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Fatal Varicella Generalisata in a Child with Immunopathy and Hereditary Neurological Syndrome

A Report with Autopsy, Electron Microscopy and Virus Isolation

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Tödliche generalisierte Varicelleninfektion bei einem Kind mit Immundefekt und hereditärem neurologischem Syndrom

Fallbericht mit Autopsie, Elektronenmikroskopie und Virusisolierung

Zusammenfassung. Ein 4 Jahre altes Mädchen mit Immundefekt und hereditärem neurologischem Syndrom [frühere Publikation in Acta Paediat. Scand. **55**, 264 (1966)] verstarb an einer generalisierten Varicelleninfektion. Bei der Sektion fanden sich ausgedehnte hämorrhagische Nekrosen im Bereich der Haut, Leber, Lungen, Milz und des Pankreas. Lichtmikroskopisch konnten intranucleäre Einschlußkörper in der Leber, Milz und in den Lungen nachgewiesen werden. Außerdem wurden elektronenmikroskopisch Viruspartikeln in der Leber, Milz, den Lungen und im Pankreas beobachtet. Eine für Varicellen charakteristische Virusisolierung gelang durch Übertragung von Herzblut, Haut- und Lungengewebe auf menschliche embryonale Zellkulturen. Im Gehirn fanden sich die Zeichen einer Fehlbildung in Form von Nervenzelldysplasien in der Hirnrinde und den basalen Ganglien sowie einer Heterotopie von Nervenzellen in der weißen Substanz. Im Kleinhirn war ein unregelmäßiger Schwund von Purkinjezellen — wahrscheinlich ebenfalls als Ausdruck einer Dysplasie — nachweisbar. In den dorsalen Wurzelganglien und in den lateralen corticospinalen Bahnen bestand eine unspezifische Degeneration. Ein jüngerer Bruder zeigt ein sehr ähnliches neurologisches Syndrom wie die verstorbene Schwester. Es wird daher die Annahme vertreten, daß das neurologische Syndrom genetisch determiniert ist. Ob auch bei dem Bruder ein Immundefekt vorhanden ist, ist vorerst noch nicht bekannt.

Summary. A 4-year-old girl with immunopathy and a hereditary neurological syndrome [previously described in Acta Paediat. Scand. **55**, 264 (1966)] succumbed with varicella generalisata. At autopsy hemorrhagic lesions were found in the skin, liver, lungs, pancreas and spleen. With the light microscope intranuclear inclusion bodies were seen in the liver, lungs and spleen. Under the electron microscope viral particles were found in these three organs and in the pancreas. Virus isolation in human embryonic cells with characteristics of varicella proved positive for heart-blood, skin and lungs. In the cerebrum there was a dysplasia of nerve cells in the cortex and basal ganglia and heterotopic nerve cells were found in the white matter. In the cerebellum there was a patchy loss of Purkinje cells, probably a dysplasia. Non-specific degeneration was seen in dorsal root ganglia and in the lateral corticospinal tracts. A younger brother of the patient shows a similar neurological syndrome. It seems reasonable to assume that the neurological syndrome is genetically determined. Whether an immunopathy is present in the brother is not known at present.

Death is an uncommon complication in varicella and is usually due to concurrent disease and decreased resistance. We have encountered such a case in a child, previously described (Hansson et al., 1966), with immunopathy and hereditary neurological syndrome. Electron microscopy and virological examination were performed on material obtained at autopsy. The present paper will give a brief description of the case.

Case Report. Girl, born 6th January 1962, the first of 2 siblings. Normal delivery, weight at birth 3,000 g.

At the age of $8^1/_2$ months she was vaccinated against smallpox. The course of the vaccination was normal at first, then a vaccinia gangraenosa developed which took 7 months to heal after treatment with N-methylisation-β-thiosemicarbazone (Marboran) and plastic surgery.

The complication and its background have been comprehensively described in a paper by Hansson et al. (1966).

It was shown that the serum concentrations of IgG, IgA and IgM were normal and that she had isoagglutinins in the serum. Antibody response after previously administered triple vaccine was normal, and vaccinia antibodies were found in serum 4 months after vaccination. It was considered probable that the explanation of the vaccination complication was to be sought in a defect in the tissue immunity, which thought was supported by, among other things, an abnormal reaction to intracutaneously injected vaccinia antigen.

A late psychomotor development was observed in connection with the illness, and it could be confirmed later, that the girl had an atactic diplegia. A younger brother, born in 1964, displays the same signs (to be published in Acta Paediatr. Scand.)

Apart from chronic left side otitis, treated in her hometown with antibiotics, the girl was well during the following year.

At the age of 4 years and 10 months the patient became ill, with loss of appetite, nausea, itching, skin haemorrhages and fever. She had dark urine and bleached stools. She was admitted to her local hospital on the 28th November 1966. On the same day, and on the preceding day she was exposed to varicella by contact with another child. It was established at the local hospital that she had severe anaemia (Hb 4.9 g/100 ml) and a slight bilirubinaemia (1.9 mg/100 ml).

The condition was taken to be haemolytic anaemia and she was treated with repeated blood transfusions.

On 9th December 1966 she was transferred to the pediatric dept., University Hospital, Uppsala, for further examination and treatment. On admission she was feverish, with a temperature around 39°C. Blood analyses showed: Hb 12.2 g/100 ml, which in 4 days sank to 5.8 g/100 ml. Serum bilirubin 2.4 mg/100 ml. Haptoglobin 5 mg/100 ml. Bone marrow smears showed sparse erythropoiesis, increase of eosinophilic cells and absence of plasma cells. Immunoelectrophoretic examination disclosed an increase in IgA to 270 mg/100 ml (normal range 7—87 mg/100 ml).

Prednisolon was given from the 12th December (the varicella incubation was not known of at that time) the dosage being 75 mg per day, whereupon she immediately became afebrile. The reticulocytes increased rapidly from 4.8 to 30.8%.

On 15th December scattered blisters were observed on one upper arm and on the trunk. As the diagnosis varicella was to be suspected she was transferred on the same day to the Department of Infectious diseases of the University Hospital. The patient was then obviously pale but the general condition was otherwise on the whole good. Hb value was 7.7 g/100 ml. There was a leukocytosis of 21,000 peripheral white blood cells per mm^3 for no apparent reason. She had no fever. The prednisolon dosage was reduced to 45 mg per day. As an unfavourable development of the varicella was feared on account of the steroid treatment and the immunopathy, human gammaglobulin was given intramuscularly to a total amount of 92 ml of a 12% solution over a period of 7 days.

The patient's condition was fully satisfactory for a few days. The Hb value rose to 11.8 g/100 ml and the haematocrit from 20% to 36%. The reticulocyte value was constant around 30%. On the 3rd—4th day after debut of varicella the blistered eruption increased in intensity and began to take on a malignant appearance, with bleeding.

On the 5th day were added pains and tenderness in the abdomen, which became steadily more meteoristic. As appendicitis with perforation could not be excluded, laparotomy had to be performed on the 7th day of the illness. The appendix was, however, innocent, but copious quantities of thin liquid were found in the abdomen, and a number of adenites in the mesentery. Appendectomy alone was performed.

Her post-operative condition gave no cause for alarm at first. She received intravenous fluids. 5 hours after operation supervened suddenly hyperventilation, cyanosis and peripheral chill. After several more hours, when she had temporarily improved and slept, came nasal haemorrhage, increasing torpor, slow, irregular breathing and blood pressure fall. The girl died on the 8th day after the debut of varicella, at the age of 4 years and 11 months.

Post Mortem Examination

Macroscopical Findings. Autopsy was performed 4 hours after death. There were scattered lesions of healing varicella eruptions distributed over the entire body, with the exception of the peripheral parts of the extremities. At the right lower segment of the abdomen, there was a well-sutured scar of 8 cm.

The trachea showed oedema and diffuse hyperemia with several small ulcers. The pleurae contained 40 ml light-yellow fluid. On the surface of the lungs there were on the left side 6, on the right side 7 cockade-formed lesions, the biggest 7 mm in diameter. These lesions were slightly elevated, gray-white and solid with a hemorrhagic, umbilicated center and a peripheral hemorrhagic zone. Such lesions were also found on the cut surface of the parenchyma.

The thymus consisted of 2 small pieces of parenchyma and weighed 2.3 g. The pericardium contained 15 ml sanguinolent fluid. Its visceral surface was thickened and slightly fibrosed. The heart (75 g) was normally configurated. Subendocardially in the left chamber there was a hemorrhage of 2.5×0.6 cm. The abdominal cavity contained 500 ml blood coloured fluid and in the operation field about 100 ml bloodclots. In the gastrointestinal tract there were shallow erosions in the ventricle and small intestine.

The spleen was tense, dark red with numerous small hemorrhagic necroses, about 4 mm in diameter, on the surface and throughout the parenchyma.

The liver was pale and swollen, studded with hemorrhagic necroses, about 2 mm in diameter, on the surface and throughout the parenchyma. The kidney showed acute congestion. Pancreas showed numerous small hemorrhagic necroses.

In the brain and the meninges no abnormalities were visible to the naked eye.

Light Microscopical Observations. In the trachea there were shallow ulcers with round cells. No inclusion bodies were seen.

The necrotic areas of the lungs were often delimited by the lobular septa. They contained erythrocytes, a few inflammatory cells, oedema and fibrinous material, sometimes resembling poorly developed hyaline membranes. Especially at the border between normal parenchyma and the outer hemorrhagic zone, there was a fairly large number of sometimes multinucleated macrophages. In this area intranuclear inclusion bodies were found in macrophages and in septal cells. In the remaining parts of the lungs, scattered areas of oedema were found.

The thymus was atrophic and consisted essentially of the spindle-shaped reticular cells and only few lymphocytes and occasional Hassall's bodies. There was much fat within the gland (Fig. 1).

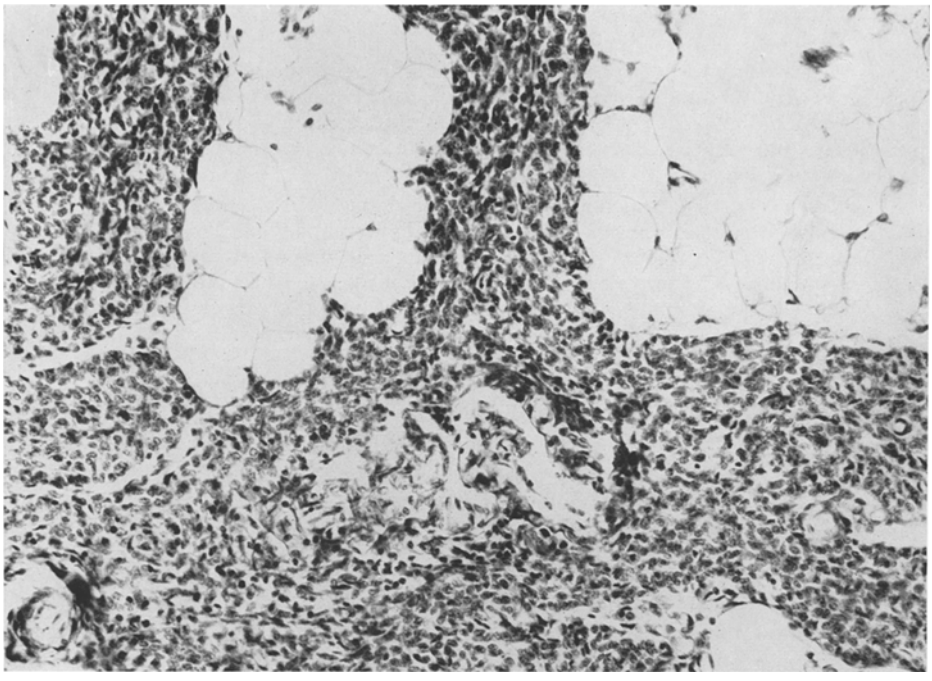

Fig. 1. Section of thymus. Note the atrophic gland poor in lymphocytes. Hematoxylin-van Gieson. ×150

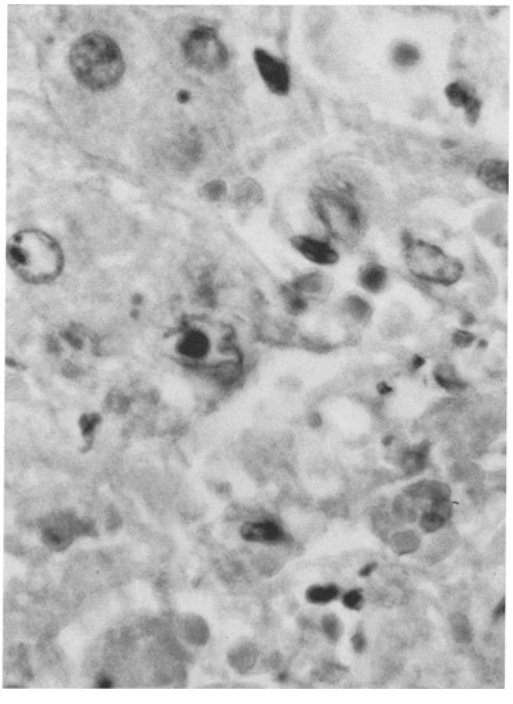

Fig. 2. Liver section. Part of the borderline to a hemorrhagic necrosis. A nuclear inclusion body is seen in the centre of the figure. Normal liver cells are found in the upper left corner. Lendrum's stain for inclusion bodies (hematoxylin-phloxin-tartrazine). ×1,000

No inflammatory changes were found in the myocardium, though a large number of sections was examined.

The stomach and intestine showed small erosions but no inclusion bodies.

The liver showed several well demarcated foci of hemorrhagic necroses all over the lobuli, infiltrated by a few polymorphonuclear leucocytes. Intranuclear inclusion bodies were seen in parenchymal and Kupffer cells in every lesion, especially in the peripheral parts of the foci (Fig. 2).

The pancreas showed small hemorrhagic necroses with few inflammatory cells. Inclusion bodies were not encountered.

In the spleen the sinusoids were congested. There were numerous, small, poorly demarcated, often confluent foci of hemorrhagic necroses containing a few inflammatory cells. Intranuclear inclusion bodies were found in a large number of sinusoidal cells and histiocytes.

In some of the mesenterial lymph nodes a large number of plasma cells were found.

The bone marrow was poor in mature polymorphonuclear leucocytes, slightly hyperplastic, and normal in other regards. Inclusion bodies were not found.

Examination of the Nervous System

Methods

The right cerebral hemisphere was taken unfixed for chemical analysis while the remaining parts of the brain were fixed in 10 per cent formaldehyde for histological examination. Specimens from the left frontal, temporal and occipital lobes, basal ganglia, pons, cerebellum, medulla oblongata, various levels of the spinal cord, several spinal nerve roots and dorsal root ganglia were embedded in paraffin. 7 μ thick sections were stained with Luxol fast blue-cresyl violet for myelin and Nissl substance, Palmgren's silver technique for neurons and their axons and Holzer's method for fibrillary glia. A number of lipid histochemical methods (according to Adams, 1965) were applied on frozen sections.

Cerebral Cortex and White Matter

The cytoarchitectural pattern particularly of the temporal cortex but also of the frontal and occipital cortex was somewhat irregular with columns and clusters of frequently disoriented neurons displaying a remarkably large nucleus, sometimes containing two nucleoli, and a scanty cytoplasm with well stained Nissl bodies (Fig. 3). The hippocampal cortex did not reveal any definite changes. A moderate number of single, heterotopic nerve cells were seen in the subcortical white matter of the lateral temporal gyri between thin and widely separated myelin sheaths (Fig. 4). There were no signs of anoxic-vasal lesions nor any proliferation of glial cells in the cortex and white matter of the hemispheres. Unsaturated, hydrophobic lipids including triglycerides and cholesterol esters could not be demonstrated.

Basal Ganglia

The same "immature" appearance of nerve cells which was observed in the neocortex was also noted in the caudate nucleus and the putamen while the nerve cells in the pallidum and in the thalamus appeared normal.

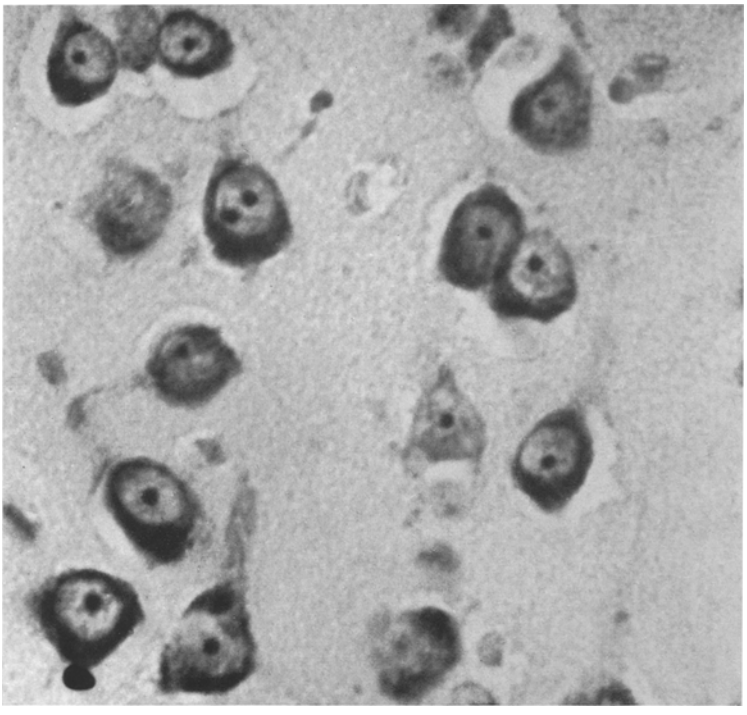

Fig. 3. Section of frontal cerebral cortex. Tendency to columnation and clustering of nerve cells with a large nucleus and scanty cytoplasm. Cresyl violet. ×280

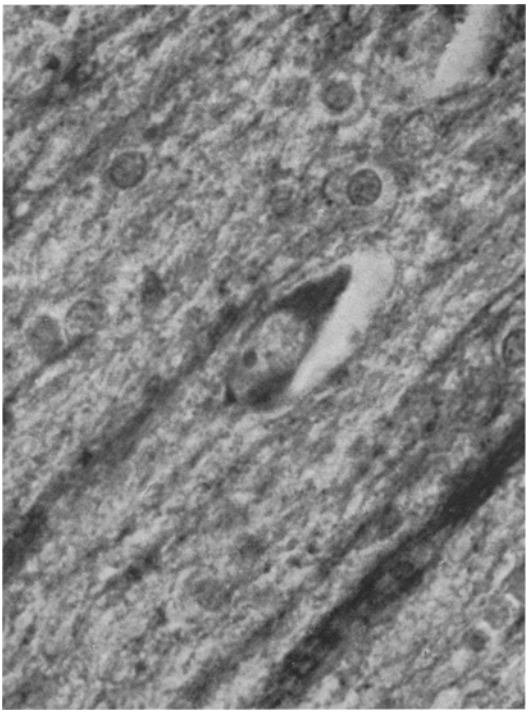

Fig. 4. Section of frontal subcortical white matter. Note heterotopic nerve cell between thin and widely separated myelin sheaths. Luxol fast blue and cresyl violet. ×350

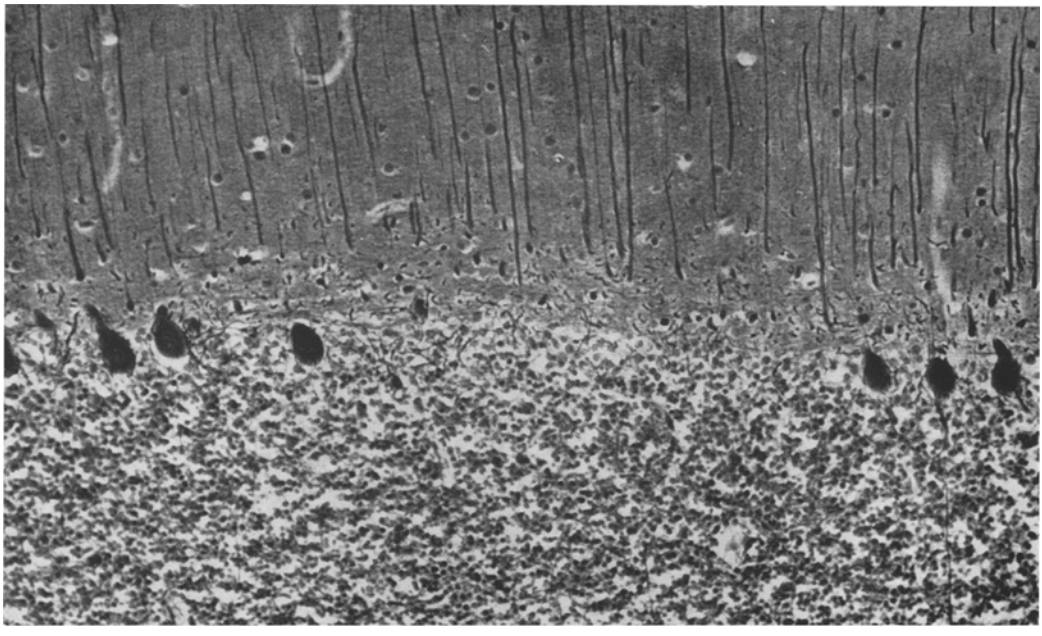

Fig. 5. Section of cerebellar cortex. Loss of Purkinje cells without associated proliferation of Bergmann glial cells. Note the straight, unramified course of the dendrites. Palmgren's silver stain. ×175

Cerebellum

Both in the vermis and in the hemispheres there was moderate, patchy loss of Purkinje cells without concomitant proliferation of Bergmann glial cells (Fig. 5). Many of the Purkinje cells had lost their baskets and the dendrites appeared in places remarkably unramified running a straight course up to the surface of the molecular layer. Only a few torpedoes were seen on the axons of the Purkinje cells. The granular layer was of normal thickness but the white matter of the folia appeared somewhat reduced.

Spinal Cord

Myelin stained sections from the lower lumbar cord showed considerable loss of myelin sheaths in the dorsolateral parts of the lateral corticospinal tracts. The columns of Clarke and the spinocerebellar tracts appeared unaffected. The large motor nerve cells of the anterior horns were well preserved.

Spinal Nerve Roots and Dorsal Root Ganglia

The myelin sheaths in the juxtaganglionic part of the spinal nerves and in the dorsal nerve roots were broken up into poorly stained fragments. Although the axons appeared better preserved than the myelin sheaths many of them showed numerous varicosities and some fragmentation. There was a slight increase in the number of endoneurial cells. The dorsal root ganglia displayed some loss of nerve cells and a marked proliferation of perineuronal satellites and capsular cells (Fig. 6). A considerable number of neurons showed chromatolysis and various

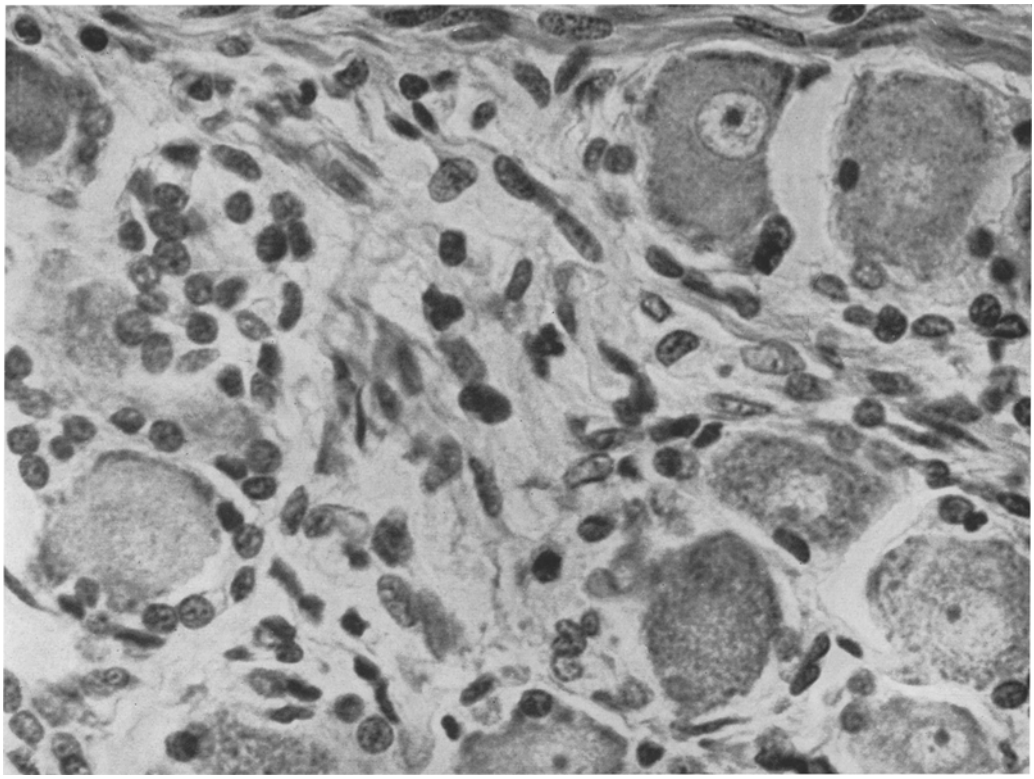

Fig. 6. Section of dorsal root ganglion. Proliferation of interstitial and capsular cells, particularly in the vicinity of degenerating neurone (at the left). Luxol fast blue and cresyl violet. ×700

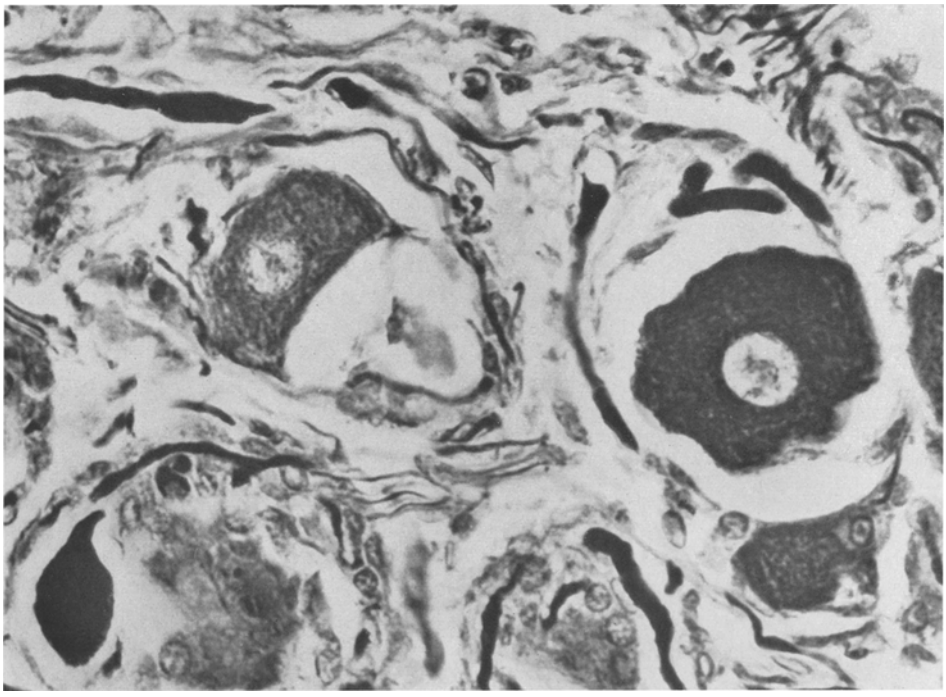

Fig. 7. Section of dorsal root ganglion. Note marked fragmentation and swellings of neuronal processes. Palmgren's silver stain. ×700

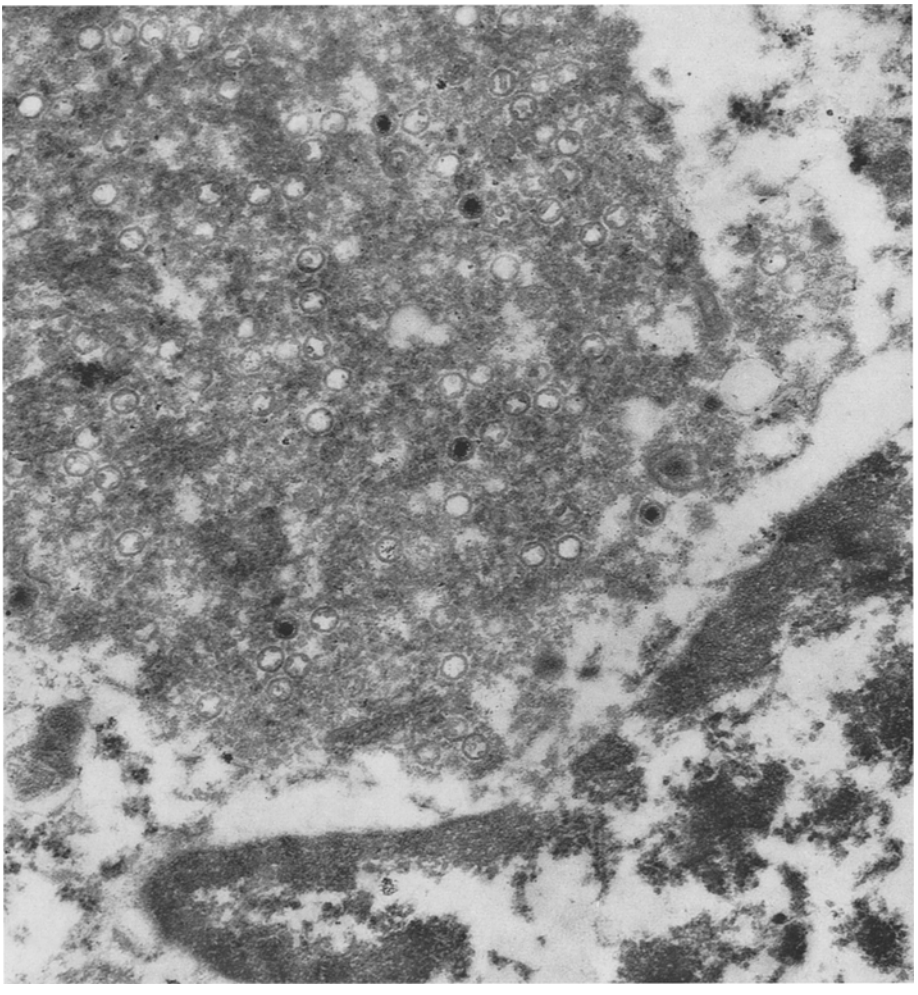

Fig. 8. Electron micrograph of liver section. The larger part of the photo is occupied by a necrotic nucleus with numerous virus particles, most of them with hollow cores. Uranyl acetate-lead citrate. ×38,000

degrees of cytolysis. Their processes showed fragmentation and club like swellings (Fig. 7). A moderate number of solitary mast cells were seen in the ganglia but there were no inflammatory cellular infiltrations and no intracellular inclusions.

Electron Microscopy

Technique. The tissues had been fixed in 10 per cent formaldehyde for a few days. They were postfixed in glutaraldehyde and osmic acid according to Hübner (1966) and embedded in Epon. Sections were cut with an LKB ultramicrotome, stained with uranyl acetate-lead citrate and examined under a Siemens Elmiskop I electron microscope. At optical microscopy the intranuclear inclusion bodies were best seen in the periphery of the hemorrhagic necroses in the lungs, spleen and liver. Slices for electron microscopy were therefore taken from these regions.

Observations. Under the electron microscope virus particles were found in a large number of cells in the lungs, spleen, and the liver. In the liver they were

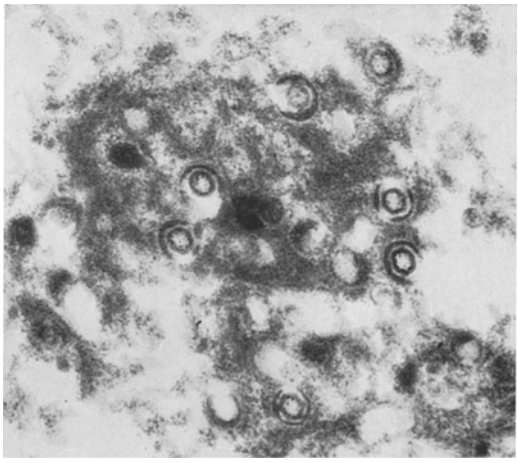

Fig. 9. Electron micrograph of liver section. Enveloped virus particles. Due to necrosis and autolysis it could not be determined, whether the particles were situated in the nucleus or in the cytoplasm. Uranyl acetate-lead citrate. ×37,000

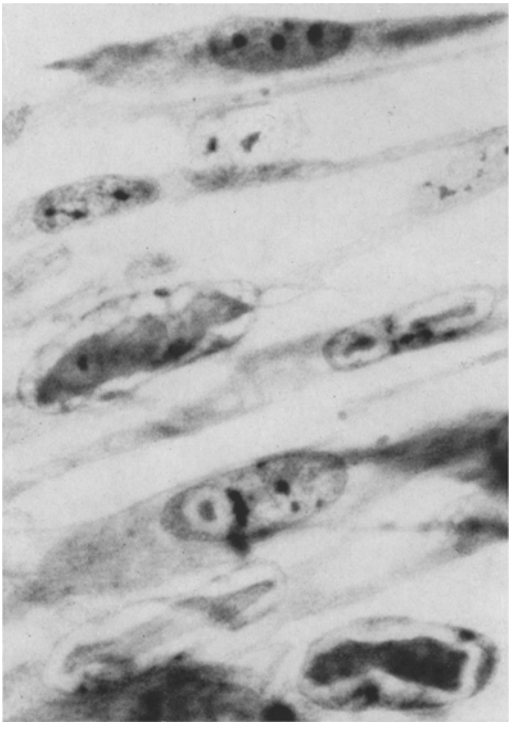

Fig. 10. Monolayer of human fibroblasts inoculated with material from lung. Large intranuclear inclusion bodies are found in several cells. Hematoxylin-eosin. ×1,050

found in both parenchymal and Kupffer cells. Several of the affected cells in lungs and spleen seemed to be of endothelial nature. In the pancreas virus particles were only seen in mesenchymal probably endothelial cells. The virus par-

ticles had the same appearance and localization in all cells and organs. They were found mainly in the nuclei but also in the cytoplasm, as a rule near the nuclear membrane. In the nuclei they were often found in dense masses in the central parts but were also encountered in other parts of the nuclei. The virus particles were of two types, particles consisting of a ring with hollow cores, and particles with a dense core (Fig. 8). There were also intermediate types with small masses on the inside of the rings. A few virus particles appeared to be enveloped (Fig. 9).

Virus particles were not found in stomach, intestine, kidneys, heart, spinal ganglia or bone marrow.

Virological Examination

Material and Methods

Virological examination was performed on autopsy material from skin, lung, spleen, liver, intestine, bladder, kidney and heart blood taken by heart puncture. A 20% (v/v) solution of autopsy material, homogenized in Eagle's minimal essential medium (MEM) with antibiotics and clarified by centrifugation 1,000 rpm for 10 minutes, were inoculated in amounts of 0.5 ml into each of two Leighton tubes of the two different cell types employed (BS-C-1 from Grivet monkey kidney, and primary, human, embryonic, mixed skin-muscle-lung fibroblasts). After an adsorption period of two hours, the tubes were washed with MEM and refed maintenance medium (MEM with antibiotics and 10% calf serum). When 50—75% of the cell layer showed cytopathic effect, the cell sheet, after brief trypsinization, was transferred to new tissue culture tubes, giving continuous human fibroblast and BS-C-1 cell lines infected with V-Z virus. The diagnosis was obtained by microscopical examination of cultures stained with hematoxylin-eosin (Fig. 10).

Observations

The cytopathic effect, characteristic of V-Z virus was observed after 4 weeks in cultures inoculated with material from skin, lung and heart blood.

Discussion

It is well known that varicella can take a serious course and lead to death, if the patient at the same time has a malignant disease, particularly leukaemia, or other disease engaging the immunologic defense mechanism (Kredba and Bradáčová, 1959; Pinkel, 1961; Bodey et al., 1964). This applies especially if steroids are administered at the same time. The clinical experience gathered by Falliers and Ellis (1965) suggests that the combination of varicella and corticosteroid therapy can be injurious in diseases with defective immunity mechanisms. However, steroid therapy in progress may not, according to Kaiser (1967), be interrupted on account of supervening varicella.

In the present case the patient's immunopathy, which has been thoroughly discussed by Hansson et al. (1966), would seem to bear the chief responsibility for the lethal course of the varicella. The rather brief steroid treatment may have contributed to this course. The thymus atrophy observed at autopsy may have been due to the steroid therapy, but may also have been part of the girl's immunopathy. As regards the immunopathy, we here want to stress that plasma cells were found in the lymph nodes.

Certain experience (Ross, 1962; Iriarte et al., 1965) seems to speak for an improvement in the course of varicella if large doses of gammaglobulin are given

within 3 days of the date of exposure. In the present case this was not feasible, but treatment was tried anyway, though without effect.

Pronounced varicella lesions were found in lungs, liver and spleen, which are all well-known target organs of varicella, but also in the pancreas. The histological picture essentially agreed with that previously described (Nakano and Kojima, 1965; Wöckel and Meerbach, 1968). The account was given in some detail to make it possible for the reader to compare the extension of the histological lesions with the results of the electron microscopical and virological examinations. The abdominal pains and peritoneal exudate was probably also due to varicella, as liver, pancreas and spleen were affected. The erosions in the stomach and the small intestine, probably related to the cortisone treatment, may have contributed to the pains. No inclusion bodies or virus particles were found in stomach or intestine.

It is well known that herpes zoster, which is thought to be caused by the same virus as varicella, gives an inflammatory reaction in the posterior roots and ganglia. No such changes were found in the present case nor were any virus particles detected.

The electron microscopic part of the examination revealed virus particles, almost all of them situated intranuclearly, in the liver, spleen, pancreas and lungs. They were of the same appearance as the particles found in human epidermal lesions in varicella (Tournier et al., 1957).

Considering the patients clinical symptoms and the isolation of varicella-zoster virus from skin, lung and blood, the virus particles demonstrated in the present paper may be considered to be varicella virus. Enveloped virus particles, which are generally found in the cytoplasm of cultured cells infected with the varicella-zoster virus, and extracellularly, were only occasionally encountered in the present examination. A fairly thorough search of the literature failed to disclose any papers demonstrating, under the electron microscope, varicella virus particles in internal lesions of the human body. It may be of interest that in the affected organs virus particles were found in endothelial cells and in one organ, pancreas, were probably present only in these cells. These observations agree with the assumption of a viremia in varicella and suggest the endothelial cells to be an early target. It is therefore interesting that virus was isolated from the blood in this patient. The isolation of virus from lungs and skin also agree with the morphological observations. It is notable that virus could not be isolated from liver, spleen and pancreas, though the lesions were advanced in the two former organs.

Varicella can give rise to perivenous encephalomyelitis characterized by foci of demyelination and microglial proliferation in the white matter (Walthard and Walthard, 1958). In the present case such changes were entirely lacking. The histological changes observed in the nervous system consisted of a slight dysplasia of the cortical grey matter in the cerebrum and possibly also in the Purkinje cell layer of the cerebellum, marked degeneration of dorsal root ganglia and dorsal spinal roots and deficient myelination of lateral corticospinal tracts at the level of the lower lumbar cord.

The interpretation of the changes in the nervous system in the present case offers some difficulty. The isolated nerve-cell heterotopia can not be granted

any definite diagnostic importance. These can occur even in "normal" brains (CROME and STERN, 1967). The white matter was intact, with the exception of a certain thinning-out of the myelin sheaths, subcortically in the temporal gyri. Thus there were no signs whatever of demyelination process, gliosis, inflammation or vascular changes in the white matter of the brain; changes that all occur in encephalomyelitis postvaricellosa (WALTHARD and WALTHARD, 1958). The changes in the cerebellum were moderately pronounced and were chiefly manifested as patchily accentuated loss of Purkinje cells, without accompanying gliosis. The changes in certain dendrites are worthy of observation. As reactive changes in the cerebellar cortex in the form of glia cell proliferation are lacking, the changes in the cerebellum may be interpreted as a slight dysplasia in the Purkinje cell layer.

The changes in the spinal ganglia and dorsal roots and in the juxtaganglionic section of the spinal nerves can be characterized as degenerative. Whether it is a question of a slowly progressive current process, or one that was mainly finished cannot be determined. Lipid histochemically there were no signs of current breaking-down into triglycerides and cholesterol esters. The changes in the spinal ganglia can be either primary, or secondary to an ascending degeneration. As peripheral sections of spinal nerves were not available the question of how far the degeneration extends remains unsolved.

The clinically observed ataxia may be connected with the changes in the spinal roots, spinal ganglia and perhaps also with the changes in the cerebellum. The changes in the lateral pyramidal tracts in the lower lumbar part of the spinal cord are also remarkable and difficult to interpret. It may be a retarded myelination.

The younger brother, born in 1964, shows a neurological syndrome with an atactic diplegia and slight mental retardation very similar to that of his sister. The delayed motor development has been noted since 7—8 months of age. He has not received any vaccinations, and he had varicella without complications at the same time as his sister.

It seems reasonable to suppose that the neurological syndrome of the two siblings is genetically determined. Whether an immunopathy is present in the brother also is not known; further immunological studies have not yet been possible to perform but are planned and will be published later on toghether with a clinical follow up of the neurological signs (to be published, Acta Paediat Scand).

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The case was briefly reported at Medicinska Riksstämman, Stockholm, Sweden, Dec. 1, 1967 (Acta path. microbiol. scand. **72**, 448—449 (1968)).

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