Storage of Polyvinyl Pyrrolidone

— Report of Three Autopsy Cases —*

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Polyvinyl pyrrolidone (PVP), a high-molecular-weight product of the polymerization of vinyl pyrrolidone, has been widely used as a plasma expander. The molecular-weight range of PVP commonly used in Japan is 12,000 to 50,000 and usual concentrations utilized in the human subjects are 3.5 to 6.0 per cent, dissolved in isotonic solution or Ringer's solution with frequent mixture with amino acids and other substances.

As to storage of PVP in the tissue, earlier negative findings on dogs and man were reported by Korth and Heinlein.[1] However, increasing number of papers on PVP storage in experimental animals and in human subjects has appeared, reporting not only a simple storage phenomenon but tissue injuries due to deposit of PVP.[2-9]

In our recent autopsies and also in biopsy materials, we have experienced increasing number of cases in which foamy, basophilic material was markedly deposited in the organs of reticuloendothelial system frequently causing tissue injuries of various severity. From the result of staining reaction of this material, the deposits were presumed to be mainly composed of PVP introduced intravenously. In this paper, three autopsy cases in which marked deposition of PVP was recognized in various organs were presented with special reference to morphological changes due to infused PVP.

REPORT OF CASES

Case 1

Clinical History :

The patient, a 61-year-old female, was admitted to the orthopedic clinic of

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Yamaguchi Prefectural Hospital in December, 1962, because of osteomyelitis of the left femur of long duration. After admission, she was treated with various kinds of antibiotic for a year without noticeable effect. In March, 1964, amputation of the left lower extremity was performed. Immediately after operation, she began to have productive cough and fever. A chest film disclosed homogeneous increase in density in the right lower field. Bacteriological examination of sputum revealed streptococcus aureus and viridans, and she was diagnosed as having pulmonary abscess. During and after operation, she was administered PVP preparation by intravenous injection. The total volume of injected PVP was approximately 810 gm. She became increasingly emaciated and expired in June, 1965. During admission, paper electrophoresis of serum protein showed continuous increase in gamma-globulin and generalized amyloidosis was suspected. With congo-red test, uptake of the dye was slightly increased but it was not diagnostic for amyloidosis.

Examination of the peripheral blood and blood chemistry about a month prior to her death were as follows ; RBC 306×10^4, WBC 7600, Hb. 9.6g/dl, serum protein 9.0 g/dl, albumin 1.9 g/dl, globulin 7.1 g/dl, gamma-globulin 67.5%, blood sugar 57 mg/dl, icteric index 3, CCFT 3, NPN 32.5 mg/dl, urea N 28.0 mg/dl, alk. phosphatase 1.5 u, cholesterol 124 mg/dl, phenol turb. t. 10.8 u, GPT 22.3 u.

Autopsy Findings :

An autopsy was performed about 12 hours after the death. The body was that of a markedly emaciated woman. Examination of the skeletal system showed the surgical absence of the left lower extremity. The heart was 210 gm in weight and was normal except for fibrous thickening of the pericardium. There was dense adhesion of the pleural cavity bilaterally. Both lungs were voluminous, and the left was 550 gm and the right was 460 gm in weght. Cut surface of the right lower lobe was dark red in color and markedly consolidated. Other lobes were congestive and slightly firm in consistency. The liver was 700 gm in weight and the capsule was thickened. Section through the liver disclosed distinct lobular pattern, but cut surface was rather lusterless. The spleen was normal in size and was 100 gm in weight. Cut surface of the spleen was moderately congestive. Both kidneys were normal in size and shape, and section through the kidneys revealed no gross abnormality. The lymph nodes in the peritoneal cavity, retroperitoneum and anterior mediastinum were enlarged up to 1 cm in diameter. Cut surface was gelatinous and yellowish white in color. Grossly, there was no abnormalities in the other organs except for arteriosclerosis and atrophy of the thyroid gland.

Microscopic Findings :

Deposits of PVP or a derivative of it were recognized in many organs showing

conspicuous morphological changes.

In the liver, clumps of vacuolar substance were observed within Kupffer's cells or free in the sinusoid (Fig. 1). The liver cell cords were markedly atrophic and partially dissociated. The sinusoidal space was only visible by the presence of erythrocytes. In the interlobular connective tissue, granulomatous lesion due to deposits of pale basophilic, globular material were seen with frequent infiltration of lymphocytes and plasma cells. (Fig. 2). In such a lesion, slight fibrosis was common. With hematoxylin and eosin stain, most of the deposits appeared to be pale basophilic, vacuolar aggregations of microscopic size, and the outer membrane of these vacuoles showed the tendency to be more basophilically stained than the inner portion. With congo red stain,[10] depostits of PVP were stained orange to red (Fig. 3). In hematoxylin and eosin stained preparations, minute vacuoles, most of which were not sudanophilic, were frequently found in the cytoplasm of the liver cells, and some of them were congo red positive (Fig. 4).

In the lung, most of the lobes were displaced by granulomatous lesion with abundant deposition of vacuolar substance. The right lower lobe was most markedly involved and was completely displaced by granulation, in which marked deposition of basophilic vacuoles and frequent appearance of multinuclear giant cells were observed (Fig. 7). In other areas, nodular deposition of vacuolar material and foamy swelling of the alveolar epithelium were common features.

In the spleen, small clumps of basophilic vacuoles were recognized in the sinus and in the lymphatic tissue. Most of the endothelial lining cells showed hydropic swelling. In the lymph nodes, deposition of basophilic material was remarkable (Fig. 8). Multinucleated giant cells, which frequently contained basophilic droplets and small vacuoles, were offen encountered in the distended sinus and in the lynphatic nodules. Although reactive centers were poorly developed, the medullary cord showed marked proliferation of plasma cells. Deposits of PVP were not evenly stained; some were pale basophilic and the others were more deeply stained with hematoxylin and eosin (Fig. 9). In the adrenal, band-likedeposits of globular substance were observed in the sinus. Bone marrow of the ribs also revealed moderate proliferation of foam cells and occasional aggregates of basophilic substance were recognized with resultant decrease of myeloid cellular elements. In the kidney, nodular deposition of basophilic material with infiltration of lymphocytes and occasional giant cells was observed in the interstitium (Fig. 10). Tubular epithelium of the proximal and distal convolution showed typical hydropic swelling and numerous colloidal casts were recognized in the lumen. The endothelial cell of the glomerular tufts were occasionally swollen, probably due to deposition of PVP.

In addition to the reticuloendothelial system, deposits of PVP were found in

the connective tissue, fatty tissue and in the inflammatory lesion. In the heart, such deposits were observed in the pericardial fatty tissue and in the interstitium of the myocardium (Fig. 11). Aortic wall also contained vacuolar substance, especially in atheromatous area. Vacuolar deposit of PVP were commonly found in the mucosal layer of the gastrointestinal tract rarely forming granulomatous lesion. The epithelium of the urinary bladder was completely desquamated and surface area was displaced by granulation, where clumps of basophilic material was abundantly seen (Fig. 12). Furthermore, deposit of PVP were recognized in the tongue, thyroid gland, pancreas, uterus and ovarium in such a degree as shown in Table 1.

Table 1. Deposition of PVP in various organs.

	Case 1	2	3		Case 1	2	3
Liver	⫼	++	⫲	Tongue	++	−	+
Spleen	⫲	+	++	Heart	+	−	+
Lymph node	⫼	+	++	Aorta	++	−	−
Bone marrow	⫲	+	++	Ovarium	+		−
Lung	⫼	+	++	Uterus	+		+
Kidney	⫲	+	⫲	Testis		+	
Adrenal	++	+	+	Cerebrum		++*	
Pancreas	++	−	++	Prostate		+	
Thyroid	+	−	+	Gastrointestinal tract	++	+	+
Urinary bladder	++	−	++				

⫼, ⫲ : severe ++ : moderate + : slight
* : necrotic lesion in tumor

Electron Microscopic Findings :

At the time of autopsy, the liver and spleen were fixed in osmium tetraoxide, dehydrated in serial ethanol and embedded in Epon 812. Thin sections were cut using Porter-Blum ultramicrotome. After staining with lead citrate and uranyl acetate, the sections were examined with a JAPAN ELECTRON OPTICS LAB. JEM-5HS electron microscope.

Fig. 15 and 16 show the electron micrograph of Kupffer's cells, the cytoplasm of which contains many vacuoles. The same vacuoles are also seen in the sinusoid. These vacuoles, though almost round or oval in shape, are varied in size. They have homogeneous internal matrix of various density and some of them have distinct outer membrane.

Fig. 17 and 18 indicate vacuolar deposits of PVP in the cytoplasm of liver cells. These vacuoles have almost similar characteristics to those observed in Kupffer's cell, but internal structure of the vacuoles has decreased density.

Frequently, at the periphery of the vacuoles in the cytoplasm small dense droplets, which might be lipid droplet, are seen.

Case 2

Clinical History :

The patient was 24-year-old male, who suddenly began to have vomitting about ten days prior to admission. After hospitalization, vomitting still persisted and he developed visual disturbance, headache, hearing difficulty and ataxic gait. Examination of the nervous system revealed hyperactive knee and ankle reflexes. The Romberg sign was positive. Alternating movement and coordination were disturbed. The diagnosis of tumor of the truncus cerebri was made and he was given radiation therapy with use of telecobalt unit. To prevent the increase of cerebrospinal fluid pressure, PVP preparations were administered intravenously for approximately 8 months. Total volume of injected PVP was 1400 gm. With progression of emaciation, he expired in October, 1965, about one year after the onset of his illness.

Autopsy Findings :

Postmortem examination disclosed a large irregularly shaped necrotic mass at the truncus cerebri. Cut surface of the tumor mass was grayish white and hemorrhagic lesions were scatteringly seen. The heart was normal. The lung and kidney were moderately congestive. The spleen was 115 gm in weight, and section revealed dark red pulp. The liver was normal in size and shape, and on section no gross abnormalities were found. In the stomach, relatively recent ulcer was found at the posterior wall near the pylorus. The mesenteric lymph nodes were moderately enlarged and cut surface was yellowish white.

Microscopic Findings :

Histologically, cerebral tumor was astrocytoma grade 3, with occasional appearance of giant cells. Deposit of PVP was found in the liver, spleen, lymph nodes, lung, gastrointestinal tract, kidney, prostate, thyroid gland, testis and brain (Table 1). In the liver, Kupffer's cells were markedly swollen with abundant foamy cytoplasm, compressing adjacent liver cells (Fig. 5 and 13). Deposition of PVP was more prominent in the mid-central area. The lymphatic tissue of the spleen also contained clumps of PVP. The endothelial cells of the sinus showed foamy swelling. The sinus of the lymph nodes were completely displaced by proliferated reticulum cells with foamy cytoplasm, and appearance of multinucleated giant cells was occasionally encountered. In the necrotic area of cerebral tumor, vacuolar deposition of PVP with slightly basophilic outer membrane was recognized.

Case 3

Clinical History :

A 76-year-old female was admitted to the medical clinic of Yamaguchi Pre-

fectural Hospital in April, 1965, with the chief complaints of chill and fever. About 6 months before admission, she began to have fever ranged from 38°C to 39°C intermittently. After admission she still had remittent fever and complained of upper abdominal pain. Clinical diagnosis of cholelithiasis was made and various kinds of antibiotic were administered. Because of low blood pressure, she was given PVP preparations as a plasma substitute by intravenous drip infusion for a long time. The total volume of injected PVP was approximately 2260 gm. Her course gradually went downhill and she expired at the end of January, 1966.

Results of laboratory examination a month prior to her death were as follows; RBC 280X10⁴, WBC 5500, Hb. 12.6 g/dl, serum protein 4.2 g/dl, A/G ratio 0.83, icteric index 6, CCFT 3, alk. phosphatase 1.4 u, cholinesterase 0.23, cholesterol 82 mg/dl, NPN 19.6 mg/dl, Urea N 9.1 mg/dl, GPT 18.2 u, GOT 5.2 u, amylase 112 u, ASLO 50 Todd u, Wasserman reaction negative.

Autopsy Findings :

The body was that of an emaciated old woman. There was pretibial edema bilaterally and the abdominal cavity contained 8,000 ml of a clear straw-colored fluid. The liver was 1,800 gm in weight and cut surface had a translucent waxy appearance with indistinct lobular pattern. Yellowish bands of connective tissue surrounds islets of liver tissue or indivisual lobules. The wall of the gall bladder was moderately thickened and the lumen contained pigment stones. The spleen was 110 gm in weight and was firm in consistency. On section, the parenchyma was dark red. Both kidneys were slightly enlarged and cut surface was pale red with distinct cortico-medullary junction. The endometrium revealed fresh hemorrhagic lesion. Enlargement of the lymph nodes was not remarkable.

Microscopic Findings :

Severe morphological changes due to deposit of PVP were found in the liver and kidney. In the liver, stellate cells of Kupffer were markedly swollen and liver cells showed vacuolar degeneration. Atrophy and dissociation of the liver cell cord was remarkable (Fig. 14 and 19). In the kidney, tubular epithelium of the paroximal and distal convolution revealed typical hydropic swelling characteristic to "Kollidonnephrose" (Fig. 20 and 21). In this lesion congo red positive material was not demonstrated. However, in the medulla, congo red positive substance was found in the interstitial tissue and also in the tubular epithelium with occasional colloid cylinder in the lumen (Fig. 6).

The spleen was moderately congestive and clumps of basophilic vacuolar substance was deposited around the central artery. Endothelial lining cells of the sinus showed slight foamy swelling. Sinusoidal lining cells of the adrenal also revealed marked swelling with resultant atrophy of the cortical cell (Fig. 22).

Nodular infiltration of the lymphocytes was found in the thyroid, where vacuolar deposit of PVP was seen (Fig. 23). The lymph nodes of the mesenterium and in the retroperitoneum contained abundant volume of vacuolar substance in the sinus with frequent appearance of foreign body giant cells (Fig. 24). In a giant cell of the hilar lymph node, typical asteroid body was found (Fig. 25). Appearance of foamy cells was also remarkable in the bone marrow (Fig. 26). Deposit of PVP was observed in the other organs as shown in Table 1.

DISCUSSION

Polyvinyl pyrrolidone was first administered to many soldiers and civilians in Germany during World War II. Since then, it has been widely used as a plasma expander, antitoxic and diuretic with good result. Early reports agreeded that retention of PVP in the tissue were only tentative and did not cause severe damage to the tissue.[1] However, there appeared several reports on the morphological changes due to storage of PVP in the reticuloendothelial system[2-9]. In this paper, the authors presented three autopsy cases in which severe deposition of PVP was found in the reticuloendothelial tissue, and described morphological changes of various organgs in detail.

Common finding observed in these cases were storage or deposition of foamy, vacuolar material chiefly in the reticuloendothelial system with frequent appearance of granulomatous lesion. Direct histological identification of PVP is rendered difficult by its ready solubility in water and alcohol, but it is satisfactorily stained red to orange by congo red method described by Freiman and Gall[10] as a suitable staining for the detection of PVP in tissue section. Though at first sight deposited PVP appeared to have lipid nature, staining for lipid was negative. This finding would be very important point to differentiate from histiocytic proliferation containing lipids in the cytoplasm. Furthermore, in all cases reported here abundant volume of PVP was administered by intravenous injection for long duration. Therefore it would be reasonable to presume that the substance responsible for the appearance of the foam cell or for vacuolar deposits in the tissue is mainly derived from injected PVP or its derivatives.

As to the morphological changes in experimental animal and human subjects due to deposit of PVP, there are several reports[2-9]. The changes reported here were essentially similar but were more severe than those reported before. Immediately after injection of PVP, evidence of PVP storage in the form of "foam cells" are promient in the reticuloendothelial tissue, and epithelial swelling of the renal tubules is characteristic. Such hydropic swelling of the tubular epithelium of the kidney has been designated as "Kollidonnephrose" in Germany, but such foamy swelling is not necessarily means the storage of PVP and

offen encountered after administration of hypertonic sucrose and dextran.

Then deposited PVP aggregates and forms clumps of vacuoles, the outer membrane of which tends to be stained basophilic. At that time, occurence of multinucleated giant cells is prominent and formation of granulomatous lesion is frequent. Besides vacuolar deposits, basophilic droplets probably derived from PVP is also recognized in the cytoplasm of giant cells or free in the sinus of the lymph nodes. Such changes of morphological appearance of the material suggest condensation and possible binding of PVP molecules with the substances in the body, such as proteins, lipids, carbohydrate and others. Though PVP molecule itself has no antigenicity, combined PVP would be enough to induce antibody formation and hypergammaglobulinemia would occur just as observed in Case 1. Hübner[9] demonstrated proteins, carbohydrates and lipid in PVP storing cells with histochemical technics, and he describes that the PVP is surrounded by these substances in a capsule-like manner. We also observed the similar finding in electron microscopic study. In vacuolar PVP in the liver cell, lipid droplets were seen at the periphery near the outer membrane of the vacuole.

Excretion and distribution of PVP in man and experimental animals were studied by means of radioactive-tracer technics. Loeffler and Scudder,[11] using carbon-14 labelled PVP-macrose as a tracer, studied excretion rate in man. They reported that about one-third was excreted in the urine in the first 6 hours after injection, two-thirds in the first 24 hours, and small amounts were also excreted in the feces. The unexcreted portion showed a distribution consistent with that of any inert material of large molecular size chiefly in the liver, lung, spleen, kidney and lymph nodes. However, distribution in the body of retained portion showed considerable variation both among indivisual patient and even among different parts of the same and paired organs. They could not find any histologically demonstrable damage caused by storage of PVP. Ravin et al.[12] also studied excretion and distribution of PVP tagged with I^{131} and C^{14} in rat, dog and man. They confined that the retention of PVP in the body was intimately related to increasing molecular weight and the reticuloendothelial system retained PVP with large molecular weight for a long time without being metabolized to any significant degree.

Although molecular weight of PVP infused in all three cases reported here was below 40,000, and would be thought to be easily excreted through the kidney. However, total amount of PVP was too abundant and was administered for a long time, and so it would be beyond the ability of excretion through the kidney and finally retained in the tissue mainly in the reticuloendothelial tissue. Furthermore, when phagocytic activity is accelarated such as in case of inflammation, or when excretion from the kidney is disturbed, administered

PVP would naturally stored in the body more abundantly.

When PVP is stored in the form of foamy cells or hydropic swelling, deposition might be only tentative and it would be gradually excreted from the body. On the contrary, PVP is deposited in the tissue forming clumps of vacuoles or basophilic droplets occasionally combining with other substances, then deposited PVP remains in the body for a long time and would be difficult to be completely excreted. Marked deposition of PVP would be enough to cause harmful effect such as disfunction of the liver and kidney and blockade of the reticuloendothelial system with resultant decrease of protective ability against infections. Such cases would be one of iatrogenic disorders and more clinical attention should be payed hereafter.

SUMMARY

1. Postmortem examination disclosed marked storage of PVP in three patients who had received abundant volume of PVP preparations by intravenous drip infusion.
2. Storage of PVP or derivative of PVP was observed in many organs especially in the reticuloendothelial tissue causing tissue damage of various degree.
3. Morphological changes due to deposit of PVP were characterized by the appearance of "foam cell" and multinucleated giant cell with frequent formation of granulomatous lesion accompanied by a mild inflammatory exsudate. Deposits of PVP or of its derivative were characteristically stained red to orange with congo red.
4. Electron microscopic study of the liver revealed deposition of PVP not only in the Kupffer cells but in the cytoplasm of the liver cell.

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EXPLANATION OF FIGURES

Figures 1 to 4 are microphotographs of Case 1.

Fig. 1. Foamy, basophilic material is deposited in the sinusoid with resultant atrophy of the liver cell cord. H. E. X 400
Fig. 2. Granulomatous lesion due to deposit of PVP in the Glisson's capsule of the liver. H. E. X 400
Fig. 3. Clumps of congo red positive substance are abundantly seen in the sinusoid and also in the periportal connective tissue. Congo red stain. X 100
Fig. 4. Congo red positive material is frequently found in the cytoplasm of the liver cell. Congo red stain. X 400
Fig. 5. Case 2. Kupffer cells are remarkably swollen having abundant foamy cytoplasm. H. E. X 400
Fig. 6. Case 3. Congo red positive substance deposited in the interstitium of the kidney. Congo red stain. X 100

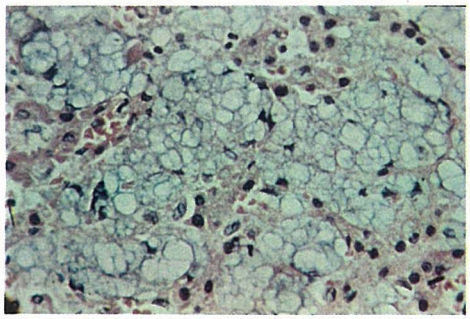


Fig. 1.

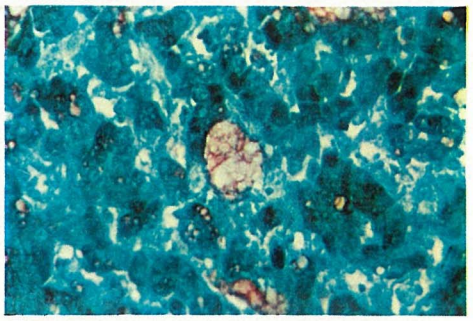


Fig. 4.

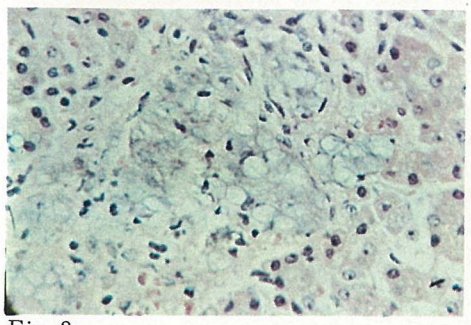


Fig. 2.

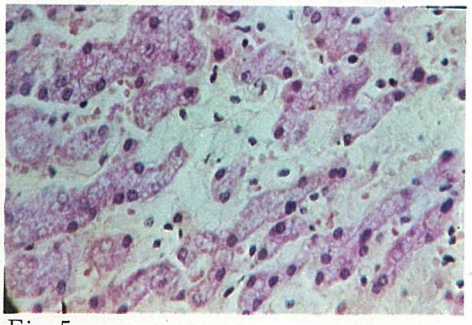


Fig. 5.

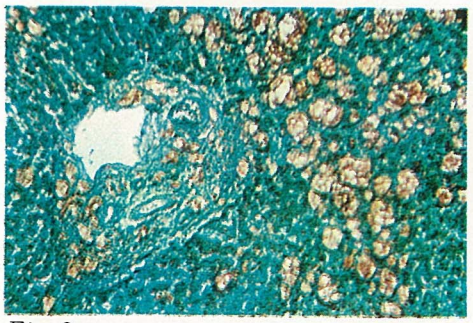


Fig. 3.

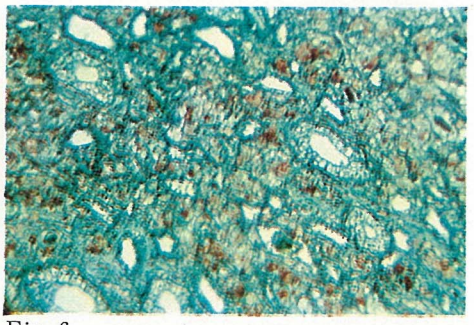


Fig. 6.

Figures 7 to 12 show microphotographs of Case 1.

Fig. 7. Granulomatous lesion in the lung, where basophilic material is deposited and appearance of multinucleated giant cells are frequent. H. E. X 100

Fig. 8. Basophilic vacuolar material deposited in the mesenteric lymph nodes. H. E. X 100

Fig. 9. High magnification of basophilic substance in the sinus of the mesenteric lymph node. H. E. X 400

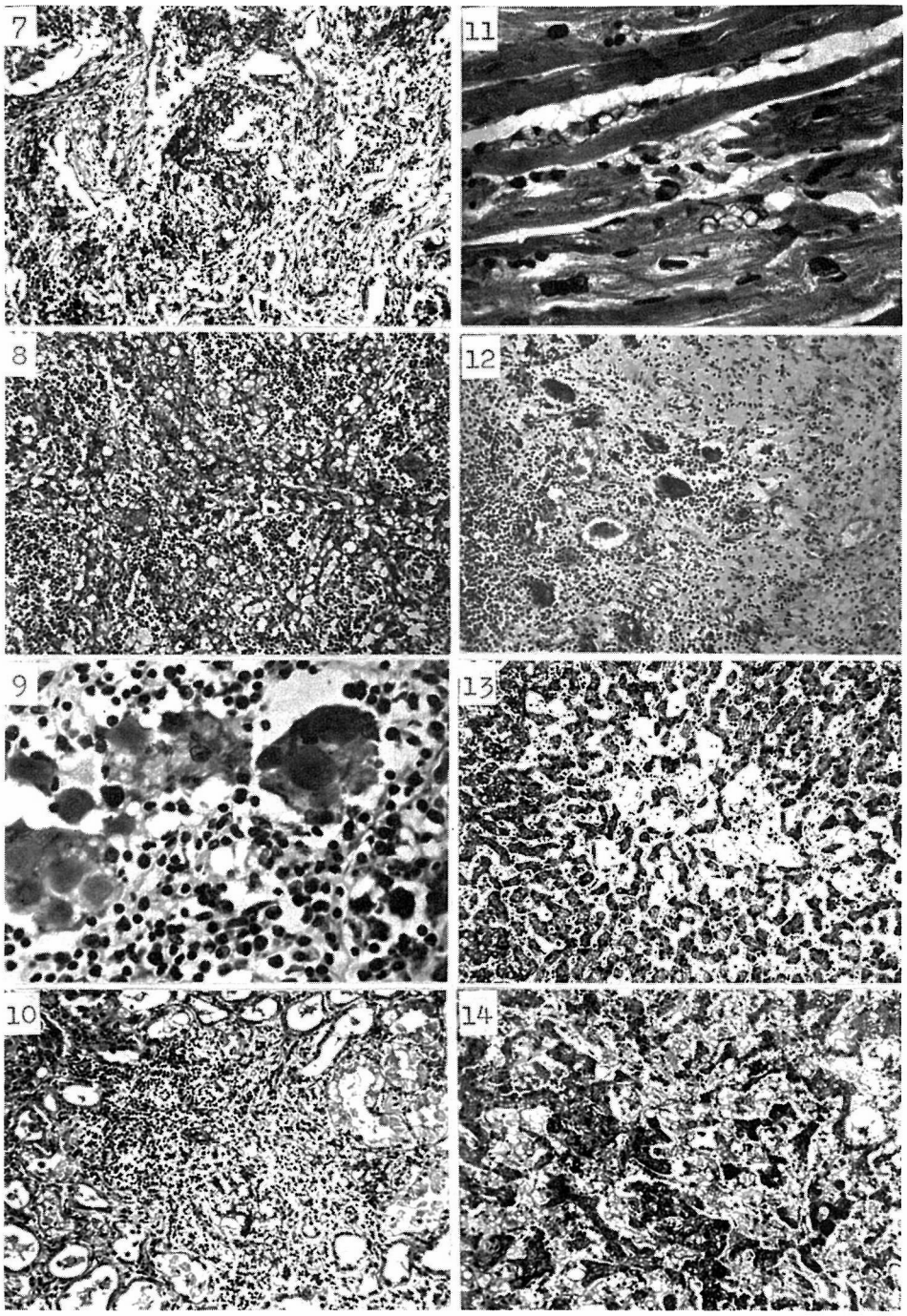
Fig. 10. Granulation in the interstitium of the kidney. In the center of this lesion, basophilic substance is seen. H. E. X 100

Fig. 11. Vacuolar deposit of PVP in the myocardium. H. E. X 400

Fig. 12. Clumps of PVP deposited in granulomatous cystitis. H. E. X 100

Fig. 13. Case 2. Foamy swelling of the Kupffer cell due to storage of PVP. The liver cell cord is moderately atrophic. H. E. X 100

Fig. 14. Case 3. Abundant volume of PVP is deposited in the sinusoid of the liver and the liver cells show marked degenerative changes. H. E. X 100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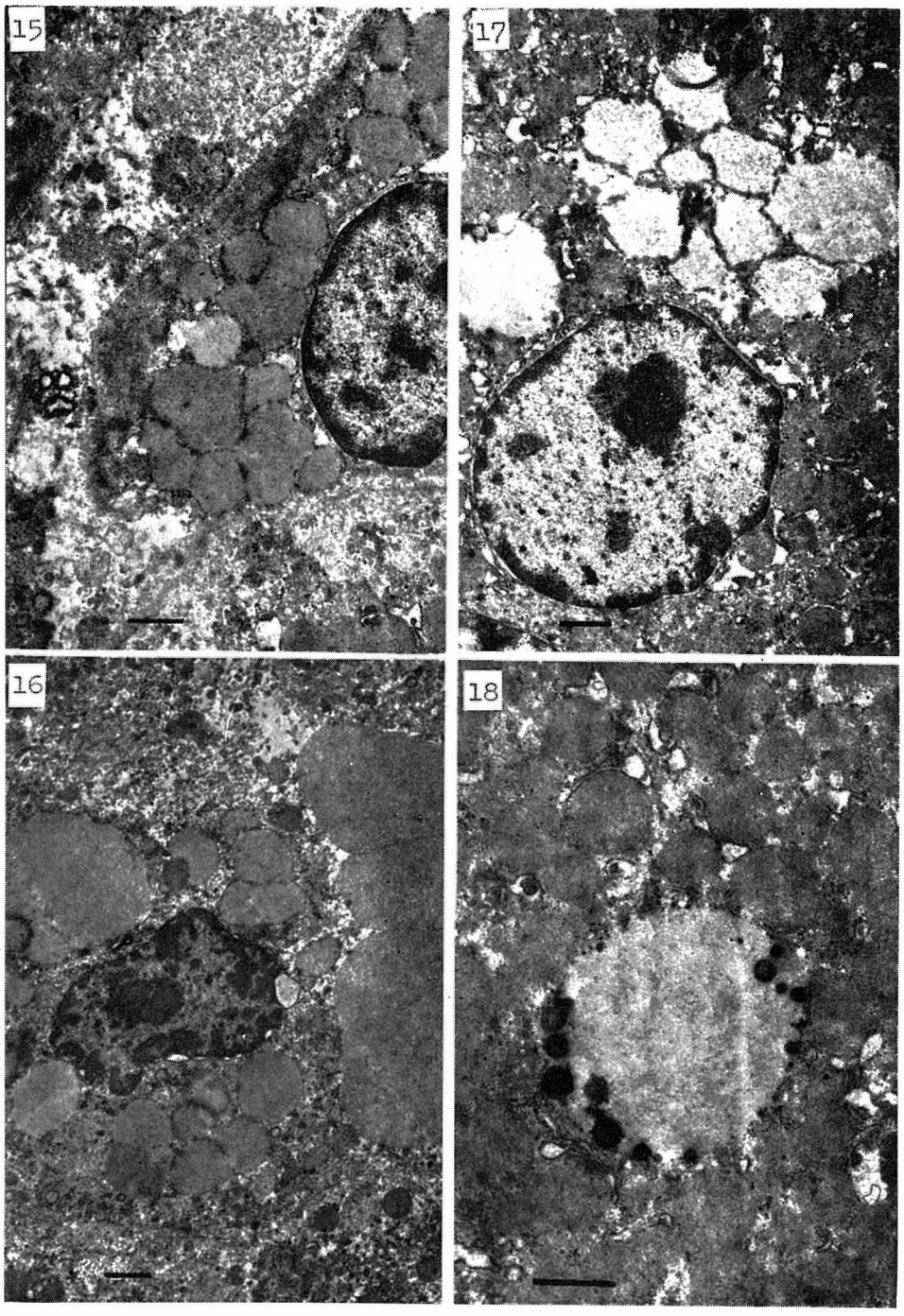
Figures 15 to 18 are electron micrographs of the liver in Case 1.

Fig. 15. Vacuolar deposits of PVP in the Kupffer cell. These deposits are almost round in shape and are moderately dense. Original magnification X 4000

Fig. 16. This micrograph also shows deposits of PVP. Most of them are phagocytosed by Kupffer cell, but some of them are seen freely in the sinusoid. Original magnification X 3000

Fig. 17. Vacuolar deposits of PVP in the liver cell are less dense than those seen in the Kupffer cell. Most of them have distinct outer membrane. Original magnification X 4000

Fig. 18. Lipid droplets are contained in the vacuolar deposit in the liver cell. They are mainly located at the periphery of the vacuole. Original magnifcation X 5000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Figures 19 to 26 are microphotographs of Case 3.

Fig. 19. Marked deposition of PVP in the sinusoid and severe degenerative change of the liver cell. H. E. X 400

Fig. 20. In the kidney, tubular epithelium of the convoluted tubule shows hydropic swelling, which is characteristic to "Kollidonnephrose" described in German literatures. H. E. X 100

Fig. 21. High magnification of hydropic swelling of the tubular epithelium. H. E. X 400

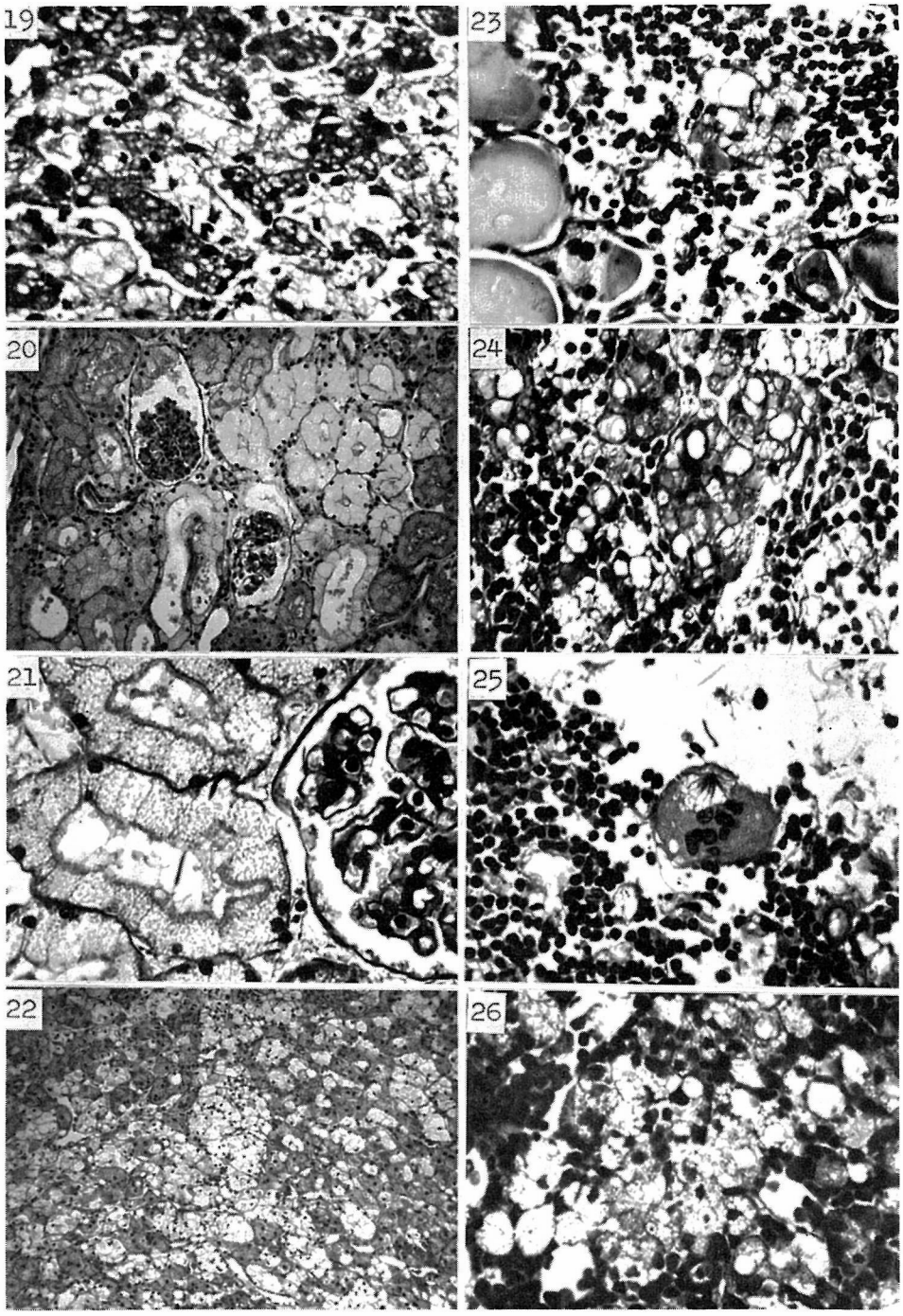
Fig. 22. In the adrenal, deposits of PVP are seen in the sinus. H. E. X 100

Fig. 23. Nodular infiltration of lymphocyte in the thyroid gland, where deposit of PVP is also found. H. E. X 100

Fig. 24. Pale basophilic, foamy deposit of PVP in the lymph node with frequent appearance of giant cells. H. E. X 400

Fig. 25. Asteroid body in the giant cell observed in the hilar lymph node. H. E. X 400

Fig. 26. Many foam cells in the bone marrow. They show negative reaction for lipid stain. H. E. X 400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