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CHANGES IN THE CENTRAL NERVOUS SYSTEM IN UREMIC CONDITIONS

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The morphologic pattern of pathological lesions in the central nervous system associated with uremia is discussed. Three illustrative cases are reported.

The first case concerns a 70-year-old female patient in whom uremia was the outcome of a preterminal exacerbation of chronic glomerulonephritis. The morphologic changes in the brain, besides those characteristic of uremic encephalopathy, showed signs of allergic encephalitis typical of para-infectious and postvaccinational encephalitis.

The second case concerns a 73-year-old male patient. Uremia was presumably connected with hydronephrosis caused by urinary retention due to prostatic adenomas. The changes in the brain in this case were few, with predominance of edema and moderate atherosclerotic lesions.

In the third case, that of a 24-year-old male patient, uremia developed as a result of bilateral destruction of the kidneys by a tuberculous process. The morphological findings in the brain closely resembled those of typical uremic encephalopathy.

In all three cases uremia was the result of renal disease, but the pathogenetic mechanism was different in each case. In the opinion of the authors, different pathogenetic mechanisms may be the reason for the different morphological changes in the central nervous system.

Clinical neurologic syndromes present in uremia are sometimes so rich in signs and symptoms that they often form striking contrasts with the macroscopic findings in the brain at the autopsy. In these cases the anatomical examination usually gives only an imperfect diagnosis of brain edema besides more or less significant changes in the vascular system. These changes are related either to the degree to which the vessels are filled or to the more or less pronounced atherosclerotic damage to their walls. The concomitant presence of atherosclerosis complicates the evaluation of the influence of the increased nitrogen level compounds in the blood on the condition of the brain tissue.

The clinical picture, however, may present a whole scale variants, from neurotic or psychotic syndromes to severe syndromes resembling encephalitis and to focal changes as well.

Knutson and *Baker* (1945) differentiated three types of neurologic complications observed in the course of uremia.

1. The syndrome of decreased activity of the central nervous system characterized by apathy, increasing psychic and somatic fatigue, impairment of intellectual functions, and general muscular weakness. This condition slowly passes into stupor and deep uremic coma.

2. The syndrome of increased irritability of the nervous system characterized by increased muscular tone, motor hyperexcitability, increased reflexes and general readiness to seizures usual has a lethal outcome in an epileptic status.

3. Finally, focal disturbances may appear, due to monoparesis of an extremity or hemiparetic syndromes, general ascending paralysis of the Landry type. The characteristic feature of these pareses is their course with remissions and recurrences, and ever increasing deterioration with every recurrence. Of course, mixed forms are possible forming transitions between these clinical syndromes.

The variety and great number of the clinical signs remain unexplained and this not only in the above mentioned anatomical findings in the brain but it is also the case with the interpretation of the pathogenesis of the effects of uremia in the central nervous system, even with due consideration to its renal and extrarenal origin.

The lack of correlation between the clinical symptomatology and the pathogenesis in uremic conditions was strongly stressed by *Scheinberg* (1954). During investigations on the influence of various forms of uremia on cerebral circulation and metabolism of the brain he constantly found a strikingly decreased level of oxygen and glucose in the arterial blood, with normal oxygen level in the venous blood. This observation might be a proof of the nervous cells decreased ability to utilize oxygen. No correlation, however, can be found between these disturbances and the level of non-protein nitrogen in the blood and neurological status of the patient.

In his classification of uremic conditions *Bull* (1955) accepted a very broad definition of uremia. He defined all the conditions in which „the kidneys cannot maintain the internal chemical balance of the organism because of disturbances in the normal production of metabolites and their excretion with this term". Basically this definition applies to the uremia constituting the final stage of renal failure, as well as to uremic conditions of extrarenal origin. It takes into consideration all possible chemical disturbances: disorders of the acid-base balance, of water metabolism, the shifting of electrolytes in the intracellular and extracellular compartments.

The difference in the condition of the brain in uremia resulting from glomerulonephritis, for instance, and in uremia of extrarenal origin would be then based on the presence of a „renal" vascular factor in the former, preceding the special uremic changes. In fact *Bodechtel* and *Erbslöh* (1958) in accordance with *Volhard* use the term „pseudo-uremia" (acute or chronic) to designate these mixed conditions. The state of the brain in pseudo-uremia corresponds

to the picture of *encephalopathia hypertonica* (*van Bogaert* 1959), with secondarily superposed new changes due to a sudden impairment in oxygen supply and an increase in the transudative processes.

The morphological correlates of these conditions are: edema situated mainly in the white matter (*Wollheim* and *Moeller* 1960, *Beckman* 1947, *Grinker* 1951) causing the development of localized small necrotic foci showing no topographical relation to the vessels supplying this region *(Beckman)*; secondary breakdown of myelin with sudanophilic accumulations *(Knutson, Baker)*; smaller or greater perivascular hemorrhages and minute extravasations *per diapedesim* showing particular preference for localization in the midbrain *(Bodechtel* and *Erbslöh)*; relatively great progressive and regressive changes in the glia *(Greenfield* 1958, *Wertham* 1934, *Bodechtel* and *Erbslöh)*; slight reaction of the mesenchymal elements (*Knutson* and *Baker*, *Hechst* 1932); final neuronal damage either with slight changes of the acute, chronic or ischemic type (*Hechst*, *Rives* 1923), or with loading of the neurons with a peculiar metachromatic material the chemical structure of which is not yet known (*Hechst*, *Uchida* 1929).

In purely extrarenal uremia, especially in experimental conditions, mainly glial reactions were observed, above all the reactions of the perivascular glia (*Alpers* 1930). This monotonous picture was considered by *Alpers* to be the effect of purely uremic toxemia.

In a clinical case of extrarenal uremia *Tichy* observed a strikingly active mesenchymal reaction resembling the findings special to encephalitis *(encephalitis uraemica)*. He too considered this condition to be a morphological expression of specially uremic toxemia.

From the view point of *Bull's* definition there are no grounds, on which the pathogenesis of both these forms could be differentiated. In both conditions deeply lying disturbances in the chemical composition of the circulating blood must appear accompanied by consequent disorders in the exchange of fluids between the vascular system and the surrounding tissues. It would seem, however, that in renal uremia these disturbances are more profound because they are preceded by damage to the vascular system itself, with all the ever increasing consequences. In extrarenal uremia these changes are more violent, with a shorter period of survival which does not allow for a full development of morphological symptoms. Both these pictures could then be considered as representing two stages of the same process.

This unitarian interpretation cannot, however, explain the varieties of development of the clinical pictures.

The cases described below add some new observations to this problem. They show that the morphological pictures can also take rather different forms and that these differences suggest the influence of certain incidental factors not associated with the chemical mechanism of uremia, but with earlier links in the chain of events in the pathogenesis of the disease.

Case 1 (PAN 38/62). Patient B. S. aged 70 (Department of Neurology, Grochowski Hospital in Warsaw). The patient has suffered from headaches for some years. For three days before admission she experienced speech disturbances with slurring of the words, motor restlessness of the extremities and of neck muscles, increased drowsiness, general weakness, vomiting. The history of the events preceding actual illness was without significance.

On the day of admission the objective status was: the patient was drowsy but conscious. Involuntary movements were present in the head, neck, shoulders and upper extremities. No distinctly abnormal findings were elicited in the internal organs. Heart sounds were rather dull, pulse 100/min., temperature 36·5°C, arterial blood pressure 170/70 mm Hg. No changes in the cranial nerves, nor in the ocular fundi. In the upper extremities the muscular tone was increased on the right, periosteal and tendon reflexes were more pronounced on the right. No abdominal reflexes were present. In the lower extremities the muscular tone was increased, more so on the right side, where the reflexes were also more pronounced.

During further observation neck rigidity appeared and stupor increased gradually.

Laboratory investigations: blood urea level 280 mg%, with gradual increase to 400 mg%. Alkaline reserve in the serum ranged from 32 vol% to 18 vol%. Urinalysis: protein 0·16‰, erythrocytes from 15 to 60 per field, specific gravity 1012. In the blood the number of erythrocytes was only 2,580,000, index 1·07. In the cerebrospinal fluid protein — 99 mg%, protein reactions weakly positive, 2 lymphocytes in 1 mm^3. Other investigations were without significance.

The patient died five days later. The diagnosis was: *Status praecomatosus. Uraemia. Arteriosclerosis diffusa cerebri. Pyelonephritis chronica exacerbata.*

Autopsy was performed in the Department of Pathology, IV Community Hospital in Warsaw, 22 hours after death.

The results of autopsy: chronic glomerulonephritis; left ventricular hypertrophy; edema and emphysema of the lungs; bronchopneumonia situated in the lower lobe of the right lung; moderate atherosclerosis; ischemia of the organs.

Macroscopic section of the brain: (dr *Z. Kraśnicka*) — the brain was of normal size. The vessels at its base showed no atherosclerotic changes. Its anatomical details were visible.

Large sections from the frontal, central, parieto- occipital regions, from three levels of the basal ganglia, from the cerebellum and the brain stem were taken for microscopic examination. The material was frosted. Staining: cresyl violet, hematoxylin-eosin, Spielmeyer.

Microscopic examination: the structure of the process. Striking pathological changes, marked even at low magnifications, were evident in the form of dense glia in the all white matter and an increase of the glial elements in the

cortex and subcortical ganglia. On the background of uniform gliosis plaques of denser glia were evident appearing perivascularily (Fig. 1) in the form of microglial infiltrations with an admixture of astrocytes, lymphocytes and often of extravasated erythrocytes (Fig. 2). Besides that microglial nodules were evident in some places, laying loosely in the tissues (Fig. 3). The vessels were usually packed with blood cells, in some places larger perivascular extravasations appeared as well. The capillaries were filled with blood, especially in the white matter. There were evident signs of edema shown by a separation of the fiber systems recognizable by the presence of rows of oligodendrocytes along them and enlarged perivascular spaces. In certain places these signs were fairly pronounced. Macrophages loaded with hemosiderin were frequently encountered in the vessel walls. Rather discrete lymphocytic infiltrations were present around many vessels of larger and smaller dimensions (Fig. 4), only rarely were they homogenous. They mostly had an admixture of microglia, which is a considerable component in perivascular infiltrations. The infiltrations were mainly localized around the venous vessels of the white matter. No concomitant atherosclerotic changes were observed in the vessels walls. The gray matter was damaged in a lesser degree. Only in certain areas of the cortex was an increased number of capillaries to be seen, with hypertrophic often proliferating endothelium, and single lymphocytes. Dense glia was, however, seen in the molecular layer, with not infrequently appearing typical microglial rods (Fig. 5). Cell loss was not very pronounced and it was mostly masked by more numerous astrocytes. Some loss of cells, especially in the larger elements, was observed in the striatum. Nerve cells showed severe changes, often acute changes (as far as could be assessed from the frosted material). Nowhere were evident typically ischemic changes. Increased satellitosis was visible, but without evidence of real neuronophagy. In the cortex as well as in the basal ganglia the presence of small granules was observed in many neurons and astrocytes. They were stained pale blue with cresyl violet in contract with the strong violet staining of normal cellular components and the yellowish stain of lipofuscin. In the meninges, an increased endothelial proliferation was observed along with loose lymphocytic infiltrations in some places and small round or oblong haemorrhages.

With Spielmayer's method round perivascular areas where myelin stained poorly were visible (Fig. 6). They corresponded to the sites of the most pronounced microglial infiltrations. More frequently, incomplete diffuse perivascular, poorly staining areas were observed passing without sharp limits into normally staining tissue. In greater magnifications a more or less pronounced fragmentation and myelin sheath loss corresponded to the areas of poor staining.

Localization of the process. The described types of changes were most pronounced in the prefrontal and frontal areas in volving both cortex and white matter. In the basal ganglia the anterior crus of the internal capsule, the head

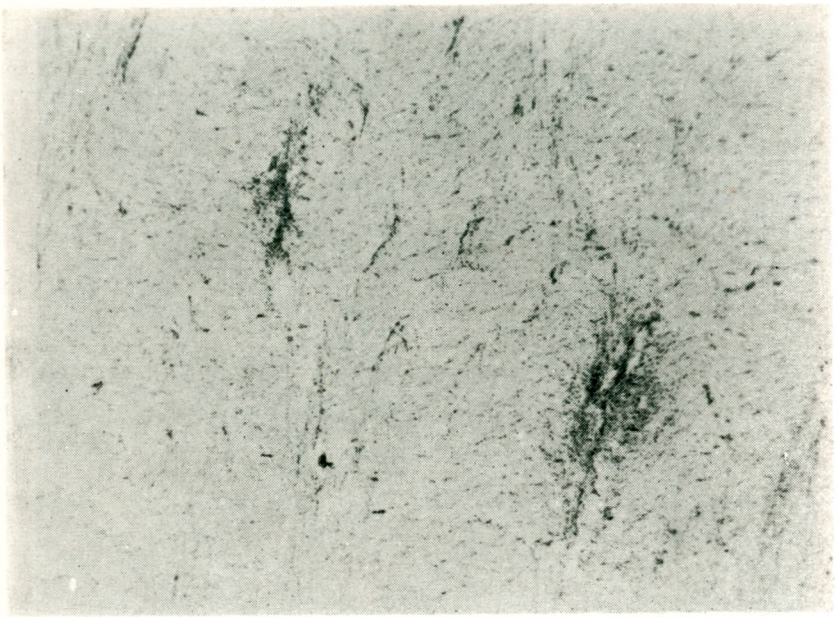

Fig. 1. Case 1. Diffuse perivascular foci of glial proliferation in the internal capsule. Cresyl violet. Magn. × 40.

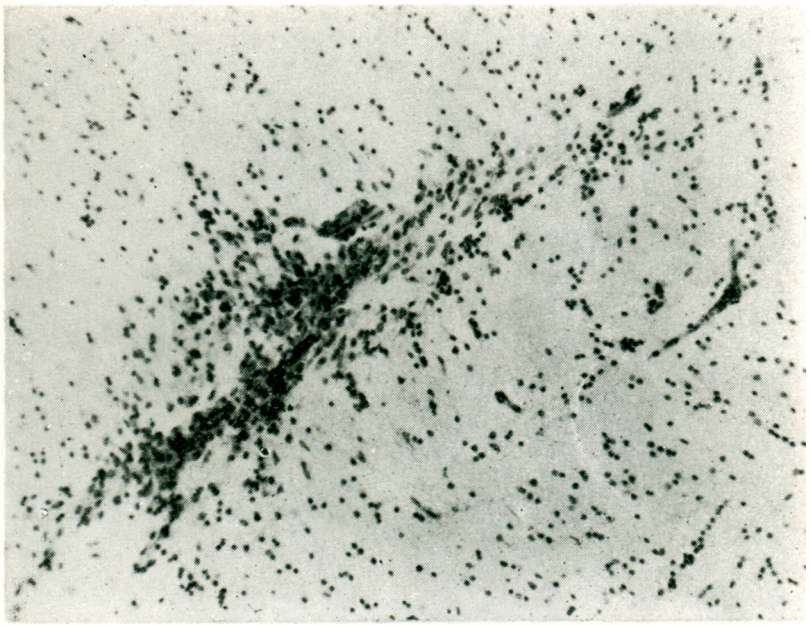

Fig. 2. Case 1. Focus of perivenous glial proliferation, composed of Hortega cells, astrocytes and small number of lymphocytes. Cresyl violet. Magn. × 150.

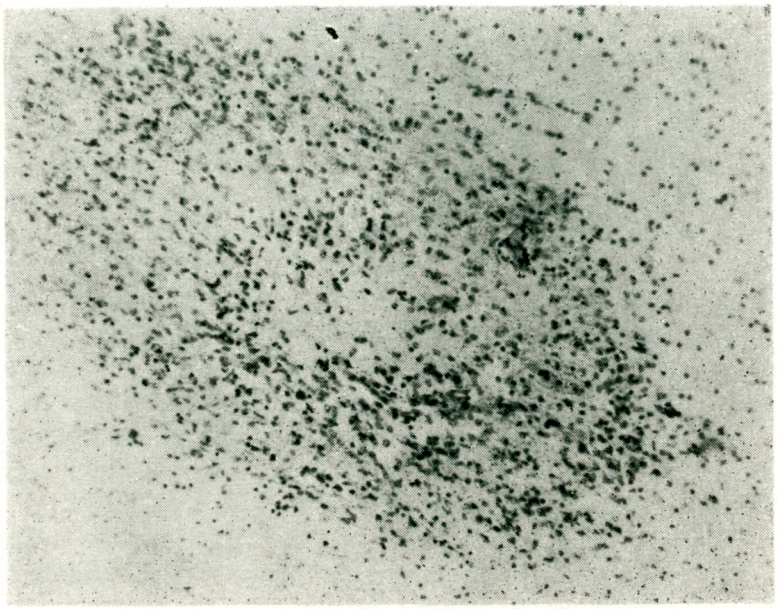

Fig. 3. Case 1. Focus of glial proliferation unconnected with blood vessels in the white substance of a cerebral hemishere. Cresyl violet. Magn. × 120.

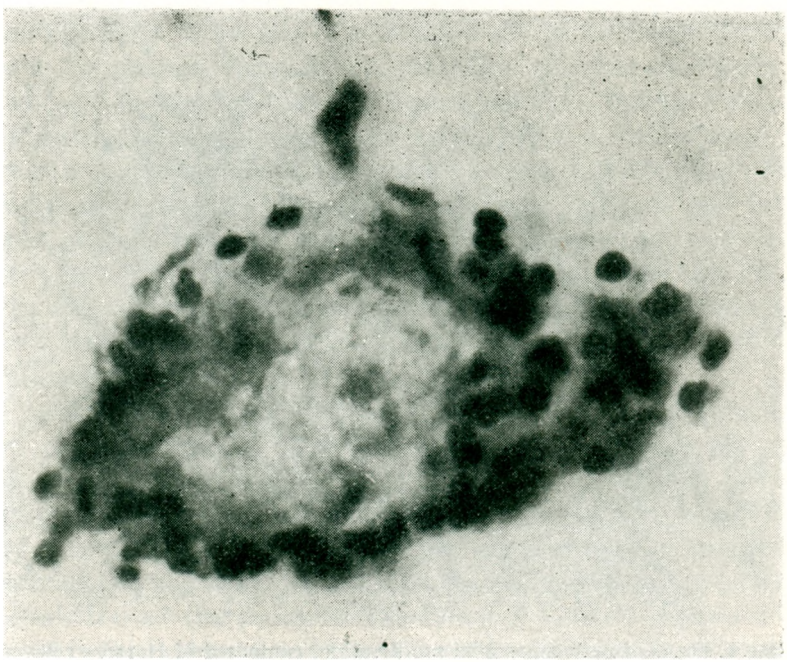

Fig. 4. Case 1. Lymphocytic perivascular infiltration. Cresyl violet. Magn. × 550.

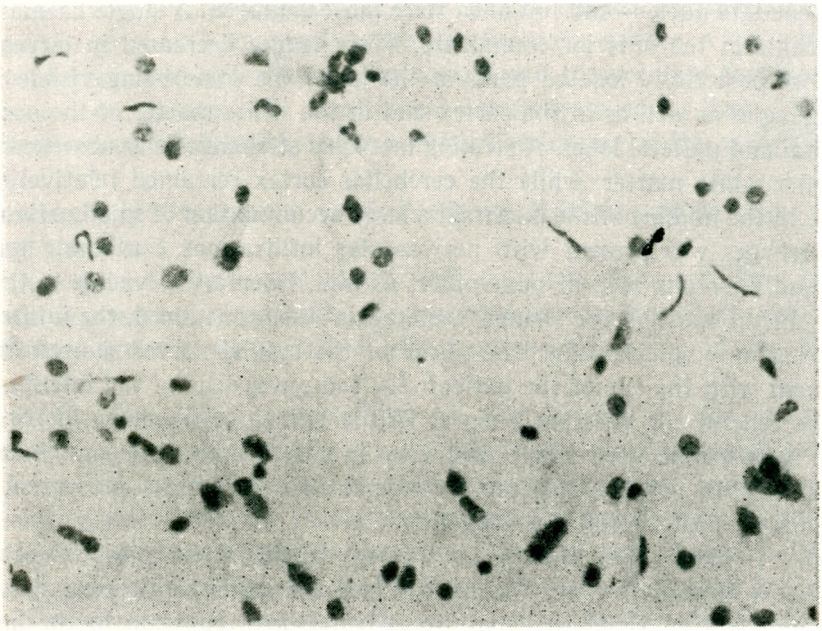

Fig. 5. Case 1. Proliferation of hypertrophied (rod) microglia in the molecular layer of the cerebral cortex. Cresyl violet. Magn. × 420.

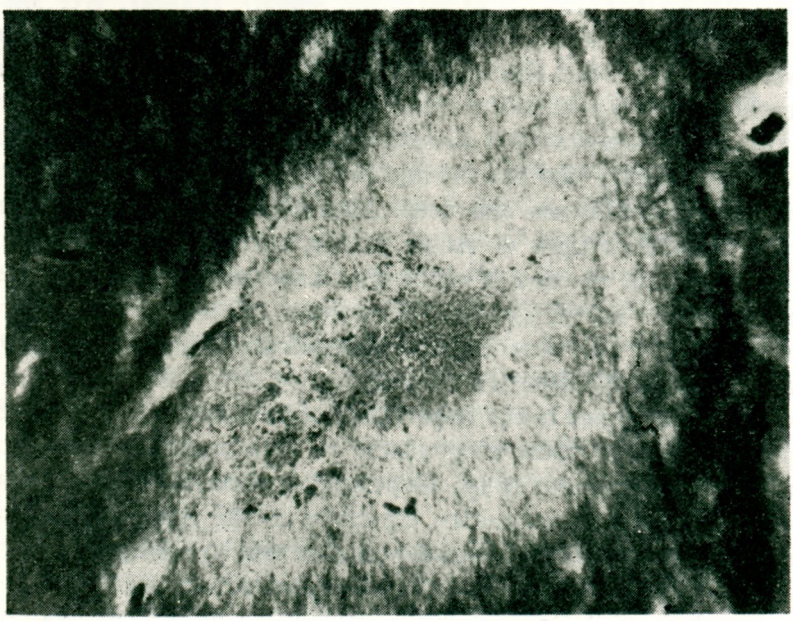

Fig. 6. Case 1. Perivascular demyelination at the site of microglial-lymphocytic infiltration. Spielmeyer. Magn. × 120.

of the caudate nucleus and putamen were most damaged. A single haemorrhage was visible in the anterior commisure. The changes decreased in intensity in the more posteriorly located parts of the brain the same being visible in the basal ganglia as well as in the cortex and in the white matter of the occipital, temporal and parietal lobes. A striking intensity of changes was observed in the cerebellar white matter, while the cerebellar cortex remained relatively uninjusted. In the midline of the midbrain a large accumulation of small perivascular haemorrhages was present with perivascular infiltrations containing lymphocytes and microglia seen in some places as well. Edema was visible in the long tracts. In the medulla the changes were again less pronounced, the infiltrations appearing only sporadically. The nuclei of the cranial nerves showed changes consistent with the age of the patient, the same was true of the inferior olives and the cells of the substantia nigra. In the spinal cord edema of the white matter was visible with single, not very intense lymphocytic and microglial infiltrations. In general, this picture resembled the changes present in post-infectious or post-vaccinial encephalitis.

Case 2 (PAN 109/62). Male aged 73 (Department of Neurology, Grochowski Hospital in Warsaw). Illness began two months earlier with general malaise and complaints of weakness. Three days before his admission to the hospital a psychomotor agitation appeared then passing into gradually increasing stupor. The patient ceased to eat, incontinence appeared. No details were obtained concerning his health before his illness.

Condition on the day of admission. Somatic changes: over the upper lung lobes, the breath sound was a little harsh, numerous rales were heard over the lower lobes. The heart was increased in size, and its sounds were dull. The liver reached two fingerbreadths below the costal margin.

Neurological status: the patient was stuporous and did not answer question. Neck rigidity was present and Kernig's sign was positive bilaterally. The left nasolabial fold was less deep. Abdominal reflexes were absent. The extremities showed no signs of visible paresis, reflexes were weak and equal. The patient died on the day of admission. Laboratory examinations showed blood urea level — 430 mg%, blood sugar level 160 mg%.

Clinical diagnosis was: *Arteriosclerosis generalisata. Myodegeneratio cordis in stadio insufficientiae circulatoriae. Uraemia.*

Autopsy was performed in the Department of Pathology of the IVth Warsaw Municipal Hospital, 18 hours after death.

Results of general autopsy: Hypertrophy of the right cardiac ventricle. Transudates in the pleural cavities, especially in the right one. Central and peripheral atherosclerosis of medium degree. Bilateral hydronephrosis. Prostatic adenoma. Pulmonary emphysema. Muco-purulent bronchitis. Chronic fibrous apical tuberculosis of both lungs, more pronounced in the left one.

Macroscopic examination of the brain (dr *K. Renkawek*): several atheromatic plaques in the basal vessels. On the lower surface of the cerebellum a slightly marked invagination of the tonsils into the occipital foramen, more pronounced on the left side. Anatomical details were easily seen. The white matter was broad in relation to the cortex. The lumina of the ventricles were slit-like.

Macroscopic diagnosis: cerebral edema. Moderate atherosclerosis of the cerebral vessels.

Sections from the left basal ganglia, left occipital region and from the area between the central and frontal regions were taken for microscopic examination. Paraffinized sections were stained with hematoxylin-eosin and van Gieson's method.

The microscopic examination of the brain: in the microscopic picture the signs of brain edema predominated; the oligodendroglial structures were irregularly separated, the brain tissue was spongy (Fig. 7), with transition in distinct areas of necrotic rarefaction around the vessels. Around the nuclei of astroglia and oligodendroglia edematous „haloes" were observed. The perivascular spaces were wide and in the basal ganglia had became formed into systems of paravascular sinuses. In the white matter the glia was slightly denser around the vessel (Fig. 8) and showed a circular arrangement. However, there were no distinct glial plaques to be seen anywhere. The cortical capillary net was moderately injected, the endothelium hypertrophied, no capillary fibrosis was evident. On the other hand fibrous changes in the capillaries of the white matter and fairly intense fibrosis of the adventitia and hyalinization of the media in medium-sized vessels was noted in the striatum. Relatively frequently fairly discrete lymphocytic infiltrations appeared around these vessels, showing characteristics of a symptomatic reaction to perivascular malacia. The vessels were mostly filled with blood, in some places slight perivascular extravasations were noted too. In the cortex there was a striking diffuse cell loss especially pronounced in the frontal and central regions. Many cortical cells were placed in edematous clear spaces, which resulted from the shrinking of the material in paraffin. In the striatum considerable cell loss was present too and in the thalamus a most intense lipoid accumulation in the neurones. The surviving cortical cells showed mostly chronic and sclerotic changes. A slight proliferation of the endothelium was visible in the meninges.

Microscopic diagnosis: cerebral edema with developing edematous necrosis of Jacob. Senile cortical atrophy. Moderate atherosclerotic changes in the cerebral vessels.

Case 3 (PAN 2076). Patient G. S. aged 24 was admitted to Department of Neurology, Medical Academy, Warsaw on August 11, 1958 in the state of coma. Information as to his past history was most incomplete, it was only known that

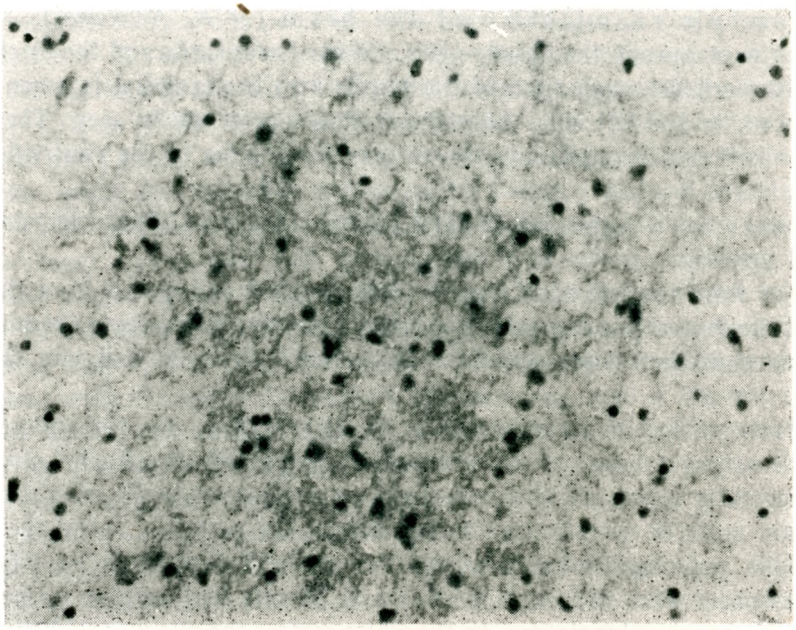

Fig. 7. Case 2. Spongy rarefaction of nervous tissue of the white substance of a cerebral hemisphere due to marked edema of the brain. Hematoxylin-eosin. Magn. × 200.

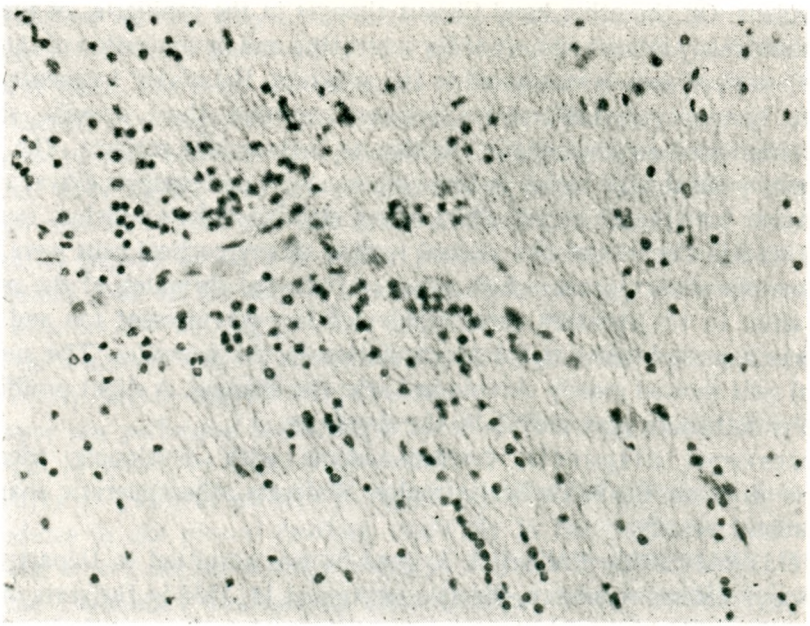

Fig. 8. Case 2. Circular condensation of glial cells around small blood vessels in cerebral white substance. Hematoxylin-eosin. Magn. × 200.

during the week before his admission to the Department he had had several general seizures with spells of unconsciousness. The last seizure occurred on the day preceding his admission to the Department and he did not regain consciousness after that. During the physical examination changes were revealed during the auscultation of the lungs. The heart rate was increased. Diffuse tenderness was elicited during palpation of the abdomen.

The neurological examination disclosed neck rigidity (two fingerbreadths), the muscle tone was decreased in the left extremities, with slightly increased deep reflexes on the same side. No pathological reflexes were discovered.

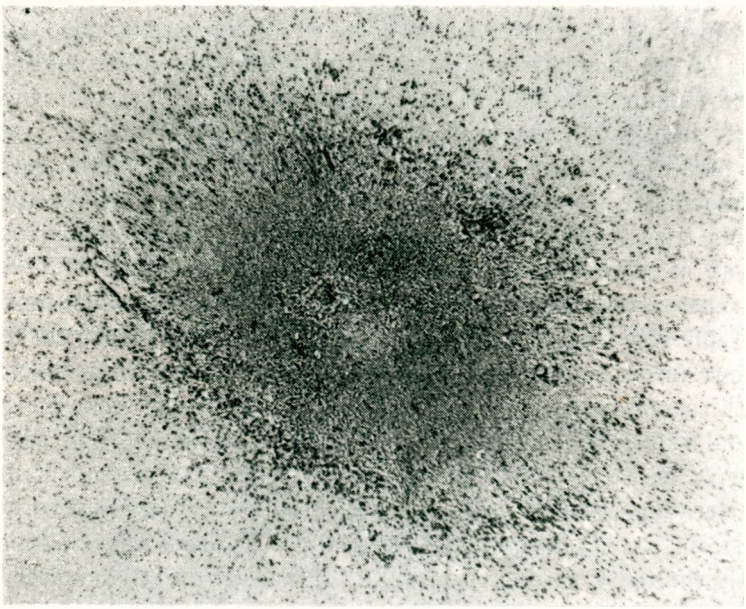

Fig. 9. Case 3. Small hemorrhagic focus in the cerebral white substance surrounded by a wall of astrocytic-microglial reaction. Nissl. Magn. × 60.

Laboratory investigations: blood urea level — 176 mg%, with an increase up to 270 mg% during the next several hours. Blood glucose level — 138 mg%. The cerebrospinal fluid was unchanged but trickled out under the increased pressure of 250 mm of water.

Signs of pulmonary edema appeared and the patient died about twenty hours after admission without regaining consciousness.

Clinical diagnosis: *Coma uraemicum. Oedema pulmonum.*

Autopsy was performed in the Department of Pathology, Medical Academy, Warsaw, 32 hours after death.

Findings at autopsy: caseous tuberculosis of the kidneys, fibro-caseous tuberculosis of the lungs with left apical cavity, general amyloidosis of the

spleen, kidneys and adrenals bilateral confluent bronchopneumonia, obliteration of the pleural and pericardial cavities. Cachexia.

Macroscopic examination of the brain (*M. Dąmbska*, M. D.) showed a symmetrical thickening and milky appearance of the meninges in the region of the Sylvian fossa bilaterally and considerable hyperemia of the meninges and the brain itself. No focal signs were visible in it.

A microscopic examination of the brain was made using sections taken from the frontal, parietal and occipital lobes, the central and hippocampal areas, basal ganlia, midbrain, medulla and cerebellum. Nissl's staining was used.

In the microscopic picture of the brain considerable edema of the nervous tissue was present, with a widening of the perivascular spaces and separation between the rows of interfascicular oligodendroglia accompanied by marked hyperemia of the meninges and brain tissue. The veins were maximally filled with blood, numerous small extravasations in the perivascular spaces were particularly frequent in the white matter. Besides, single larger hemorrhagic foci were present reaching beyond the perivascular space. The majority of the small hemorrhagic foci were not accompanied by signs of reaction in the surrounding tissue, only a focus in the left patieral lobe was surrounded by a wide wall of stimulated astrocytes and Hortega cells (Fig. 9).

Besides there were small foci of rarefaction present in the white matter of the centrum semiovale (Fig. 10). The cells filling it had morphological features of intermediate forms, among markedly stimulated microglia and macrogphages. These foci corresponded to small fresh softenings. Apart from the numerous small nodular foci of proliferation and stimulation of the glia consisting of astrocytes as well as of Hortega cells placed on a background of unchanged white matter. Some foci were situated perivascularly, others showed no relation to the vessels (Fig. 11). In certain areas glial proliferation was of a more diffuse, indistinctly limited type. Not the slightest traces of an inflammatory reaction were present in any area of the nervous tissue excluding some areas in the meninges.

Glial changes were essentially limited to the white matter of the hemispheres, in a lesser degree to that of the cerebellum. Their intensity clearly decreased in the direction of the brain stem. The medulla was practically free of changes of this type. These appeared slightly more intense in the posterior parts of the cerebral hemispheres: in the parietal and occipital lobes. The gray brain substance showed distinct changes in the appearance of the nerve cells in some parts. In the cortex areas of diffuse cell loss were evident with a marked predilection for intracortical layers (Fig. 12). Numerous cells with features of so-called chronic and severe cell disease were visible. Cells with vacuolar degeneration were also numerous (Fig. 13) and lipoid changes too advanced in relation to the age of the patient.

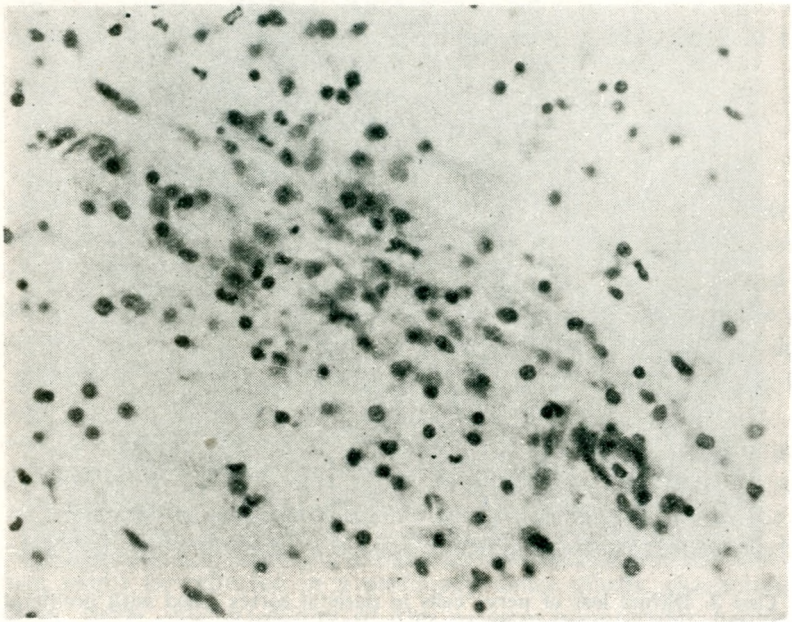

Fig. 10. Case 3. Rarefied focus of nervous tissue corresponding to recent softening. The cells filling the focus are intermediate forms between stimulated Hortega cells and macrophages. Magn. × 350.

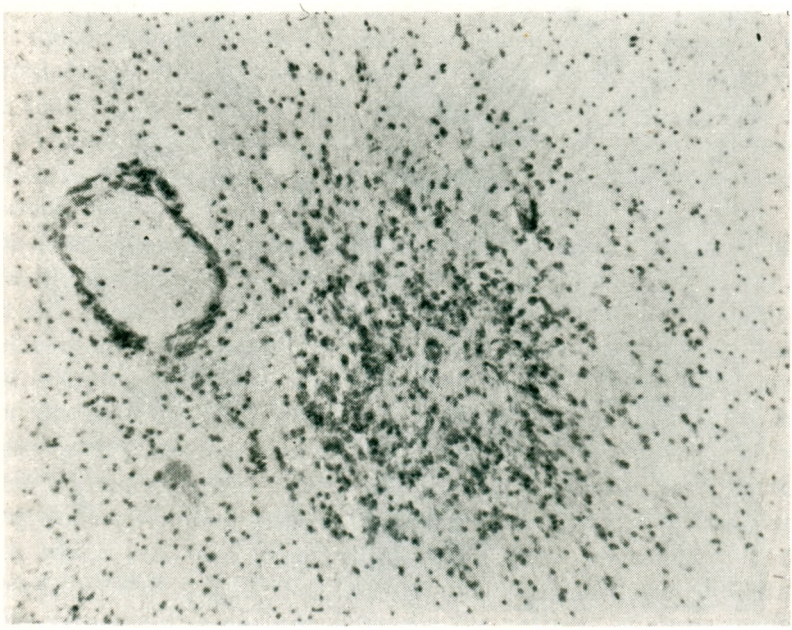

Fig. 11. Case 3. Focus of glial proliferation, not connected with a blood vessel, composed of astrocytes and Hortega cells. Congested venous blood vessel nearby. Nissl. Magn. × 120.

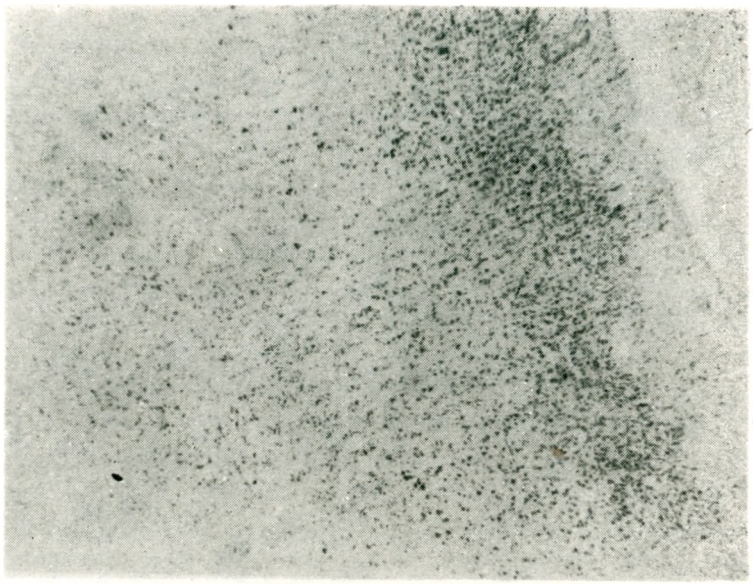

Fig. 12. Case 3. Diffuse loss of nerve cells in parietal cortex filled with proliferating glial elements. Nissl. Magn. × 50.

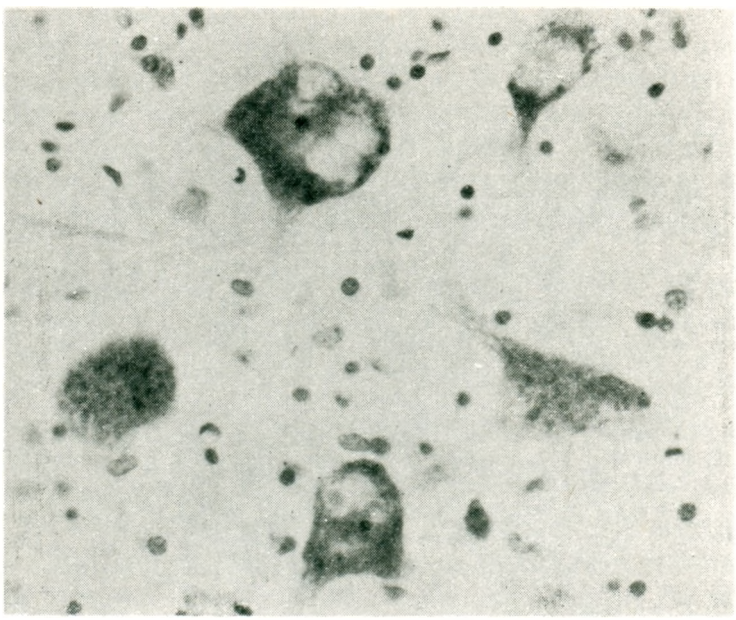

Fig. 13. Case 3. Vacuolar degeneration of nerve cells of the trochlear nucleus. Nissl. Magn. × 450.

The vascular system of the brain was not changed apart from a slight fibrosis of the small vessels of the cortex and pseudosiderosis of the vessels of the pallidum.

DISCUSSION

The cases presented differ in their pathological features and their interpretation must be different although in their pathogenesis they are all connected with uremic conditions of renal origin. Clinically, they may be placed in the classification of *Knutson* and *Baker*, with the reservation that on the ground of the presenting symptoms and signs they must be included in two different clinical groups, while the outcome in all three cases is characteristic for the first group.

However, the first case described does not correspond to the known patterns of uremic conditions, although its clinical course and the results of the autopsy permit to include it in the pseudo-uremic syndromes developing in the course of long-standing cerebral vascular lesions preceding them. Microscopically, this mechanism might be reflected in a uniformly dense gliosis, characteristic for long lasting brain edema; filling of the vessels, perivascular hemorrhages, cellular changes in the cortex and basal ganglia. It should be stressed that the cell changes were of an acute and severe type, while ischemic changes were absent. This phenomenon is considered by *Bodechtel* and *Erbslöh* as characteristic for cerebral uremia. Fairly characteristic is also the topography of the changes, similarly as in the case of *Tichy* the changes were especially intense in the frontal area. The localization in the striatum has been stressed by *Hechst* and the tendency to haemorrhages from the vessels of the midbrain is also typical. The last localization, in our opinion, seems to be more characteristic for conditions of brain edema in general (*Kulczycki* 1962) than for special for uremic conditions.

On the other hand the inflammatory character of the perivascular microglial reactions, the presence of perivenous plaques, the proliferation of the microglial rod cells in the cortex and the lymphocytic component of the infiltrations were evidence of encephalitis corresponding to the para-infectious and post-vaccinial encephalitides. Such morphological findings in the brain have not yet been described in uremic conditions as far as we know. It seems that the explanation of this phenomenon should be sought for more deeply or perhaps more remotely — in the pathogenesis of glomerulonephritis itself. If there is, according to modern views, an allergic pathogenesis in acute diffuse glomerulonephritis, which has been experimentally confirmed (*Wollheim* and *Moeller* and quoted by them: *Lange*, *Gold*, *Weiner* and *Simon*, *Pfeifer* and *Bruch*) — such a reaction could secondarily influence the patterns of tissue reactions in other organs, in this case: of the brain, during an exacerbation of the renal

process. The patient with a renal inflammatory process confirmed at autopsy, died in the course of its exacerbation. The findings in the brain were not consistent with so acute an edema that they could be a sufficient explanation for death. On the other hand they presented the full morphological characteristics of encephalitis, adequately explaining the neurological clinical symptomatology (involuntary movements of the extremities and the neck and unilateral spastic signs). It is this type of inflammation which is usually interpreted as evidence of an allergic reaction of the central nervous system.

The second case is an almost classical example of a lethal outcome in the course of acute brain edema. Uremia was in this case caused by urinary retention, probably with preceding more long-standing oliguria. This mechanism, which in this case was most probably due to prostatic hypertrophy, does not necessarily imply the presence of renal vascular damage, with consequent chronic cerebral damage. Unfortunately no histological examination of the kidneys has been performed, which would have made possible an evaluation of the character of the changes present in them.

No characteristic features of chronic edema were present in the brain. The increase in glial elements was slight, the stimulation of the perivascular glia corresponded to benign changes observed by *Alpers* in moderately severe experimental uremia of extrarenal origin. The essential change was the impregnation of the tissues with transudate fluid. In accordance with the results of electron microscope studies — this impregnation involved the protoplasm of the glial elements. Spongy necrosis contains in its meshes, fluid coagulated in the course of technical processing which, however, caused an increase of the brain volume during life, which fact is evidenced by tonsillar invagination. This anatomical change was probably the cause of the existing meningeal signs.

The atrophy of cortical cells and lipoid changes in the cells of the thalamus should be considered rather as due to the advanced age of the patient.

The morphological picture of the third case most closely approaches the classical description of uremic encephalopathy. Most morphological changes in the nervous system described in uremia were present in this case, with diffuse cell loss and degeneration of neurons, minute necrotic foci in the nervous tissue, extravasations of erythrocytes, diffuse and focal glial proliferations. This case differs from the first one in the lesser intensity of the pathological process and the absence of changes of the type of allergic encephalitis, it differs from the second case in the greater intensity and greater morphological diversity of the pathological process in the central nervous system also in the absence of atheromatous and arteriosclerotic vascular changes. In this it can be considered as an intermediate form.

The difference of the clinical picture of the third case consists in the occurrence of seizures following one another at short intervals. The question arises, if the cellular changes, very pronounced in this case, are related to the uremic

process alone or an additional influence of seizures should be taken into account. It is of course impossible to set a dividing line separating these changes completely. It seems, however, that in our case the small number of seizures, the absence of selective cellular damage, so characteristic in epilepsy, and the differing type of neuronal degeneration, usually not encountered in the course of epilepsy (*Scholz* 1956, *Dąmbska* 1960) — permit the exclusion of an epileptic origin of these changes. However, its presence should doubtlessly be taken into account in cases with an epileptic status, when ischemic neuronal damage appears in the morphological picture *(Hechst)*, which according to the opinion of *Bodechtel* and *Erbslöh* is not typical and rarely encountered in uremia.

The relation of the pathological changes in the vascular system in the third case appears least pronounced (the diffuseness of the nerve cell loss and glial proliferation, the lack of association of glial nodules with the vessels, the lack of correlation between focal nervous tissue necrosis and the vessels). This probably shows the general toxic action of uremia on the nervous tissue directly and not by way of a vascular anoxemic and edematous mechanism.

A less intense glial reaction in the presence of clear-cut haemorrhagic and edematous elements suggests a more acute, short-lasting character in the uremic process in the third case, in comparison with the first. The morphological differences in these two cases are increased by the presence, in the first case of an „extra-uremic" factor in form of an allergic inflammatory reaction. The second and third cases resemble one another clinically and there is presumably a similar mechanism of the pathogenesis of uremia in them. This, however, makes an explanation of their morphological differences all the more difficult.

The very marked intensity of the edematous process in the second case, leading even to the picture of edematous necrosis of Jacob may be related to chronic urinary retention and disturbances of water and electrolyte metabolism due to it most probably more intense than in the third case. Possibly the characteristics of the tissue reaction may be also influenced by the condition of the reacting substrate itself — the nervous tissue, the colloidal structure from which it is probably different in the brains of individuals in the third and eighth decades of life (*Braunmühl* 1956).

The atherosclerotic changes are slight in the second case and practically absent in the first and third. Thus the observed changes could be related with greater probability to disturbances of renal origin.

However, while the second and third cases presented known morphological manifestations of uremia in the central nervous system, the first case showed that it was necessary to consider the co-existing factors in the disease process, which factors could even have preceded the appearance of actual uremia. It is supposed that such factors doubtlessly present in many cases of uremia, can explain the diversity of the clinical courses.

Translated by P. Słomski, M. D.

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