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Dysoria, a New Dimension of Pathology* ** ***

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Summary. The starting point of our research was the recognition that such pronounced brain-toxins as lead, manganese and thallium affect the central nervous system without being present there and that they operate through *mediators*. Other poisons which permeate easily the brain are also dependent on mediators to produce lasting brain injury. Representatives of this group are ethyl alcohol and tellurium.

Amongst the mediators most prominent are the toxic deficiencies of thiamine, of riboflavin, of vitamin E and of the very important Geiger's liver factors. All these deficiencies result in *dyskrasia*, in the terminology of Rokitansky's humoral pathology. The dyskrasia which interfere with the energy metabolism have morphological correlates while other non interferring ones, as LSD, marihuana, and the opium alkaloids do not. This cognizance instigated a series of investigations of the *dyskrasic dysergosis* (dys = faulty and ergon = work, i.e. energy) which produce structural changes only when chronic. In contrast chronic hypoxia, hypoxemia and cardiopathic oligemia have no neuropathology because of the brain's adaptational mechanisms against chronic circulatory disorders.

Another basic difference is that while the brunt of the damage in hypoxic hypoxemic and cardiopathic dysergosis is borne by the neuron, the prime target of the dyskrasic dysergosis is the blood-tissue barriers, the dysfunction of which results in *dysoria* (Schürmann and McMahon, 1933). The dysory plays a decisive role in such a vast number of chronic degenerative diseases of the brain and of the extracerebral organs, that it amounts to a new dimension of pathology.

Key-Words: Toxic, Nutritional and Hepatic Deficiencies — Dysory — Antagonistic Relationship Vitamin E-Tellurium — Antagonistic Relationship Riboflavin-Thallium — Vitamin E Deficiency and Involution.

Zusammenfassung. Der Ausgangspunkt dieser Untersuchungen war die Erkenntnis, daß so ausgesprochene Hirngifte wie Blei, Mangan und Thallium das Zentralnervensystem beeinträchtigen, ohne an Ort und Stelle vorhanden zu sein, d. h. sie wirken durch Mittler oder, um Bonhöffers Ausdruck zu gebrauchen, durch pathogenetische Zwischenglieder. Das gilt auch für die Gifte, die ins Gehirn eindringen, wenn sie dauerhafte Schäden anrichten. Beispiele dafür sind Alkohol und unerwarteterweise Tellurium.

* Excerpt from a manuscript on "Toxic, nutritive, hepatic and constitutional deficiencies".

** To Willibald Scholz, Munich.

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Die wichtigsten Mittler sind die toxischen Thiamin-, Riboflavin-, Vitamin E-, und Geigers Wirkstoffe-Mangelzustände. Sie alle bewirken eine *Dyskrasie*, im Sinne der Rokitansky's Humoral-pathologie. Nur die Dyskrasien, welche den Energiestoffwechsel beeinträchtigen, haben ein morphologisches Substrat, im Sinne von irreversiblen Strukturveränderungen. Die anderen, die das nicht tun, wirken auf einer anderen völlig unerforschten Ebene, die man summarisch die *pharmakologische* Ebene nennen könnte. Beispiele dafür sind, LSD, Marihuana, und die Opiate. Systematische Untersuchung der *dysergotischen* (dys = falsch und ergon = Arbeit, d. h. im heutigen Sinne Energie) Dyskrasien ergaben die merkwürdige Tatsache, das sie Strukturveränderungen nur bei *chronischer* Einwirkung verursachen im Gegensatz zu den chronischen hypoxischen, hypoxämischen und kardio-pathischen Dysergosen, die sich wegen adaptiver Mechanismen gegen hämodynamische Störungen auf funktionelle Unregelmäßigkeiten, wenn solche überhaupt vorhanden, beschränken. Was die dyskrasischen Dysergosen bewirken ist Beeinträchtigung der Blut-Gewebeschranken, mit nachfolgender Dysorie, wogegen es eben keine wirksamen Schutzeinrichtungen gibt. Das ist verhängnisvoll, da die Dysorie von entscheidender Bedeutung bei der Entstehung einer großen Anzahl degenerativer Erkrankungen des Zentralnervensystems und vieler Körperorgane ist. Dementsprechend wird die *Involution* und der *natürliche Tod* nicht durch Abnutzung der Parenchymzellen (Abiotrophie), sondern durch Versagen der sie schützenden Schranken (Dysorie) bewirkt.

Schlüsselwörter: Toxische, nutritive und hepatische Mangelzustände — Dysoria — Antagonistische Beziehung Vitamin E-Tellurium — Antagonistische Beziehungen Riboflavin-Thallium — Vitamin E-Mangel und Involution.

Introduction

The starting point of our research covering several decades, was the realization that such pronounced brain-toxins als lead, manganese and thallium affect the central nervous system without being present there, and that they operate through the mediation of specific deficiencies which they produce. Therefore, sometimes it is irrelevant whether a poison penetrates into the brain or not. So for instance the rat is "immune" to lead in contrast to thallium though neither metal is found in the central organ. The explanation is that thallium produces a riboflavin dificiency to which rats are extremely susceptible (Pentschew and Garro, 1969).

Amongst the mediators, in addition to the toxic ariboflavinosis, most prominent are the toxic deficiencies of thiamine, of vitamin E, and of the important Geiger's (1961) liver factors. These deficiencies result in *dyskrasia*, according to the terminology of Rokitansky's humoral pathology. The dyskrasias which interfere with the energy metabolism have morphological correlates while the other none interferring ones, as LSD, marihuana and the opium alkaloids do not.

As Kety (1948) stated the brain is a great deal more complicated than a furnace and to try to relate energy metabolism to the more abstruse functions of the brain is to try to bridge a very large gap. The bio-energy is analogous to the electricity which is needed to keep the filaments of the electronic tubes in a radio hot and what the tubes do with their

heated filaments is a process of entirely different order. It is at this *pharmacological* order that LSD, heroin, the tranquilizers, etc. affect the central nervous system.

The disorders of the energy metabolism, an appropriate generic name for which, would be *dysergosis* (dys = faulty and ergon = work, i.e., energy) result from: 1. lack of O_2 in the air or in the blood (hypoxic or hypoxemic dysergosis); 2. lack of combustibles, e.g. glucose (substrate dysergosis); 3. acute systemic oligemia, as in *temporary* cardiac arrest or centrogenic collapse (cardiac or collapse dysergosis); 4. inactivation of certain respiratory enzymes, e.g. cytochromoxidase by the cyanides (dysenzymatic dysergosis) and 5. lack of Co-enzymes, e.g., thiamine, riboflavin; lack of vitamin E and lack of the important though still not well defined Geiger's (1963) liver factors (hepatic dyskrasic dysergosis).

The *dyskrasic dysergosis* occupy a special place inasmuch as they produce structural changes only when *chronic*. Another basic characteristic feature is that their primary target is the barriers (blood-brain, and blood-tissue respectively) the dysfunction of which results in *dysory*.

One has to go back to 1933 to fully understand the concept of dysory. Schürmann and McMahon then published a remarkable paper with the title "Malignant nephrosclerosis and at the same time a contribution to the significance of the blood-tissue barrier". The name they gave to the effect of the blood-tissue barrier dysfunction was dysoria (dys = faulty and oros = limit, border). According to the authors the benign patchy nephrosclerosis "(arteriosklerotische Schrumpfniere") as well as the diffuse malignant nephrosclerosis "(arteriolosklerotische Schrumpfniere)" are both manifestations of *dysory* at different stages of development. Significantly, dysoric changes were also found in pancreas and spleen.

The concept of dysory entered neuropathology much earlier than it did general pathology, if at all. *Up to the present day it has not found its place in the medical dictionaries!!* Although *brain edema* was extensively studied as early as 1939 (Jacob, 1939, 1940; Hallervorden, 1940) and is now one of the main topics of neuropathology, no essential contributions to the phenomenon "dysory" were achieved because edema is not necessarily related to dysory, i.e. to accumulation of fluid in the extracellular spaces (s. Lampert, Garro and Pentschew, 1967). The ambiguity of the concept of edema is illustrated by the fact that a sharp line between "brain swelling" and "brain edema" has not yet been found.

Scholz (1941—1951) widened the scope of dysory at the edemal level by including the various morphological manifestations of its *discontinuous* form. First among them are the *microglia nodules*, which first were thought to be indicative of various virus encephalitis, (e.g. Babes nodules). Scholz compared them with the miliary abscesses in septicemia,

which may alternate with the microglia nodules. We found *miliary abscesses* spread irregularly throughout the entire CNS in monkeys fed a lead carbonate diet for several months. Since no infectious processes could be detected we concluded that the miliary abscesses are sometimes *aseptic* clusters of polymorphonuclear leukocytes, as another manifestation of a discontinuous dysory.

A turning point was the discovery of the dysory at the *subedemal level*, first suggested by the ingenious experiments of Becker and Quadbeck (1953) with Astraviolett FF, which, as a test of the permeability of the blood-brain barrier, is much more sensitive than trypan blue. We were able to prove the existence of a dysory at the subedemal level also with trypan blue. These observations were made on suckling rats whose mothers were fed a diet containing lead carbonate (Pentschew and Garro, 1966). Since the dysory at the *subedemal* level is purely functional, it is not a research object for neuropathology. However, we found, disorders of the homeostasis (Cannon, 1939) of the brain, caused by dysory at the functional level induce a morphologically perceptible and characteristic response, provided that it persists long enough (not under 2 weeks). Experimental monkeys (Pentschew, Ebner and Kovatch, 1963), chimpanzees (Pentschew, Riopelle, Kovatch and Lampert, 1966), gibbons, cats, dogs and rats (unpublished data) proved to be excellent models for investigation of this response. Later, other models, such as the encephalopathies produced by iron, selenium and tellurium, which like manganese encephalopathy were caused by hepatic insufficiency (Lack of Geiger's factors?) were added (Pentschew and Garro, 1966, 1967). Another dysoric encephalopathy produced in rhesus monkeys was that caused by lack of riboflavin or by application of its antagonist—thallium (Pentschew and Garro, 1969). The tissue and topistic patterns of ariboflavinosis encephalopathy were completely different from those of manganese encephalopathy, demonstrating the exuberance and the variability of the responses to dysory at the subedemal level, depending on the specific type of deficiency.

The protagonist of the dysoric encephalophaties (Pentschew, Garro and Schweda, 1965)—Wernicke's "Polioencephalitis hemorrhagica superior" has been with us since 1881, but no one recognized its significance. Much later Wernicke's disease was found to be the manifestation of thiamine and probably riboflavin deficiencies, superimposed on a selective liver insufficiency (probably lack of Geiger's substances).

Wernicke's encephalopathy provided additional information about the archepattern of the dysoric encephalopathies, characterized by a glio-mesenchymal proliferation, despite preservation of the nerve cell bodies (Pseudoencephalitic tissue syndrome, Pentschew, 1952). The ultimate fate of the latter was best studied in manganese encephalopathy

of the monkey. What one finds is a slowly progressing simple *atrophy* of the nerve cells, the end stage being their inconspicuous fading away. The expression "preservation of the nerve cells" refers to their morphological appearance only, but does not exclude functional disturbances. This is illustrated by the precursor of Wernicke's encephalopathy—*dellirium tremens*, which does not show neuronal or other structural changes. There is evidence that mental disturbances also in other deficiency states (e.g. in ariboflavinosis and thallium encephalopathy, respectively) are manifestations of dysory. It is very probable that Bonnhöffer's (1912) exogenous psychotic reactions belong to the same group.

The pseudoencephalitic tissue syndrome as such can occur in various brain areas and under various pathological conditions. A real dysoric encephalopathy is present however only when the dysoric alterations have *symmetrical* distribution and involve the damaged topistic unit in its entirety, without affecting the border structures, i.e. when, in Vogt's terminology, it is *holotopistic* (holos = entire). It is true that symmetrical distribution of lesions can be simulated also by the cardiopathic (Wildi, 1959) and/or *centrogenic collapse* encephalopathies. However these lesions are not holotopistic and the brunt of the injury is borne by the neurons. Another mark of distinction between the encephalopathies caused by disorders of the hemodynamics on the one hand and those related to dysory on the other is the obligatory presence of Alzheimer II cells in the latter.

The distribution pattern of the big family of the *hepatic encephalopathies*, encompassing Wilson's and Hallervorden-Spatz's diseases, Huntington's chorea, Kernicterus and Posticteric encephalopathy respectively, and Hunt-v. Bogaert's pallidum-subthalamic nucleus progressive atrophies is quite different from that of Wernicke's encephalopathy. It involves selctively striatum, pallidum, nigra reticulata and subthalamic nucleus. Ariboflavinosis affects selectively fasciculus gracilis, nucleus gracilis and in addition the *optic nerves, tracts* and *lateral geniculate bodies* (unpublished data). This finding may shed light on the controversial *retrobulbar neuritis* and on the *blindness* in the prisoners-of-war in the Far East (Burgess, 1946; Moore, 1946) exposed to malnutrition, especially to lack of riboflavin in the frame work of Gopalan's burning feet syndrome (Gopalan, 1946; Cruickshank, 1946; Stannus, 1948), and on alcoholic and tobacco amblyopia.

Experimental ariboflavinosis of the rhesus monkey has a curious resemblance to the *spino-cerebellar-atrophies* (Greenfield, 1934, 1954). This group of degenerative, often familial or hereditary diseases, is often linked to hereditary degeneration of the eye. In Friedreich's ataxia the incidence of blindness varies from 7 to 12 percent.

The spino-cerebellar atrophies are still regarded as manifestations of "*abiotrophies*" and were used by Gowers to illustrate what he meant by this term. Our experimental findings suggest that the spino-cerebellar atrophies may be due to a *constitutional* inability to utilize properly riboflavin rather than to wear and tear, which is the meaning of abiotrophy.

The climax of our research work may prove to be the experimental vitamin E deficiency in rhesus monkeys (unpublished data). Since we found that tellurium affects chiefly, though not exclusively, vitamin E metabolism, we returned to the findings of *chronic tellurium poisoning* in cats and rabbits (Pentschew, 1934, 1935, 1938, 1939, 1958) and in rhesus monkeys (Pentschew *et al.*, 1962). What emerged from these comparative and comprehensive studies was that vitamin E deficiency of long duration (between 3 and 12 months) is followed by excessive proliferation of the connective tissue with collagen deformation in numerous extracerebral organs. In contrast, the parenchymatous cells were relatively well preserved; eventually they became atrophic and slowly dwindled away. The affected organs were: kidney, pancreas, liver, spleen, lymph glands, lung and gastro-intestinal tract. The specific structure of the affected organ conferred additional characteristic features, so for instance the appearance of the kidney was reminiscent of arteriosclerotic granular atrophy and there was a selective necrosis of the Langerhan's cell of the pancreas. We interpreted our findings as an experimental model of Klemperer's (1953) *collagen diseases.*

With the inclusion of the latter and of the findings in vitamin E deficient rhesus monkeys the circle of disory begun by Schürmann and McMahon in 1933 is now completed.

In all probability vitamin E regulates the blood-tissue barriers of the extracerebral organs and presumably of the chicken brain (Pappenheimer *et al.*, 1946) and of the sensory relays nuclei in spinal cord and medulla oblongata of the rat (Pentschew and Schwarz, 1962). With the evolution of the brain vitamin E is replaced by the Geiger's liver factors, which are indispensible for the acceptance of glucose by the brain parenchym of the higher species.

A cursory glance at our material revealed that the brain changes were not uniform, suggesting that they might be reflections of the dysfunction of some of the several affected extracerebral organs. Only the abducens nuclei showed consistently typical holotopistic dysoric alterations, reminiscent of those in Richter's (1949) monkeys treated with plasmocid.

New evidence to this concept was added by the discovery that the special skill of the brain capillaries to function as a barrier depends chiefly on an adequate energy supply (Pentschew and Garro, 1966) and by the fact that the connective tissue has also an intense energy metabolism (Scheiffarth and Zicha, 1967).

Methods and Material

Since we were interested chiefly in chronic disease conditions produced by exactly measured poison-solutions, the method of long term (up to four months!) uninterrupted intravenous infusion in rhesus monkeys proved invaluable. This method for instance made possible the discovery of the convertibility of manganese encephalopathy into Wilson's disease or into the Hallervorden-Spatz's syndrome. Through the same method we found that a mixture of ferrous sulfate and manganese chloride produces invariably a most conspicuous choreo-athetotic syndrome in the rhesus monkey.

Among the experimental animals priority was given to rhesus monkeys, in which most of the extrapyramidal syndromes were reproducible with the exception of paralysis agitans, though rats were in many instances invaluable.

A fixed plan was not suitable to our specific purposes. We used instead with best results the "strategy on the battlefield".

The Yield

The presented work centered around exploring the genesis of the degenerative diseases by creating experimental models in appropriate animals, particularly rhesus monkeys. We succeeded in producing: 1. manganese encephalopathy, 2. Wilson's disease and 3. Hallervorden-Spatz's disease. Beyond this the convertibility of one into the other was demonstrated and therefore they could be incorporated into the family of the hepatic encephalopathies.

In another series of experiments we established the neuropathology of riboflavin deficiency and discovered the antagonistic relationship between riboflavin and thallium. Since optic nerve and tract were invariably affected we now have a model for study of *retrobulbar neuritis.*

In the course of investigations of vitamin E dificiency in monkeys we came upon a syndrome closely resembling *Klemperer's collagen diseases.* In unraveling the intricate functions of vitamin E the recognition that tellurium inactivates vitamin E was very helpful in that we now could utilize earlier experiments in various animals with this metal.

A homologue of progressive *muscular atrophy* was produced in monkeys by long uninterrupted intravenous infusions of minute amounts of potassium cyanide. The lesions were localized in the motor nerve cells of medulla oblongata and spinal cord without any evidence of dysoria. It may be that a primary atrophy of the neurons and their dwindling away are the characteristic tissue pattern of the infrequent *dysenzymatic dysergosis.* The yield in *rats* consited of: 1. the discovery of the long sought for morphological correlate of *Ringsteds ataxic syndrome* in vitamin E

deficient animals. The changes proved caused by dysory. This implied also to the abundant axonal bodies or "spheroids" resulting probably from permeability disorders of the periaxonal membrane, 2. producing of neonatal hydrocephalus internus through mother milk containing minute amounts of tellurium and 3. creating of a complex lead encephalopathy in the new born rat, an animal which after weanning becomes resistant to lead. This encephalopathy gave an unique insight into the functioning of the blood-brain and the bloodspinal cord barriers respectively.

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