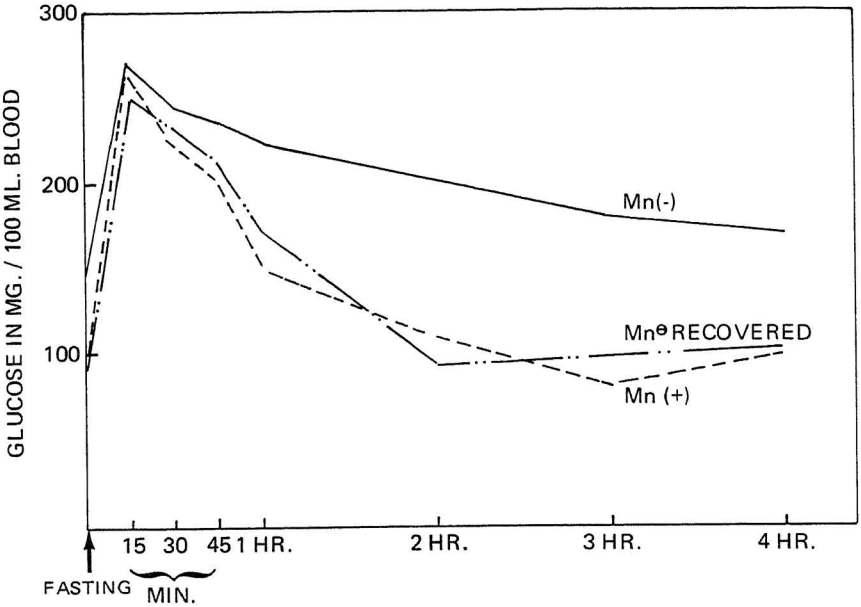


Fig. 1—Glucose tolerance curves of cannulated guinea pigs (Everson and Schrader, 1968)