PYRIDOXINE AND PANTOTHENIC ACID DEFICIENCY IN SWINE

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The present experiments, dealing with pantothenic acid and pyridoxine deficiency, were conducted in 1941 and 1942 in collaboration with the Merck Institute. Swine were chosen as the experimental animal because of their rapid growth and omnivorous dietary habits. The brains, spinal cords, and peripheral nerves of these animals were submitted to us for neuropathological examination. The data herein reported are the results of our observations of this material.**

MATERIALS AND METHODS

The pigs which were used in all of these experiments were of Jersey-Durox (Red) or Berkshire (Black) strains. The piglets were separated from the mother sow at four to eight weeks of age and placed on the basal diet. The diet was the same for all pigs except the "field control" animals which received a commercial hog feed. The ingredients of the basal diet were:

- Casein, Vitamin free (Harris) .................................. 25.0%
- Dextrose, cerulose ............................................. 54.0
- Crisco ........................................................................ 13.0
- Salt mixture .............................................................. 4.0
- Bone ash ..................................................................... 2.9
- Cod Liver oil .............................................................. 2.0
- Choline chloride ......................................................... 0.1

The salt mixture was composed of calcium, potassium, magnesium, sodium, iron, manganese, aluminum, and copper salts. All pigs received a daily supplement of 25 mgm. of alphatoxopherol daily, except Sundays. B vitamins were supplied daily in a capsule which was introduced directly into the pharynx of the animal. The dose of these vitamins was as follows:

- Thiamine .................................................................. 2 mgm.
- Riboflavin ................................................................. 4 mgm.
- Nicotinic amide ......................................................... 20 mgm.
- Pyridoxine ............................................................... 2 mgm.
- Calcium pantothenate .............................................. 20 mgm.

When the animals attained a weight of 100 lbs., the vitamin supplement was increased to 2½ times this amount. In later experiments paraminobenzoic acid and inositol were added.

Litters of pigs were divided and placed either on the basal diet plus vitamin supplements or this diet with all of the vitamin supplement except the pyridoxine or pantothenic acid. Another control group was fed the basal diet, vitamin supplements and dried liver. Finally one group was given a commercial hog feed and raised in the field (field controls).

Except for the last group of controls the animals were kept in individual pens which were cleaned several times a day to prevent coprophagy. Food and water were offered ad libitum.

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** For much of the clinical data and for the formalin fixed tissues which were made available to us we are indebted to Dr. Molitor, Dr. Klaus Unna and Dr. Siegel, of the Merck Institute, Rahway, New Jersey.
in metal containers with overlapping edges so designed that food scattering was minimal. Larger animals who willfully scattered food were fed by automatic feeders.

A total of 58 pigs were used in this study, but some were not suitable for pathological study because the experiment was interrupted before lesions developed or the animals were treated with the missing vitamins before ataxia had appeared. In all we obtained material from 30 animals 16 of which were deficient in one of the 2 vitamins and 14 of which were controls.

The animals took readily to the diet. They were weighed twice weekly and the food consumption was measured daily. Paired feeding experiments were carried out on two control pigs which received the same amount of food as consumed by deficient litter-mates on the previous day.

The animals were kept under careful observation. Blood cell counts were made at regular intervals. The time at which gait abnormalities or seizures first appeared was noted and these abnormalities were recorded by moving pictures. Electroencephalograms were done on some of the animals of both the experimental and the control groups.

The missing vitamin was given to a few of the experimental animals when death appeared to be imminent. Other animals were permitted to die or were killed. A complete post mortem examination was conducted as soon as possible after death.

A. CLINICAL OBSERVATIONS

The control animals manifested no gross signs of deficiency. The animals receiving the synthetic diet grew slightly less rapidly than the control group receiving dried beef liver. After three months the synthetic diet control animals were of about the same length as those receiving liver or commercial hog feed but were not as fat and their back was somewhat hunched. All the control pigs were somewhat stiff in their hind limbs but ataxia was not observed. This stiffness was more marked on cold days. The animals raised in the field and given commercial hog feed did not show any stiffness of the legs or other abnormality of gait. After two months two of the synthetic diet controls with stiff legs were transferred from the pig sty to the field and the peculiarity of gait disappeared. At the end of eight months the field animals were approximately one hundred pounds heavier than the control animals receiving a synthetic diet with or without dried beef liver.

Pyridoxine deficient animals. All of these animals were placed on the basal diet at four weeks of age and received the same vitamin supplement as the controls except that pyridoxine was omitted. Within two to four weeks all the pigs developed an anemia which was characterized by hypochromia and microcytosis. The volume of packed red corpuscles dropped from forty per cent to twenty per cent or less, hemoglobin from 10–12 gms. to 6 gms. and the number of red corpuscles decreased from 7–9 million to 5–7 million.

A disturbance of gait began about the same time. This first appeared in the hind quarters and consisted of a slight broadening of the base, unsteadiness, twisting movements of the leg as the step was taken and swaying of the rump. This gradually increased in degree and later the forelegs were similarly affected. Finally after about two months the animal showed considerable difficulty in walking with unpredictable crossing and buckling of the legs.

Convulsions appeared after the ataxia and weakness were well established. They were generalized seizures affecting both sides simultaneously and lasting several minutes at a time. They sometimes occurred singly or in series and left the animal in a weakened, exhausted condition. Death usually occurred within a few days after the onset of seizures, but if a small dose of pyridoxine was administered, the seizures were prevented.

Clinical examination of the animals after the beginning of ataxia showed muscular weakness and a preservation of some sensation at least as judged by response to pricking or pinching. The tendon reflexes were present in the early stages of the experiments and were not examined later.

In general the animals gained very little weight. For example one animal weighed only thirty pounds at 126 days of age, whereas the field control animals were over one hundred pounds at the same age. There were no significant changes in their coat or tongue.
Pantothenic acid deficiency. These animals were placed on the basal diet at different ages varying from four to eleven and one-half weeks. The animals which were started on the diet at four weeks of age developed a diarrhoea within two weeks and tongue lesions shortly afterwards. The stools were watery and at times mixed with blood and mucous; they were so frequent as to be almost continuous. The pigs were extremely untidy and did not grow. After about eight weeks a disturbance of gait appeared. The hind legs were placed wider apart than usual, the hips were flexed, and the knees which were stiff were lifted six to nine inches off the ground in a sort of "goose-step." Sometimes this high stepage would continue in one leg while the animal was standing still. The movements of the leg in the performance of this high step were not always grossly ataxic; in some pigs they were quite smooth so that the stepage was much more striking than the ataxia.

Pigs which were started on the diet at eight and nine and one-half weeks showed much less diarrhoea. The stools were loose but not watery and the tongue lesions were milder. These animals gained weight for several weeks. Ataxia and high stepage gait developed after they had been on the diet for six to ten weeks. The ataxia progressed quite rapidly, and in these pigs was often more marked than the high stepage gait.

Pigs which were eleven and one-half weeks of age when placed on the experimental diet did not develop diarrhoea, but the ataxia and stepage gait were more pronounced. One animal which was dosed with pantothenic acid, after it had collapsed, recovered within a day but the ataxia and gait abnormality persisted. Another animal which had been deprived of pantothenic acid for twelve weeks was treated daily with this vitamin for five and one-half months. There was a gain in strength and weight but the ataxia was not influenced.

B. PATHOLOGICAL CHANGES

Segments, both distal and proximal, of the brachial and lumbosacral plexuses, of the spinal cord, brain stem and cerebral hemispheres were available for study. The material was fixed in 10 per cent neutral formalin for at least two weeks and suitable blocks were then prepared for frozen, paraffin and cellloidin sections. The following staining techniques were used: Swank-Davenport modification of Marchi method for early myelin degeneration (1); cresyl-violet and hematoxylin and eosin for cell changes; Kultschitzsky-Weigert and Spelmeyer techniques for myelin; Bielschowsky, Cajal silver and Bodian techniques for axis cylinders and oil red-O counterstained with hematoxylin for fat.

We received pathological material from thirty animals of which 11 had been deficient in pantothenic acid, five deficient in pyridoxine and 14 on control diets. Of the latter, 11 had been given a purified diet supplemented by all the known vitamins, two were field control animals on commercial hog fodder, and one a synthetic diet control animal receiving all the known essential vitamins and biotin. Two of the pyridoxine deficient animals and one pantothenic acid deficient animal were treated after symptoms of deficiency were well established.

In the control material there were numerous small rings and rounded masses of black material in the periphery of the spinal cord and medulla, just underneath the pia, in sections stained by the modified Marchi method. These were seen in all of the animals on the purified synthetic diets and in one of the two field control animals. In as much as axis cylinders were unchanged and the myelin sheaths were intact these changes were considered to be identical to those observed previously by Swank (2) in starved control pigeons; their significance is not known.

Pantothenic acid deficiency. In those animals which had been ataxic for only a few weeks the myelin sheaths were swollen and fragmented into globular particles. This alteration of myelin was well demonstrated in the oil red-O stain where the degenerating myelin was of a more orange color than the normal myelin. In a few nerves more chronic pronounced changes were manifest; macrophages were present next to and within degenerated particles of myelin. These cells could be seen, in oil-red-O stains, to contain cholesterol esters. Swelling and disintegration of the axis cylinders accompanied the myelin degeneration.
Fig. 1. Pantothenic Acid Deficiency

a) Peripheral nerve showing fragmentation of myelinated fibers. (Spielmeyer stain)
b) Peripheral nerve showing disappearance of some of the axis cylinders and irregular swelling of some of the remaining ones. (Bodian stain)
c) Anterior horn cells of the lumbar spinal cord. (Nissl stain)
d) Bodian stain of Dorsal root ganglion. Some of the ganglion cells have disappeared and there are within the capsules of these cells perineuronal satellites and histocytes. Note the fragments of axis cylinders. (Bodian stain)
FIG. 2. PYRIDOXINE DEFICIENCY

a) Peripheral nerve showing degeneration of some of the myelinated nerve fibers. Note scattered fragments of myelin. (Spielmeyer stain)

b) Peripheral nerve. Some of the axis cylinders have disappeared and others are swollen and fragmented. (Bodian stain)

c) Dorsal root ganglion. Note two empty capsules filled with satellite cells and the vacuolated cell. (Bodian stain)

d) Dorsal root. Many of the axis cylinders are broken up, swollen, and tortuous. (Bodian stain)

The larger fibers in the more distal parts of the peripheral nerves of first the lumbo-sacral and later the brachial plexuses were affected (fig. 1a, b). The smaller fibers were involved to a lesser extent. The degeneration proceeded proximally and was finally present also
Fig. 3. Posterior Columns of Spinal Cord (Swank-Davenport Modification of Marchi Stain)

a) Normal. Synthetic diet control.
b) Scattered black particles of degenerating myelin in the posterior roots and the posterior columns from animal deficient in pantothenic acid.
c) Similar findings in posterior columns of spinal cord from an animal deficient in pyridoxine.
in the dorsal roots. In none of the cases were all of the myelinated nerve fibers degenerated. In the most ataxic animals a number of large fibers were still intact. In no instance were degenerating fibers observed in the ventral spinal roots.
The degree of damage in the posterior roots was relatively slight even in those animals in which there had been the most pronounced changes in the peripheral nerves. The type of change in the posterior roots was the same as the earliest change in the peripheral nerves.

In all of these animals there were lesions in the posterior root ganglion cells (fig. 1 c, d). These consisted of swelling, perinuclear chromatolysis and later shrinkage and dark staining or vacuolization. Some of the cell bodies had degenerated and were represented in routine cell stains by capsules filled with satellites and macrophages. Fragments of myelin and destroyed axis cylinders were still visible in appropriate stains. In none of the cases had more than about 20 per cent of the ganglion cells degenerated though a larger proportion exhibited chromatolysis. The severity of degeneration of the posterior root ganglion cells, and of the posterior roots and posterior columns of spinal cord was much less than in the peripheral nerves.

In all of the cases the changes in the posterior columns of the spinal cord were relatively mild, and of about the same degree as in the posterior roots. The posterior column lesions were demonstrated best by the modified Marchi stains (fig. 3 b) and less well by Bodian stains. They were not of sufficient age to be well shown by fat or myelin stains. Little change was shown in Spielmeyer preparations (fig. 4 a). In a few of the sections of the spinal cord there were scattered fenestrations and swollen axis cylinders but no areas of paling glial reaction, or alteration of anterior horn cells. No lesions were present in other parts of the spinal cord.

Nissl and Bodian stained sections of the medulla oblongata, cerebellum, basal ganglia and cerebral cortex revealed no definite abnormalities. The striated muscles of the limbs appeared to be normal.

Pyridoxine deficiency. In microscopic sections of the peripheral nerves there was moderately severe degeneration. The changes were of the same type as those seen in the pantothenic acid deficient animals. Swelling and fragmentation of the myelin sheath and axis cylinder, phagocytosis of the remnants of degenerated fibers, and proliferation of endoneurial connective tissue were the outstanding pathological findings. The peripheral nerve lesions (fig. 2 a, b) were not as pronounced as in the pantothenic acid deficient animals. In the most advanced lesions only part of the larger fibers were damaged. Again the larger fibers in the distal parts of the nerves were most vulnerable. Only a few fibers in the posterior roots (fig. 2 d) and no fibers in the ventral roots were involved.

The posterior root ganglia were altered to a lesser degree than in the pantothenic acid deficient animals. Many of the ganglion cells had undergone chromatolysis and a very few had degenerated, being replaced by mononuclear phagocytes and satellite cells (fig. 2 c). No anterior horn cells were involved.

There were no definite lesions in the spinal cords of the pyridoxine deficient animals. A few rings and balls of black material were seen in the modified Marchi stains but these were no more numerous than in the control animals. No abnormalities were seen in sections of the medulla, cerebellum, basal ganglia or cerebral cortex in Nissl preparations.

There were no definite changes in the striated muscles of the limbs.

DISCUSSION

The pathological lesions observed in our pantothenic acid and pyridoxine deficient swine were essentially identical. They consisted of degeneration of nerve fibers beginning first in the distal parts of the peripheral nerves and progressing centralward for a distance determined by the severity of the deficiency. Degenerative changes occurred later in the posterior root ganglion cells, some of which ultimately disappeared, and in the central axones of these cells in the posterior roots and posterior columns of the spinal cord. The order of development of these latter changes could not be ascertained from our material. They were
however, all less marked and were more recent than those in the peripheral nerves. The anterior horn cells of the spinal cord were unaltered but degeneration of their axones in the peripheral nerves could not be ruled out. It can be stated, however, that these changes, if present, were much less severe than those in the sensory neurones. Moreover, there was no definite atrophy or degeneration of the skeletal muscles. The large nerve fibers appeared to be the first, and the most severely damaged. The actual proportion of difference cannot be given for actual counts of fibers were not made.

The sensory neuronal changes explain adequately the ataxia which developed first in the hind legs and later in the forelegs. However, the high steppage gait or "goosestep" which was observed in many of the pantothenic acid deficient animals would appear to require additional lesions, presumably at a higher level for its explanation since it had more the appearance of a spastic disorder. We were unable, however, to demonstrate such lesions in the spinal cord or brain. Also the convulsions observed in the pyridoxine deficient animals are not explained by the observed lesions. Here we are faced in all likelihood with a functional disturbance on a chemical basis which was not accompanied by histological change.

Lesions similar to those described above have been observed by Zimmerman and Burack (3) in the peripheral nerves, posterior roots and posterior columns of spinal cord of dogs which were deficient in the B₁ group of vitamins. Their animals had received what were considered to be adequate amounts of vitamin B₁ in the form of rice polishings. These findings were later confirmed by Wintrobe, Mitchell and Kolb (4) who in addition noted pathological changes in the posterior root ganglion cells. The latter workers were able to clarify the situation further because crystalline thiamine and riboflavin were then available and were included in the diet. In subsequent papers Wintrobe and his associates (5) showed that these same lesions could be produced in swine by diets which are deficient in pyridoxine and pantothenic acid. The present paper corroborates their observations. In a more recent communication, however, Follis and Wintrobe (6) concluded that the changes in these two deficiency states are not identical. In pantothenic acid deficiency they found that chromatolysis of the posterior root ganglion cells preceded the other changes whereas in pyridoxine deficiency the first lesions were in the central and peripheral processes of these cells. We were unable to find these differences; in both deficiency states the peripheral nerves exhibited significant changes before the posterior root ganglion cells, posterior roots and posterior columns of the spinal cord.

Although the evidence suggests that pantothenic acid and pyridoxine deficiencies cause degeneration of peripheral nerves this has not been established with certainty because satisfactory curative experiments have not been performed. Wintrobe et al. (5) treated 5 of their ataxic swine with the missing vitamins but 2 of them died in a few days, one continued to become more ataxic and the other 2 improved slightly over a period of 2 months. We too were unable to obtain significant improvement in ataxic pantothenic acid and pyridoxine deficient swine after replacement of the missing vitamin for as long as 5½ months. Moreover, the control animals which received a completely synthetic diet ade-
quate in all known vitamins and other substances failed to grow as well as the field control animals. All of these facts suggest that another factor or factors, as yet unknown, played some part in the production of the ataxia.

In view of these observed effects of pantothenic acid and pyridoxine deficiency all previous experiments in which a dietary deficiency of thiamine was believed to have resulted in similar changes in the peripheral or central nervous system must be analyzed critically. This was done by Meikeljohn (7) and later by Wintrobe and his associates (8). Both came to essentially the same conclusion that thiamine was not an "antineuritic" vitamin. Meikeljohn pointed out that up to 1940 crucial experiments in which peripheral nerve lesions were produced by diets deficient only in thiamine and repaired by replacement of this vitamin had not been performed.

There is little doubt that much of the early experimental work on vitamin B₁ or thiamin deficiency is open to criticism. The experiments of Vedder and Clark (9) and McCarrison (10) and many others were performed at a time when our knowledge of vitamins was so incomplete that it is impossible to determine whether the diets which were used were deficient only in thiamine or in several vitamins. However, in a recent study of the effects of thiamine deficiency (Swank and Bessey, 11; Swank, 2) it was found that if pigeons were made rapidly deficient in thiamin by the tube feeding of a highly purified diet opisthotonus always developed. Ataxia and later leg weakness, on the other hand, occurred only if the animals were depleted of thiamin more gradually. Furthermore, there were few or no degenerative changes in the peripheral nerves in the birds with opisthotonus whereas definite peripheral nerve lesions were found in the birds with ataxia or leg weakness. The changes first appeared in the distal part of the peripheral nerve and extended centralward. When the degeneration had approached to within 1–2 cm. of the spinal cord many cells in the posterior root ganglia exhibited "axonal reaction" (swelling, chromatolysis, eccentricity of nucleus). The large sensory fibers were affected first and as the deficiency became more severe, progressively smaller neurones were involved. The severe leg weakness which developed after the ataxia in some pigeons suggested involvement of the motor nerves also, but this was never verified pathologically. Control pigeons were fed the B complex free ration plus thiamin, or this diet plus thiamin and autoclaved yeast. These birds continued in good health for 8 to 12 weeks, whereas the deficient animals developed symptoms in from 2 to 3 weeks.

In subsequent experiments (Swank and Prados, 12) it was shown that the opisthotonus, unless extremely acute and of very short duration, was accompanied by lesions in the vestibular system which were identical in type to those in the peripheral nerves of pigeons with ataxia or leg weakness. Here the lesions occurred first in the terminations of the vestibular nerves, both centrally and peripherally. From both points the degeneration progressed centralward towards the cell bodies in Scarpa's ganglion. Here again the large nerve fibers suffered first and the smaller ones later. The secondary vestibular connections and the terminations of the optic nerves in the optic lobes of the thalamus were also affected.

The administration of thiamin cured both the ataxia and weakness of the
legs, and the opisthotonus. The leg signs were abolished slowly, sometimes requiring 6–8 weeks, and the opisthotonus cleared up in a few hours to a day. In either instance recovery was achieved just as rapidly with the administration of thiamin alone as with all the B complex vitamins (11, 2, 12). In additional curative experiments it was observed that there was recovery from ataxia and weakness of the legs which had been produced by a diet containing approximately 40 per cent of the daily requirement of thiamin when the thiamin was increased to 60–80 per cent. The diet still contained insufficient thiamin for the total needs of the animal since cardiac failure with death often occurred during or after complete recovery from the neuritis, or on occasion, the ataxia disappeared only to reappear again and then be cured permanently by increasing the thiamin intake above the daily requirement. When starvation was also present, much smaller amounts of thiamin (20–40 per cent of the normal daily requirement) allowed repair of nerves to proceed at a normal rate. This would seem to explain why cruced nerves regenerate as fast in cats made partially deficient in thiamin as in normal animals (Berry, Neumann, and Hinsey (13)).

From these experiments it seems fairly clear that a diet deficient only in thiamin will cause a neuronal degeneration in pigeons which can be abolished by the subsequent administration of this one vitamin, without the presence in the diet of other members of the B complex group of vitamins. For the pigeon at least this should satisfy Meiklejohn’s (7) criticism of previous experiments, that they had not shown that the ataxia and leg weakness produced by thiamin deficient diets could be repaired by thiamin alone. Wintrobe et al. in recent experiments (8) failed to produce leg weakness in swine on a thiamin deficient diet. Yet earlier experiments by these same workers (4) cannot be reconciled with these conclusions. In these experiments pigs were placed on a standard diet containing none, or inadequate amounts of the B complex. When the growth of the animals had stabilized, intramuscular injections of thiamin and/or riboflavin were given. Concerning one animal, which had not yet received thiamin, the following observation was made (page 210): “In pig A4-60 (Chart I), at 70 days of age the hind legs became weak and by the 73rd day the animal was unable to stand; on this day thiamin, 25 mg., was injected. The next day the animal was able to walk and within a week had completely recovered.” It is clear from this protocol that Wintrobe and collaborators did observe leg weakness which was cured by intramuscular injections of thiamin in at least one thiamin deficient pig. Apparently this observation was forgotten since they failed to refer to it in later papers on the same subject, and concluded on the basis of subsequent negative data on 19 swine that thiamin deficiency did not produce leg weakness. Possibly if their studies had included more animals and the experiments had been more varied, ataxia and leg weakness would have become manifest, and their earlier observation confirmed. The failure of Wintrobe and collaborators to produce leg weakness in swine does not negate the conclusions relative to pigeons because animals and birds may differ considerably in their susceptibility to thiamin deficiency.

From the preceding consideration it is clear that thiamin deficiency can cause degeneration of peripheral sensory nerves, and that these changes can be reversed to normal by giving the missing vitamin. Furthermore, these changes are similar
in distribution to those which Wintrobe and his collaborators and we ourselves have observed in pantothenic acid and pyridoxine deficient swine. It should be noted, however, that the lesions in the dorsal root ganglia and posterior columns of the spinal cord in thiamin deficient pigeons, although similar, were never as severe as those observed in pantothenic acid and pyridoxine deficient swine, that received large supplements of thiamin. Histological differences may have been due to the much greater chronicity of the lesions in the swine, or to species differences. Certainly the similarity of the pathological lesions in the three deficiencies does not prove an identity of their cause. It does show, however, that each of the deficiencies can impair the metabolism of the same type of cell in a manner that leads to similar pathological changes. The absence of satisfactory curative experiments and the poor growth of the synthetic diet control animals suggests that a deficiency of one or more other factors may have also been present in the swine which consumed the pantothenic acid and pyridoxine deficient diets.

CONCLUSIONS

In swine, synthetic diets deficient in pantothenic acid and pyridoxine will produce degeneration of peripheral nerves, posterior roots, posterior columns of the spinal cord, and sensory ganglia. Except for differences in degree the lesions in these two deficiency states are alike, being less severe in pyridoxine deficiency. Although these experiments suggest that pantothenic acid and pyridoxine are both essential for normal functioning of the peripheral nervous system, the cause and effect relationship between the specific vitamin defect and the neural lesions is not yet established, since satisfactory curative experiments have not been reported.

ABSTRACT OF DISCUSSION

Dr. M. T. Moore, Philadelphia: I would like to ask Dr. Adams whether electroencephalographic studies were performed on these animals. I note that they had frequent convulsions but no explanation was offered. We know that thiamine plays a role in the carbohydrate metabolism of nervous tissue and that nicotinic acid is one of the mediators in the enzymic system with respect to hydrogen and oxygen. I am just wondering whether or not that may not have been a factor in the production of these convulsions and whether electroencephalographic studies, if done, would give us some information in that respect.

Dr. R. D. Adams: I am able to say that the electroencephalographic studies were done but that the tracings were in the hands of Dr. Robert Morrison of the Rockefeller Foundation and Dr. Dempsey of Harvard Medical School. They are, I think, going to report on them at some future date. I do not know the electroencephalographic findings. I am not certain that I understand your query about the nicotinic acid. Do you mean to question whether it is responsible for any of the cerebral disorders that we have observed?

Dr. M. T. Moore: I meant to imply that perhaps pyridoxine as a member of the B Complex may play a role similar to that of nicotinic acid in hydrogen and oxygen metabolism of the brain.

Dr. R. D. Adams: I see, I think that may be so. I can offer no opinion on this matter.

BIBLIOGRAPHY