EXPERIMENTAL TOXIC ENCEPHALOMYELOPATHY

(*Diffuse sclerosis following subcutaneous injections of potassium cyanide*)*

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The problem of the etiology and pathogenesis of diffuse sclerosis and multiple sclerosis has been put forth in the last few years especially in connection with acute encephalomyelopathies following infectious conditions of childhood. The desire of reproducing experimentally these pathological conditions of diffuse or multiple sclerosis has been in the mind of numerous investigators, but unfortunately up to date, with the exception of very few reports, nothing definite has entered our current literature.

Diffuse sclerosis and multiple sclerosis are pathological conditions so closely related that I feel partly justified in applying to the etiology of diffuse sclerosis some of the knowledge we already possess in regard to multiple sclerosis.

The various theories concerning the etiology of multiple sclerosis relate to either infections or toxins. The theory of infectious origin of multiple sclerosis has particularly developed under Pierre Marie's[1] influence. Later on, based on the work of Bullock,[2] 1913, the possibility of a filtrable virus was considered. Besta and Ceni[3] thought of aspergillis fungatis as one etiological factor. We all know in this connection the work of Chevassut and Purves-Stewart,[4] which unfortunately has not been substantiated by further investigations of Carmichael,[5] Tronconi,[6] Arthur Weil,[7] and others. On the other hand, Steiner[8] thought the condition due to a spirochetosis, a conception which, however, still lacks substantial proof.

The toxic theory has three groups of supporters: one following Marburg's[9] idea that a ferment acts destructively on the myelin sheaths; a second one inspired by Strümpel[10] and Müller's conception of an endogenous origin of the disease in the form of a primary involvement of the glia, and a third one believing the toxic

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factor to be an unknown endogenous substance which would primarily act on the myelin covering of nerve fibers.

Following Marburg's inspiration, Brickner[11] again took up the lead and tried to establish that the process of demyelination is due to a lipolytic ferment (lipase) present in the blood of multiple sclerosis patients.

The theory of a primary disease of the glia elements does not seem to have found very numerous advocates with the exception, possibly, of Scholz,[12] Collier and Greenfield,[13] who feel this to be the case in diffuse sclerosis. Coenen and Mir[14] in diffuse sclerosis also speak in terms of a primary disease of the oligodendroglia, while Wertham[15] feels that neuroglia reaction may be set up irrespective of the process of demyelination.

Among the advocates of an endogenous origin related to an unknown toxin we can mention Hassin,[16] A. Weil, Claude,[17] and recently Putnam,[18] who succeeded in reproducing the pathological lesions of multiple sclerosis following intraperitoneal injection of tetamus toxin in 2 out of 48 dogs. A. Jakob[19] also feels that in diffuse sclerosis an endogenous metabolic toxin may be at the base of the pathological lesions.

Aside from such rather fragmentary reports I have been unable to find in the literature any investigation in which experiments carried on a large scale have given constant results in the reproduction of lesions which histopathologically can be classified either as multiple or diffuse sclerosis.

Following the lead of a supposed toxic origin of multiple sclerosis and because of the possibilities of diffuse sclerosis being also a toxic condition, I have tried to reproduce from an experimental standpoint the lesions characteristic of such conditions through the use of a substance, potassium cyanide, which, as we all know, interferes with the oxidizing power of the living cells. According to Warburg[20] cyanide affects the respiratory enzymes and, therefore, inhibits the respiration of tissues. F. O. Schmidt and O. H. A. Schmidt[21] have established that oxygen consumption of resting nerves of the green frog may be practically completely inhibited by cyanide and that the ability of cyanided nerve to conduct an

impulse is affected in the same way as in asphyxiation by a complete failure after variable periods of time.

From this physiological approach I thought that oxygen interference might through faulty metabolism lead to the destruction of elements the result of which might end in the stage of multiple or diffuse sclerosis.

Cyanide is a part of our intermediary metabolism and, according to Werner,[22] the hydrolysis of urea by acids or bases would result in a dissociation into ammonia and cyanic acid. According to A. P. Matthews,[23] in the course of biological oxidations isocyanic acid may be formed which undergoes rearrangement with ammonia to urea. Salkowsky[24] also believes that urea may be formed by the transformation of cyanamide, and Fosse considers cyanic acid the immediate precursor of urea.

Recently Brand and Harris[25] expressed the belief that on the basis of the cyanic acid theory of Salkowsky, Werner, and Fosse, creatine may possibly arise from a side reaction between cyanic acid and glycine.

My experiments have been carried on 14 cats and 4 monkeys. The animals were injected subcutaneously with increasing doses of potassium cyanide starting with a minimum dose of 2 mg. and increasing daily by ½ mg. up to a maximum dose in one of them of 35 mg. daily. The total amount of potassium cyanide injected has naturally varied according to the resistance of the animal, one of the highest doses ever given being 600 mg. divided into 66 injections over a period of 132 days. Following each injection notes were taken concerning the clinical manifestations which can be summarized as follows:

1. Increase in the respiration rate in proportion to the amount of medicament injected.
2. Vomiting.
3. Bowel movement.
4. Twitchings, localized or generalized.
5. Occasional tremors of the head.
6. Occasional nystagmus.
7. Spasms and hyperreflexia and spasticity of the legs.
8. Following prolonged repeated injections the animals develop

a spastic paralysis of the hind legs which is, however, transitory and may last from a few hours up to a few days. If the injections are not discontinued the paralysis may remain stationary.

9. Blindness, which also seems to be transitory.

10. Generalized convulsions which may proceed from a single convulsion to a status epilepticus, lasting over 24 hours.

From a histopathological standpoint, the lesions which are found under the microscope are the following:

A. Nature of the Lesions

1. *Myelin Sheaths:* A diffuse process of demyelination which involves indiscriminately various areas of the white substance, the process being, however, more pronounced in the frontal and the occipital region (Figs. 1 and 2). The areas of demyelination are very large, for the most not sharply defined, and involve almost exclusively the white substance respecting quite often the "U" fibers underneath the cortex (Fig. 3). The intensity of the demyelination is a various one going from a process of rarefaction to a complete destruction of the myelin sheaths (Fig. 4).

The process is particularly severe in the periventricular regions though the corpus callosum seems also to be a seat of predilection having been found severely involved in practically all instances (Fig. 5). The brain stem and the cerebellum are also the seat of demyelination, especially surrounding the fourth ventricle (Fig. 6). The process of demyelination extends also to the optic nerve and the optic chiasma where isolated or diffuse patches of the lesions are very often found (Fig. 7).

At times the demyelination assumes a concentric appearance as already reported by Marburg and Balo in cases of multiple or diffuse sclerosis.* The spinal cord is also severely involved and the involvement has not the characteristic of a secondary process of degeneration, the lesions being there very diffuse and involving the descending as well as the ascending pathways (Fig. 8). At times the intensity of the process is such as to result in a diffuse demyelination of all the white substance (Fig. 9).

*Hallervorden and Spatz,[58] in an article discussing the toxic origin of diffuse and multiple sclerosis seem to favor a diffusion of the lesions through a chemical process which may particularly account for the concentric type of demyelination. Fig. 6 of this paper illustrates the existence of such concentric type of demyelination in the white substance of the cerebellum.

2. *Axis Cylinders:* The axis cylinders suffer a process of degeneration which, from a very moderate degree, may reach the stage of a more or less complete disintegration. There is not a definite parallelism between the involvement of the myelin sheaths and of the axis cylinders, the axis cylinders resisting much more the destructive process. In some areas, in fact, while the myelin sheaths are severely involved the axis cylinders are still well preserved (Fig. 10); conversely in others, both myelin sheaths and axis cylinders have completely disappeared (Fig. 11). The changes in the axis cylinders vary from the very elementary swelling to the fragmentation and to the granular disintegration of the structure.

3. *Neuroglia Elements:* Distinction must here be made between protoplasmic neuroglia and fibrous neuroglia. The fibrous neuroglia shows considerable reaction of the progressive type in correspondence to the areas of demyelination (Figs. 12, 13, 14). With the Holzer method for glia fibers a marked process of gliosis can be detected extending all over the white substance, but more pronounced in correlation with the areas where the process of demyelination is the most severe. A predominance of gliosis is also seen in the corpus callosum and in the periventricular areas. In the optic nerve (Fig. 15), chiasma, and optic tract patches of demyelination are seen in which a corresponding process of gliosis is detectable independently from areas of softening. Figs. 16 and 17 illustrates the details of two areas of gliosis; the first being subependymal and the second a diffuse process of the anisomorphe type. At the periphery of the process of demyelination, the astrocytes, as evidenced by Cajal's gold sublimate method, disclose considerable progressive changes of both hypertrophic and hyperplastic type. There is, in other words, a considerable increase in the size of the astrocytes as well as in the number of the elements (Fig. 18). In some areas of demyelination the protoplasmic astrocytes are also seen undergoing considerable progressive changes (Fig. 19), though the tendency to form glia fibers seems the dominant one. Monster glia cells are more often encountered in the areas of necrosis undergoing a process of repair or in their immediate vicinity, but in general the process of

gliosis is independent from the process of necrosis or from the softenings that are encountered only here and there.

4. *Microglia and Oligodendroglia:* The oligodendroglia elements are seen all over the white substance undergoing slight hypertrophic changes with a tendency towards vacuolization of the cytoplasm. In areas where the destructive process is very severe the oligodendroglia cells suffer a considerable reduction in number through a process of gradual disintegration. There is, however, no correlation between the process of demyelination and the involvement of the oligodendroglia as demyelination is found of a considerable importance even in areas where the oligodendroglia is present in large number.

The microglia cells are seen undergoing degenerative changes most of which tend toward the formation of fat compound granular corpuscles (Fig. 20). These elements are especially numerous in areas where the necrosis is very pronounced or in areas of softening (Fig. 21). In correspondence to areas of simple demyelination the microglia elements are better preserved though disclosing a tendency towards hypertrophy and occasionally degenerative changes of the type of clasmatodendrosis and disintegration of the elements. The fat compound granular corpuscles are seen surrounding the blood vessels even in areas free from softening where they seem to have a double origin, partly microglial and partly oligodendroglial. In areas of softening the compound granular corpuscles have also a mesodermic origin. In the midst of the cellular elements surrounding the blood vessels ameboid cells are also seen originating from astrocytes undergoing degenerative changes.

5. *Blood Vessels:* The blood vessels do not show embolic or thrombotic changes though in the most severely affected areas a swelling of the endothelium is noticeable (Fig. 22). Occasionally hyperplasia of the endothelium takes place through a mitotic process. Some of the blood vessels disclose hyaline degenerative changes—others hypertrophy of the adventitia covering. No particular increase in number of the blood vessels is noticeable in the areas where the destruction of the process is of a moderate intensity, whereas where the process of destruction reaches the degree of a true necrosis attempts toward progressive changes are seen in

the sense not only of a relative but of an absolute type of increase in the number of the blood vessels partaking in the process of repair.

6. *Inflammatory Manifestations:* Out of the 18 animals which have already been studied histologically only 2 presented definite inflammatory lesions which would satisfy the classical requirements of an inflammatory condition, that is, the combination of destructive changes, proliferative changes, and presence of exudate. In these two cases the typical perivascular exudate formed by lymphocytes and plasma cells was present not only in the white substance but extended also to the gray matter and to the meninges (Fig. 23), the histological picture being a definite one of meningoencephalitis.

In the remaining 16 cases no inflammatory lesions were disclosed though in the area of major involvement a perivascular collection of cellular elements is often seen (Fig. 24). These elements are, however, almost exclusively represented by fat compound granular corpuscles or by neuroglia and microglia cells in an early phase of reaction (Fig. 25). No lymphocytes or plasma cells were detected so that in the great majority of cases the process can be labeled as a true degenerative one.

7. *Fat Products of Disintegration:* Outside of the area of softening or necrosis where compound granular corpuscles are found in a more or less abundant number no fat products of degeneration are detectable with the Scharlach R or Fett Panceau. It is possible that the type of degeneration in the area of demyelination is influenced by the lack of appropriate oxydation and that the fat tissue does not undergo the usual transformation into neutral fat which is detectable with the Scharlach R.

8. *Areas of Necrosis:* Here and there in connection with a very intense degenerative process, areas of necrosis are found in which all the elements have undergone degenerative and destructive changes. In these cases not only the myelin sheaths and the axis cylinders have disappeared, but also the glia elements are barely detectable. The white substance is ultimately represented by granular disintegrated material. In these cases areas of softening are not necessarily present and therefore the reaction of the connective

tissue may also be absent at least temporarily while the blood vessels still maintain their continuity.

9. *Areas of Softening:* Here and there, in some of the cases where the lesions seemed to be extremely severe, foci of softening are found in which the characteristic histological picture can be detected of disintegrated nervous tissue and breaking of the ecto-mesodermic barrier so that mesodermic and ectodermic elements can be seen fusing in an attempt to repair. It is only in areas of softening that the mesodermic connective tissue is seen invading the areas of softening (Fig. 26) and together with a progressive type of reaction on the part of the neuroglia elements gradually proceed to the process of scar formation. Numerous compound granular corpuscles are here encountered, the origin of which is partly ectodermic and partly mesodermic.

The number and extension of the areas of softening is variable and occasionally large areas are found, especially surrounding the posterior horn of the lateral ventricle. The softenings do not, however, represent the main histological picture as it seems to be claimed by A. Meyer,[26] nor do the areas of softening predilect the striatum as found in dogs by the same author.*

B. Diffusion of the Lesions

1. *Involvement of the Cortex:* With the exception of the two cases in which inflammatory lesions were present in the meninges as well as in the gray matter, the remaining cases show in some instances a well preserved cortex. In a few other cases involvement of the cortical nerve cells is found consisting especially in acute degenerative changes of the severe type of Nissl (Fig. 27). These lesions do not show any seat of particular predilection and are scattered all over the various cortical areas. In a few other cases acute degenerative changes of the nerve cells are lacking,

*Mayer[59] identifies the lesion following cyanide poisoning with the lesion following carbon monoxide poisoning. He insists particularly on the symmetrical softening of the basal ganglia. In my first series of experiments I have found only twice in 18 experiments the existence of softening in the basal ganglia with predilection of the pallidus. In two other cases which I have submitted to chronic intoxication with cyanide for a period of over 6 months I have found that the softening extended to the pallidus but in association with numerous other areas of softening distributed all over the cortex and brain stem.

I here insist again on the fact that the gliosis which I have described in my cases and which in the cerebellum at times is considerably marked, may be entirely independent of any area of softening and therefore cannot be considered a reparative type of gliosis.

whereas a shrunken appearance of the element is more apt to be detected. Occasionally small areas of softening are found in some instances, especially in cases where the convulsive manifestations have been a dominant factor of the clinical symptomatology.

Altogether there is a marked discrepancy between the severity of the lesions in the white substance and the rather mild reaction in some cases of the cellular elements of the cortex.

2. *Optic Nerve and Optic Tract:* Patches of demyelination or large areas of the same are found in the optic nerves, optic chiasma, and optic tracts. The pathological process is fundamentally the same as the one described in the brain tissue. The intensity and the extension of the lesions vary from case to case but seems to be essentially represented by demyelination and gliosis with quite good preservation of axis cylinders.

3. *Involvement of the Spinal Cord:* As already said before, the spinal cord is severely involved though areas of softening have never been found. The posterior columns (Fig. 28) seem to suffer predominantly though the process of demyelination is a very diffuse one involving at times the whole transverse sections. The axis cylinders seem to resist somewhat more than the axis cylinders of the brain structures. The fibroglia reaction is also much less pronounced in the spinal cord than it is in the brain tissue itself. Occasionally in longitudinal sections only patches of gliosis are found and in a few cases they are not even detectable with the technique used so far (Holzer and Anderson). The nerve cells disclose often acute degenerative changes which are also detected in some of the astrocytes of the gray matter.

4. *Spinal Roots:* The process of demyelination is seen to invade also some of the spinal roots, especially the posterior ones where fundamentally the pathological process consists also in demyelination with better preservation of the axis cylinders and no areas of softening.

5. *Patches of Demyelination:* Though the process is fundamentally one of diffuse sclerosis in which the destruction of myelin sheaths and later on of axis cylinders and substitution with glia fibers is a diffuse one and symmetrical in both hemisphere, here and there in the brain and cerebellum small patches of demyelina-

tion can be found, some of them having clear-cut edges and not differing histologically from the ones described in cases of multiple sclerosis. While some of the patches seem to preserve their individuality others have a tendency to coalesce in order to form a larger patch of diffuse sclerosis.

Comments

The above reported experiments show conclusively that a condition of diffuse encephalomyelopathy possessing the histopathological characteristics of diffuse sclerosis can undoubtedly follow the administration of repeated doses of a toxic substance. There is no doubt as to the degenerative nature of the lesions which I have found in all but two of the cases and it seems to me a well-established fact that the pathological condition which I have experimentally reproduced is toxic in origin.

How far can we go now in comparing this picture of diffuse encephalomyelopathy in cats and monkeys with the condition of diffuse sclerosis in man. We all agree that we cannot expect in animals, especially of the lower scale, the exact symptomatology which we find in man. Besides, the lesions may vary according to the species of animal under experiment and we know that comparative pathology is now gradually developing, as advocated by A. Meyer.

There are, nevertheless, definite points of analogy between the experimental and the human pathological picture of diffuse sclerosis which should not be forgotten. We have, indeed, identity of facts from both the clinical and the histological standpoint. From the clinical standpoint I have reported, in the animals under the action of potassium cyanide, such symptoms as tremors, nystagmus, spastic paralysis, temporary blindness, hyperkinetic and convulsive manifestations which undoubtedly form a very important part of the clinical picture of human diffuse sclerosis. From the histopathological standpoint the analogies are still more indisputable. I have found a very definite process of demyelination with its characteristics of diffusion and symmetry. I have found the typical involvement of the axis cylinders and the typical glia reaction in the form of definite general anisomorphe type of gliosis. I

have reported characteristic areas of necrosis and softening. I have emphasized the predilection of the lesions for the white substance and their greater severity in the periventricular areas, all characteristic of the pathological process of diffuse sclerosis in man. We cannot, therefore, be extremely resistive to the suggestion of a pathological affinity and may be of an identity between the human and the experimental condition.

Though not necessarily connected with the results of my experiments we may at this point consider the question of the identity between multiple and diffuse sclerosis. In regard to this very important question I feel that those authors who, like Kufs,[27] Bouman,[28] Balo,[29] Schaltenbrand,[30] Wertham,[31] Gozzano and Vizioli,[32] Lauritzen and Lundholm,[33] believe that between multiple and diffuse sclerosis the difference is only a question of extension and intensity of the lesions and that the two pathological processes are fundamentally identical, are certainly basing their contention on facts the importance of which cannot be easily overlooked.

Indeed, in diffuse sclerosis as well as in multiple sclerosis there is a predilection of the lesions for the periventricular areas. In diffuse sclerosis as well as in multiple sclerosis the axis cylinders may be more or less respected, and though in diffuse sclerosis the involvement of the axis cylinders is more pronounced, very often in multiple sclerosis areas have been also described in which the destructive process has involved the axis cylinders as severely as it has the myelin sheaths. In diffuse sclerosis as well as in multiple sclerosis small foci can be found in which the areas of demyelination seem to be dependent on the territory of the blood vessel. Conversely, in both diffuse and multiple sclerosis territories have been found entirely independent from the blood vessels, as reported by Dawson, Falkiewicz,[34] Pette,[35] etc. In diffuse sclerosis as well as in multiple sclerosis areas of involvement have been reported in the cortex and in diffuse sclerosis, where generally the spinal cord is preserved, primary involvement of this structure has been reported (D'Antona,[36] Urecchia and Mihalescu,[37] Gozzano and Vizioli, etc.). In both multiple and diffuse sclerosis areas of necrosis and softening have been reported (Bielschowsky,[38] Lüttge,[39] Weisenburg and Ingham,[40] Wohlwill.[41]

Finally, in diffuse sclerosis several authors, among which Hallervorden,[42] Stewart, Greenfield and Blandy,[43] Kufs,[44] and Wertham,[45] Vizioli and Gozzano,[46] have reported cases in which close to large areas of demyelination small areas were found not differing at all in character from the small areas typical of multiple sclerosis.

Irrespective of the identity of multiple and diffuse sclerosis, a problem which certainly cannot be discussed at length in this short paper, the next interesting point to discuss concerns the nature of the pathological condition, if, in other words, the lesions which I have reproduced experimentally have to be considered inflammatory or degenerative in type. I repeat here that 16 out of 18 cases studied disclose purely degenerative changes and only here and there is some of the cases the perivascular spaces show presence of few lymphocytes interminged with scavenger cells. In 2 out of 18 cases we are undoubtedly dealing with a primary inflammatory process, as inflammatory lesions, in the classical sense of the word, are not only found in old areas, but in very recent areas where demyelination is not present (cortex and meninges) thus excluding the symptomatic nature of the inflammation which, as it is well known, can be found accompanying purely degenerative processes.

I am at a loss as to an explanation of the inflammatory lesions of the two above-mentioned cases and the chance that the toxic factor may have stirred up a latent infection is a possibility to be kept in mind. On the other hand, it may be possible that a toxic factor by itself can, under particular circumstances, such as a particular form of resistance of the tissue, develop a true inflammatory reaction. In this connection we also know that experimental aseptic emboli result in the early stages into a definite inflammatory lesion with exudate containing a large amount of polys, as first reported by Nissl, and recently by Cone and Barrera,[47] Putnam and Morrison,[48] and Berlucchi.[49] All these factors together lead to the conclusion that possibly our conception of an inflammatory lesion is not as yet a very firm one and that probably in the future we will have to change our standing as to the relationship between inflammation and infectious processes. It seems to me that we have more than one fact in hand in substantiation of the fact that a true type of inflammation may be produced by an aseptic condition

or by toxic factors irrespective of a definite infection. Such a unification would help our understanding of various pathological conditions in which a few authors consider the processes primarily degenerative, while others consider them as primarily inflammatory. This would apply particularly to diffuse sclerosis, where, as we all know, since Schilder[50] has described his particular variety of the disease, we distinguish an inflammatory form, a degenerative form, and possibly a blastomatotic form. It may well be that the so-called inflammatory variety may only be a different aspect of the process resulting from the same noxious agent acting under conditions still escaping our means of investigation.

That a toxic factor may be at the base of nervous complications even in general infectious pathological processes is also substantiated by the fact that following various exanthematous diseases of infancy, as measles, varicella, smallpox, etc., a diffuse encephalomyelopathy may occur. The question of the toxic or infectious nature of such a complication has been widely discussed, some of the authors favoring its infectious origin. I personally feel that we are dealing in most of these cases with a toxic condition resulting into a diffuse encephalopathy. My contention is based on the type of histological lesion found in the white matter in which no definite inflammatory changes are seen and on the typical diffuse lesions of the cortical nerve cells which in some cases described (Ferraro and Scheffer[51]) are morphologically identical to the lesions that we experimentally reproduce with exogenous toxic agents.

In considering the relationship of diffuse sclerosis to other pathological conditions it might be wise to keep in mind the contributions that have accumulated in the last few years concerning the production of areas of demyelination brought about in animal experiments by diets deficient in some vitamins. Among them we may recall the work of R. Stern and M. Findlay,[52] C. Voegtlin and C. Lake,[53] E. F. Gildea, Kattwinkel and Castle,[54] Zimmerman and E. Burack,[55] in whose opinion following a lack of antineuritic vitamin B, areas of demyelination were found not only in the peripheral nerves, but also in the spinal cord, in the pons, and in the cerebrum.

In experiments with deficiency of vitamin B, Hughes, Lienhardt, and Aubel,[56] in pigs, chickens and cows, produced impaired vision, incoordination and spasms related histologically to demyelination in the spinal cord, optic nerve, and sciatic nerve.

We also must keep in mind with due consideration the last experiments of Weil and L. Crandall[57] concerning lesions of the liver through the ligature of the pancreatic or colledocus ducts which procedure resulted in a process of demyelination and necrosis in the white substance of the brain and more so in the periventricular areas. The importance of the liver functionality seems every day to come more to the foreground because of the possibility that a toxic agent which might act primarily on the liver may impair the detoxifying capacity of such an organ and allow toxins originating from our normal intermediate metabolism to reach the blood circulation and eventually damage the central nervous system.

As ultimately the final diagnosis of a neurological condition rests with the histopathological investigation, I feel that from this angle no clear differentiation is possible between the lesions described in human diffuse sclerosis and the ones reproduced experimentally with potassium cyanide. This statement may imply that from the histopathological standpoint many conditions clinically labeled with various names may ultimately be reclassified within the bounary of diffuse sclerosis, (encephalomyelopathy or encephalomyelitis) with a qualification as to their possible etiological factor. It may also follow that very possibly the conception of diffuse sclerosis as a clinical entity will have to be abandoned and the condition considered as a syndrome or end result of various pathological conditions among which original general infections and toxic processes may both play an important role.

The work which I am presenting deals with the experimental reproduction of a toxic encephalomyelopathy (diffuse sclerosis) with one particular toxic substance, a possible product of our intermediary metabolism. It is hoped that further experimental work will be able to substantiate the protean origin of diffuse sclerosis by finding other factors capable of determining the pathological and as much as possible the clinical picture of such a disease.

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