Virchows Arch. Abt. A Path. Anat. 360, 155—171 (1973)

Liver Necrosis, Adenovirus Type 2 and Thymic Dysplasia*

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Received March 22, 1973

Summary. An association between adenovirus and liver cell damage, although suspected, has not been frequently demonstrated in the human. In this presentation the necropsy of a two month old female infant with thymic dysplasia will be reported who died with liver necrosis in the absence of pulmonary changes. Sections of the liver showed numerous Feulgen-positive intranuclear inclusions with a distinct mosaic-like pattern on high magnification. Adenovirus was isolated from the liver and identified as type 2 by hemagglutination-inhibition and neutralisation tests. Electronmicroscopy of the liver showed considerable multiplication of the virus in most of the liver cells. The characteristic para-crystalline array of the virions could frequently be seen. The appearance of the virion, its size, and cellular distribution was typical of an adenovirus.

This appears to be the first instance in which adenovirus has actually been shown by electron-microscopy in the human liver, and the third instance in which liver necrosis due to adenovirus was associated with thymic dysplasia.

"The isolation of a variety of viruses over a period of some years from patients with viral hepatitis has resulted in a heterogeneous collection of agents which have been named the 'candidate hepatitis viruses'. However, there is no evidence at present to suggest that any of these viruses is the cause of hepatitis in man. Outstanding among these viruses because of their frequent isolation, which is possibly out of proportion to what may be expected merely by co-incidence, have been strains belonging to the adenovirus group."

This recent statement by Zuckerman (1970) is a fair summary of the current attitude concerning a postulated association of adenovirus to liver damage in man (Davis, 1961; Strong, 1965; Hillis, 1965; Hartwell, Love, Eidenbock, 1966; Köhler, Apodaca, Springer, 1967; Köhler, Apodaca, Lange, 1968). Such an association has been suspected, but actual proof of it is difficult to come by. In the present paper a case will be reported in which adenovirus was not only isolated from, but actually demonstrated in the liver by electron microscopy, which appeared to be the only organ damaged by adenovirus.

I. Case 1

Clinical History. A two-month-old white female infant, the first child of normal parents, was admitted to hospital with a history of four days of irritability, poor feeding, vomiting and fever not responding to antibiotics. At one month of age the child had had a skin infection attributed to Staphylococci, which cleared with antibiotic treatment. The infant had been well until the current episode, which had started rather suddenly with a temperature of 39.4° C.

* This work was supported by Canadian Federal Public Health Research Grant No. 602-7-97 (to Dr. J. Embil). Presented at the Meeting of the Canadian Association of Pathologists, Sherbrooke, Quebec, 1972.

Physical Examination on Admission. Weight 4.9 kg, temperature 39.3°C, pulse 160/min, respiration 60/min. The liver was felt two fingers below the right costal margin. The tip of the spleen was palpable.

During the hospital stay the temperature continued to fluctuate up to 40°C. The liver became progressively larger, up to 5 cm below the right costal margin. Gradually slight jaundice developed, as well as a left-sided pleural effusion, from which about 10 ml of clear yellow fluid was aspirated. The child developed a bleeding tendency from every injection site, including the site of the pleural tap. On the third day of her hospital stay she became noticeably edematous. Despite blood transfusions and the administration of Vitamin K her condition deteriorated and she died five days after admission.

Laboratory Investigations

a) X-Ray Findings. There was evidence of fluid in the left pleural space. The lung parenchyma appeared relatively clear, although the possibility of bronchopneumonia could not be excluded.

b) Hematology: First Day of Hospital Stay. Hemoglobin: 10.3 g-% WBC: 3000/cmm (neutrophils 44%, lymphocytes 56%); Platelets: 258000/cmm; Prothrombin Time: 21 sec (control 13 sec); Prothrombin activity: 35%.

Fourth day. Hemoglobin: 5.7 g%; WBC: 10.950/cmm (neutrophils 34%, band forms 39%, metamyelocytes 5%, myelocytes 1%, lymphocytes 21%); Platelets: appeared normal; Prothrombin Time: 24 sec (control 13 sec); Prothrombin activity 26%.

Fifth day. WBC: 18500/cmm (neutrophils 44%, band forms 33%, metamyelocytes 3%, myelocytes 2%, promyelocytes 1% lymphocytes 7%). Nucleated red cells (15/100 WBC) were seen. Prothrombin Time: 60 sec (control 13 sec), Prothrombin activity: less than 8%.

c) Biochemistry: Fifth day of hospital stay. Enzymes: SGOT: 3600 units/ml, SGPT: 900 units/ml. Alkaline Phosphatase: 22 K-A units/100 ml. Total Bilirubin: 3.2 mg% (direct 2.8 mg%, indirect 0.4 mg%). Total Proteins: 4.9 mg% Blood sugar: 90 mg%. BUN: 7 mg% Electrolytes: Sodium 133 mEq/L, Potassium 4.3 mEq/L, Chlorides 105 mEq/L, Base Deficit —4.5 mEq/L.

d) Bacteriology. Cultures from blood, urine, stool and pleural fluid did not yield any significant growth.

Necropsy Findings

1. Gross Examination

The body of a well-developed, white, female infant showed jaundice of the sclerae, scanty petechial hemorrhages on all the extremities and the face, and pitting of lower extremities. The *left lung* was atelectatic and about 80 ml of blood-stained fluid were found in the left pleural cavity. The *right lung* presented only a few small hemorrhages on the surface. The *heart* was flabby and pale, with fatty change of the myocardium. The *kidneys* were markedly pale, and fatty on frozen section. The *thymus* was extremely small (1.8 g) and the surrounding connective tissue showed a distinct myxomatous change. The *spleen* (21.6 g) was of normal consistency, but very hyperemic; on cut section it appeared uniformly red. Mesenteric and other *lymph nodes* that were seen appeared small. The most striking feature, however, was the large liver (300 g) which was intensely yellow and soft. No visible necrosis was noted on naked eye examination, and the lobular pattern was only feebly indicated.

2. Microscopic Findings

Only the relevant findings will be reported here. The *respiratory system* did not show any significant changes. Despite careful examination no inclusions were seen in the bronchial epithelium, or inflammatory changes in the lung parenchyma.

Lymphatic System. The lobulation of the *thymus* (Fig. 1a) was very distinct, giving it a characteristic irregular leaflike appearance. A cortex and medulla could not be clearly distinguished, lymphocytes were hardly seen and the predominant cells in the thymus were spindle-shaped or oval "reticular" cells (Fig. 1b) with an indistinct cytoplasm. No eosinophils were seen either in the thymic substance or in the stroma, and despite very close examination no Hassall's corpuscles could be found. These changes led to a diagnosis of dysplasia of the thymus with absence of Hassall's corpuscles. The *spleen* (Fig. 2a) was characterized by an almost complete absence of Malpighian corpuscles. Only a scanty accumulation of mononuclear cells with pyknotic nuclei formed a very thin rim around some of the vessels. The spleen thus consisted largely of the red pulp with markedly distended blood vessels in which many pyknotic cells and nuclear dust were noted. The reticular cells between the blood vessels were very prominent. Occasional large cells with brownish granular pigment were noted, as well as remnants of red blood cells in some of the lining cells, indicative of erythrophagocytosis. No eosinophils could be seen. The mesenteric and tracheobronchial *lymph nodes* (Fig. 2b) showed an extremely thin cortex in which hardly any lymph follicles or lymphatic elements were seen. Lymph nodes appeared to consist mainly of "reticular" cells. Only on close examination could there be seen within the vessels and sinuses scanty numbers of small round cells which appeared distinctly pyknotic. Nowhere could there be seen any nuclear inclusions.

The *digestive tract* was characterized by a distinct paucity of lymphatic elements, which became quite obvious in the *ileum*, *appendix* and *large intestine*. The absence of lymphatic elements was particularly striking in the appendix (Fig. 3). Nowhere in the intestine could plasma cells be seen, although occasional eosinophils were present. Where lymphoid tissue aggregates could be found they appeared to consist largely of reticular cells and vascular lining cells with a few pyknotic small round cells only.

The only abnormal feature in the *pancreas* was the presence of large eosinophilic homogeneous casts distending the ducts. The peripancreatic lymph nodes, like those seen elsewhere, showed marked hypoplasia.

The changes in the *liver* were the most striking, most significant and most interesting finding. There were present irregularly distributed foci of necrosis (Fig. 4a) which varied in size from being minute to some which were already seen under the low power of the microscope. Frequently areas of necrosis obviously became confluent. The necrotic foci consisted of eosinophilic masses in which sinusoids could be identified only by the presence of aggregates of red cells. Nuclear or cytoplasmic detail could no longer be seen in these areas of necrosis which, however, merged with a border zone, whose cells presented a markedly variable appearance. Many of them were eosinophilic, in others empty vacuoles were present which, in frozen sections, could be seen to represent fat. Some other "transitional" liver cells appeared to be still less affected by cytoplasmic changes, but the most striking feature in cells, that had not become necrotic, was the widespread presence of characteristic intranuclear inclusions (Fig. 4b). These showed a rather variable appearance (Composite Fig. 5). Although an occasional nucleus was found which apparently did not contain any inclusions, most nuclei of the viable or necrobiotic liver cells showed some degree of inclusion body formation ranging from one or several small, nucleolus-like bodies (Fig. 5a) to a large, prominent, round, sometimes seemingly compact mass, more or less comple-

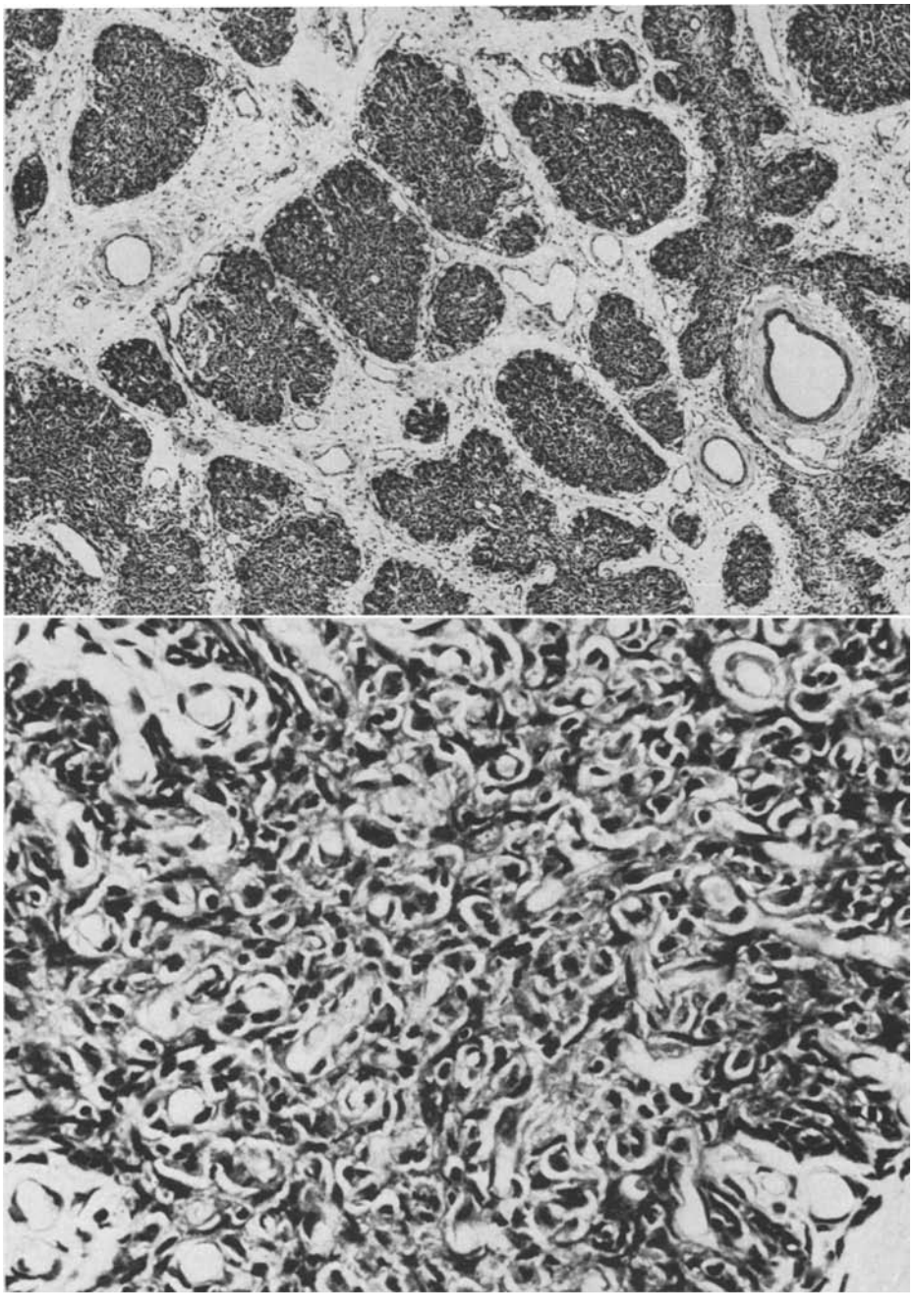


Fig. 1. a The microphotograph of the dysplastic thymus shows the irregular, leaf-like lobulation. 10% buffered formalin, 7 μ, H. E. $\times 16$. b Higher magnification of thymus to show the characteristic "reticular" cells, and the absence of Hassall's corpuscles. 10% buffered formalin, 7 μ, H. E. $\times 510$

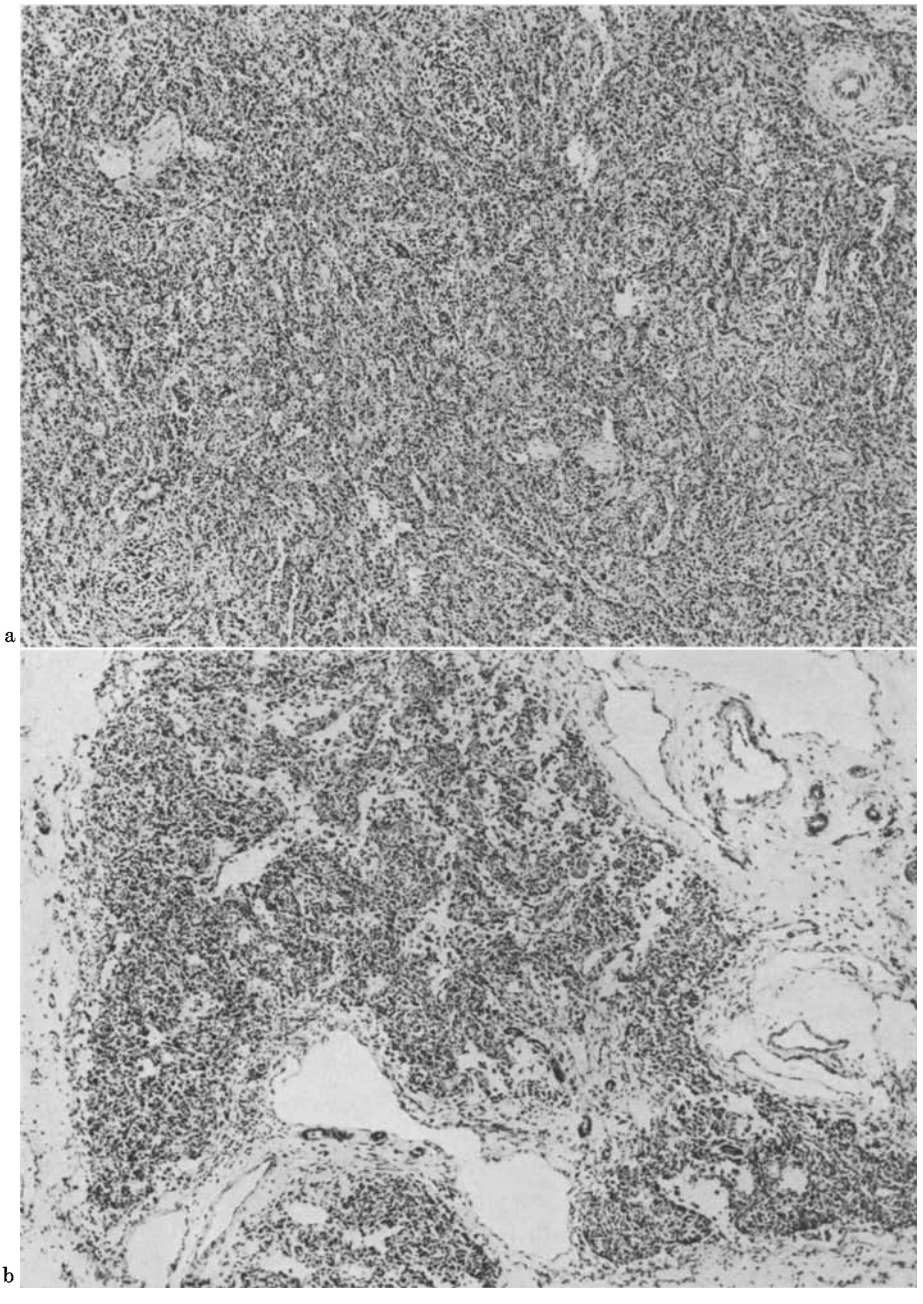


Fig. 2. a The microphotograph of spleen shows the monotonous appearance caused by absence of lymphatic elements. 10% buffered formalin, 7 μ, H. E. ×80. b Microphotograph of a lymphnode to show its hypoplasia and the absence of lymph follicles. 10% buffered formalin, 7 μ, H. E. ×80

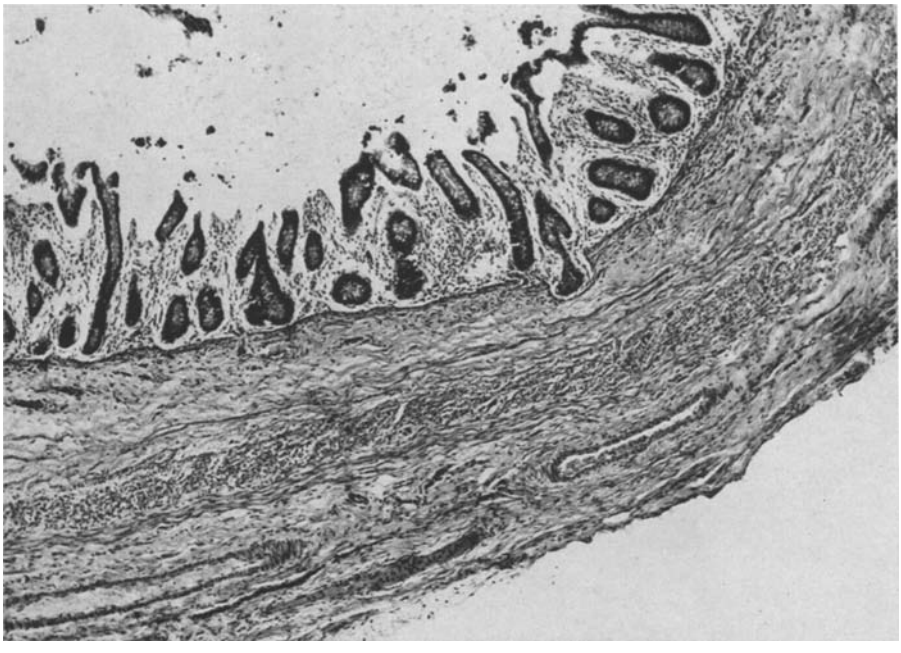
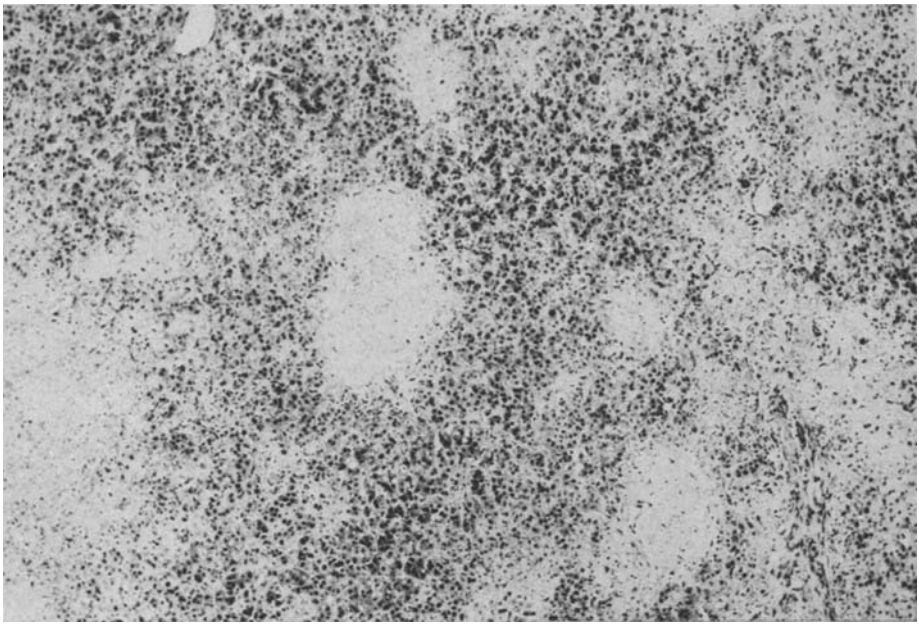
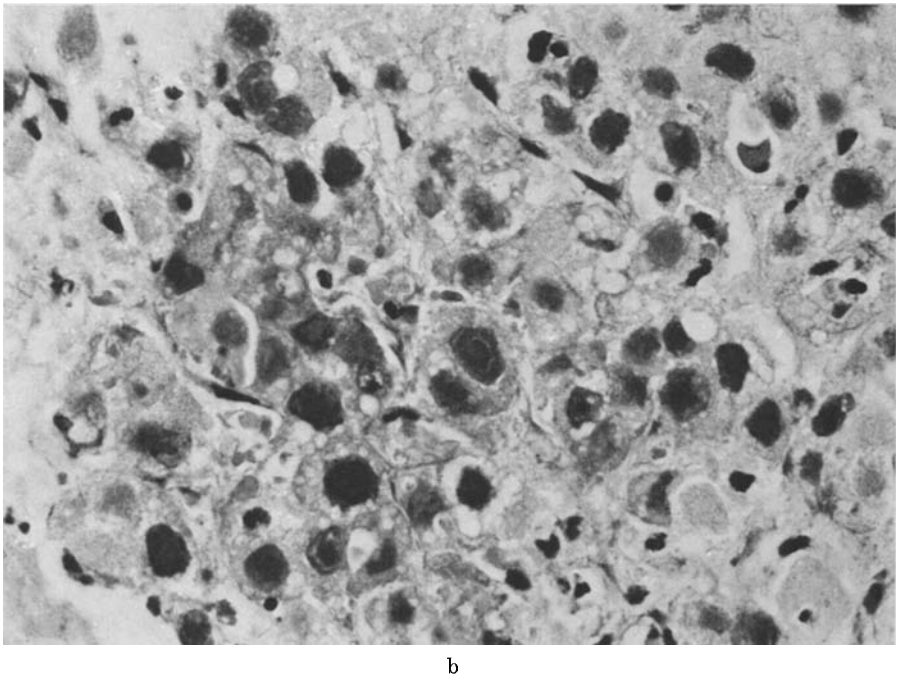


Fig. 3. Microphotograph of section of appendix. Note the absence of any lymph follicles or scattered lymphocytes. 10% buffered formalin, 7 μ, H. E. ×80

tely filling the nucleus (Fig. 5b). Some nuclei had retained their rounded outline (Fig. 5c), others, however, were irregular and distorted (Fig. 4b, 5d). Occasionally a distinct halo (Fig. 4b, 5d) separated the inclusion body from the nuclear membrane, thus creating a resemblance to an owl's "eye" appearance, but in most instances no significant halo formation was observed. Sometimes one larger and several smaller bodies were seen in the nucleus, and on occasion the outline of the inclusions appeared ill defined, or distinctly irregular, as if fusion of smaller inclusions into one larger one had taken place (Fig. 5a). In thicker sections most inclusions merely appeared as an amphophilic homogeneous mass. When, however, these inclusions were studied under the oil immerision an unexpected, but quite distinct, feature found was the presence of what appeared to be an almost crystalline "lattice work" (Fig. 5c, d). This was not seen in every inclusion, but was noted in a number of those that had become rather large. The appearance resembled the surface of a golf ball (Fig. 5c) and recalled the "honeycomb" appearance described by Zuckerman (1970) in the inclusions found in cultures of embryonic liver cells infected by adenovirus. The staining affinity of the inclusions was very striking. Most of them appeared distinctly amphophilic, some of them were almost basophilic. Eosinophilic inclusions were hardly seen, and nowhere could any intranuclear or cytoplasmic crystals be found. Feulgen stains showed that most of these inclusions were positive to a variable degree; they revealed clearly and beautifully the widespread extent of the formation of inclusions. While the inner structure of these inclusions could not be seen with the Feulgen stain



a



b

Fig. 4 a Microphotograph of liver to show irregularly distributed, confluent areas of necrosis. Even at this magnification the absence of a significant inflammatory response can be seen. 10% buffered formalin, 7 μ, H. E. ×16. b Higher magnification of surviving liver cells adjacent to an area of necrosis to show the widespread occurrence of rather variable nuclear inclusions. The margin of the necrotic area can be seen at the left border of the picture. Note the absence of inflammatory cells. 10% buffered formalin, 7 μ, H. E. ×800

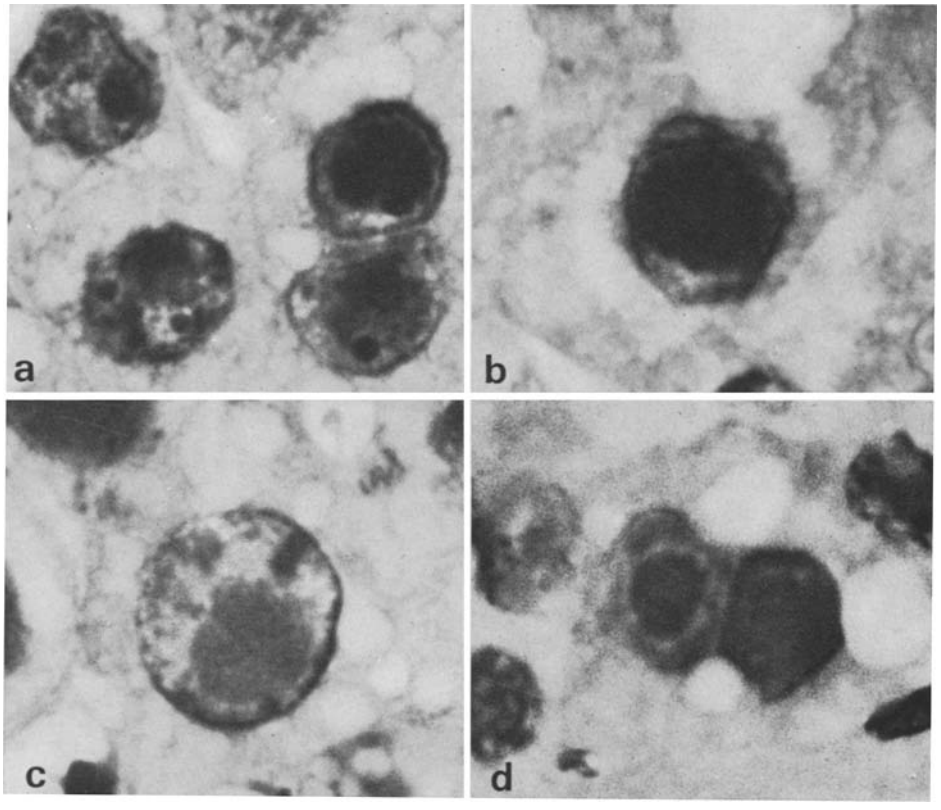


Fig. 5. The variable appearance of intranuclear viral inclusions. 10% buffered formalin, 7 μ, H. E. a Beginning inclusion formation and confluence. About ×2400. b Large intranuclear inclusion with irregular outline and seemingly "solid" appearance. About ×2700. c An intranuclear viral inclusion shows clearly a "honeycomb" internal structure which can be likened to the surface of a golfball. About ×850. d Two intranuclear inclusions which, in addition to the rather faintly visible internal structure, also show the occasional formation of a faint halo or the deformation of the nucleus. About ×2500

it was noted that in many cells surrounding the foci of necrosis there was present much Feulgen-positive inclusion debris in the form of small granules and globules, which would not have been seen in the routine stains. No cytoplasmic inclusions could be demonstrated on routine or Feulgen stains in any of the liver cells examined, but in some of the sinusoidal cells Feulgen positive debris was clearly identified. It is doubtful, however, whether Feulgen-positive nuclear inclusions as such have been seen in the sinusoidal cells.

An additional striking feature of these necrotic changes was the very conspicuous absence of a significant inflammatory response. Neither in the periportal areas nor in the zone of necrosis could polymorphonuclear leukocytes, lymphocytes or significant numbers of phagocytic macrophages be seen, if the activation of sinusoidal cells is excepted. In the periportal areas there could be found an accu-

mulation of what is interpreted as nuclear debris, or an occasional eosinophil leukocyte. The sinusoidal cells appeared to be active, but on close examination many of them also seemed to have pyknotic nuclei. They contained ingested nuclear debris and red blood cells, indicative of erythrophagocytosis. The lymphatics of the liver were markedly distended. Nowhere could bile stasis or proliferation of bile ductules be found, but some of the biliary ducts contained an amorphous eosinophilic debris.

Special Stains: Gram Stain. No fungi or bacteria demonstrated. *Warthin-Faulkner stain:* No spirochetes were seen, but a marked deposition of silver within the liver cell nuclei was noted. *Reticulin stain:* The persistence of the reticular fibers in the areas of necrosis indicated the predominantly hepatocellular nature of this process. *Iron stain:* No positive material was found within the liver cells or nuclei, but the reaction was positive in the cytoplasm of many sinusoidal cells. *Lipid stains:* Material positive with Oil red O or Sudan black was diffusely scattered throughout liver cells. *Periodic acid-Schiff stain:* An almost complete absence of glycogen in the liver cells and much PAS-positive material in the phagocytes was noted. *Feulgen stain:* The positive reaction of inclusions has already been described. In summary then the changes in the liver were: 1. Irregularly distributed foci of necrosis. 2. Necrobiosis of of surviving liver cells. 3. Scanty inflammatory response. 4. Widespread and diffuse formation of Feulgen-positive intranuclear inclusions. 5. Distinct "crystalline" or "honeycomb" structure of some of these inclusions. 6. Erythrophagocytosis.

3. Virologic Studies

Liver, lung and kidney tissues were separately prepared as 15% suspensions in Eagle's MEM diploid medium and were inoculated to stationary cell cultures of human embryo skin and muscle fibroblasts (Embil and Faulkner, 1964). After 48 hours incubation a cytopathic effect developed in the cultures from liver tissue, and after five to six days in the cultures from lung and kidney tissues. The agent was subcultured and subsequently identified by haemagglutination-inhibition (Rosen, 1960) and neutralization tests (Rose, 1969) as adenovirus type 2.

4. Electron Microscopy

Pieces of liver which had been stored in formol-saline for the standard pathological examination were reduced in size and postfixed in 1% osmium tetroxide for two hours. After dehydration the tissue was embedded in an Epon-Araldite mixture (Mollenhauer, 1964) and thin sections were cut for examination with the electron microscope. Staining was achieved both by the addition of 1% uranyl acetate to the fixative wash solution, and by treating the sections with lead citrate.

Considerable multiplication of virus had taken place in the parenchymal cells of the liver and most cells showed evidence of infection (Fig. 6). The limiting membranes of some of these cells were still intact and the nuclei contained numerous particles about 80 nm in diameter consisting of a central electron-dense core surrounded by a less dense limiting surface. Frequently the virions were present in para-crystalline array (Fig. 7, 8). Occasionally lamellar bodies, possibly composed of viral protein, were also observed in the nuclei associated with the virus "crystals". In other cells, in which infection presumably had progressed further, the nuclear membrane was disrupted and many virions were observed in the cytoplasm (Fig. 6, 7). The cell membrane itself was also frequently found to be damaged, facilitating spread of the virus. As a further indication of cellular damage membrane degeneration was apparent in the form of myelin-like whorls.

The appearance of the virion, its size and cellular distribution were typical of an adenovirus.

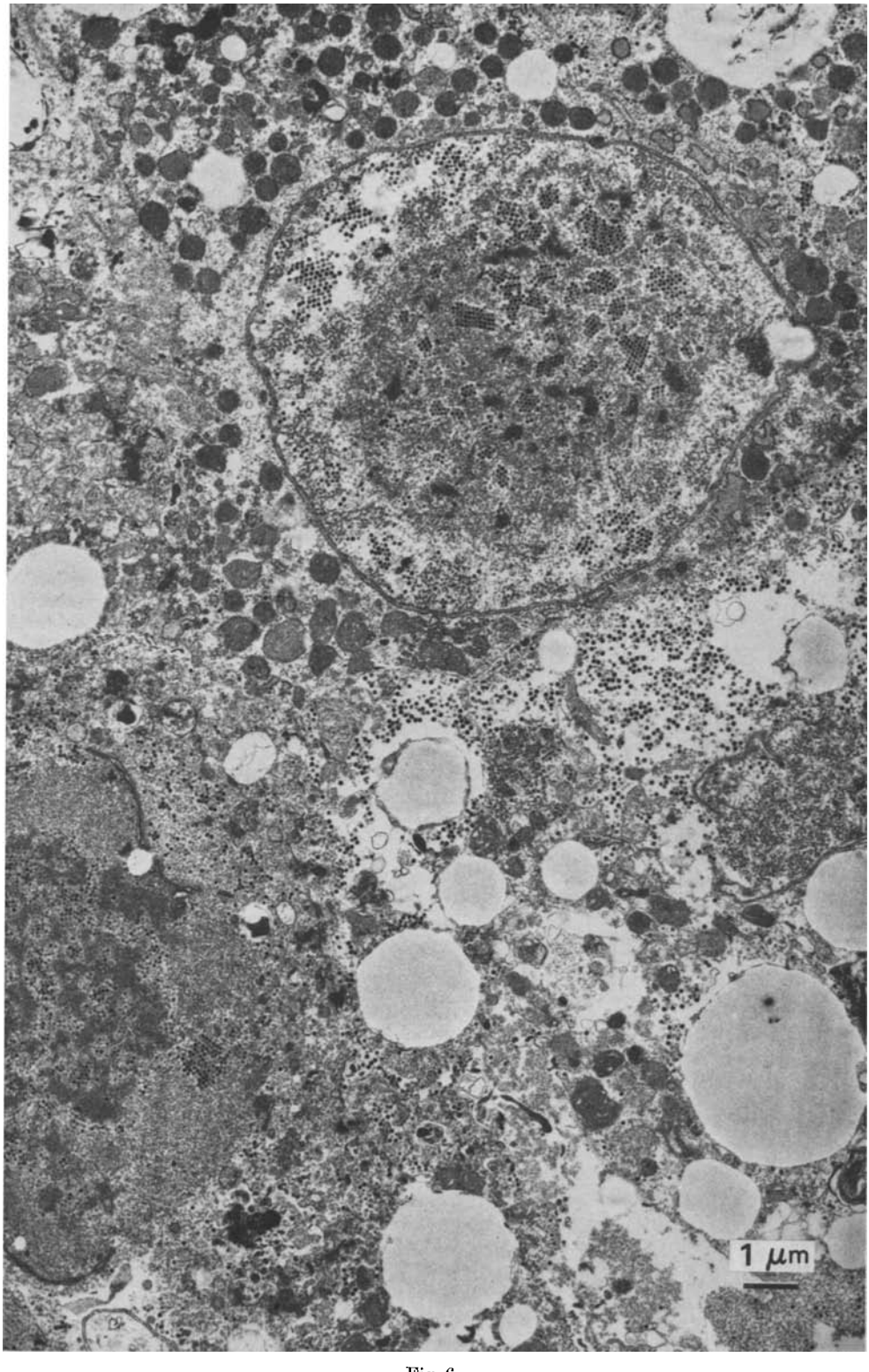


Fig. 6

5. Diagnosis

In view of all the clinical, morphological and virological findings a diagnosis of hepatocellular necrosis due to adenovirus type 2 infection in an infant with thymic dysplasia ("Swiss type") was made.

II. Case 2

About a year after the death of the first infant, the mother gave birth to a male child. This infant was admitted at the age of six months to the hospital with a history of poor feeding, diarrhea for five weeks, dry cough for one month and dyspnea, cyanosis and vomiting for the last three days. The infant weighed 6.1 kg, had a temperature of 38.3° with dehydration, dyspnea, nasal flaring, cyanosis, intercostal indrawing and poor air entry. The liver was 1 cm below the right costal margin. The spleen was not palpable. Apart from hypospadias (first degree) no other abnormal findings were noted. Despite intensive antibiotic therapy the child's condition deteriorated. He developed an attack of severe melena with a precipitous fall of hemoglobin to 5 mg% and died ten days after admission. Permission to perform a necropsy was not given.

Investigations. Electrocardiogram: Normal. The white cell count showed over a period of six days a change from a total count of 27250 cells/cmm (neutrophils 86%, band forms 8%, lymphocytes 5%, monocytes 1%) to 44150 cells/cmm (neutrophils 69%, band forms 2%, lymphocytes 8%, monocytes 1%). Immunoglobulins: IgG: 13 mg%; IgM or IgA: No demonstrable quantities.

Discussion

It has already been pointed out that there exists considerable uncertainty concerning the part played by adenovirus in the etiology of human liver disease. Even some of the transmission experiments in animals, incriminating adenovirus as a cause of liver disorder, are open to question. Zuckerman (1970) has critically reviewed some of the pertinent data, and has concluded that there is no evidence in favour of the view that hepatitis is caused by adenovirus. To a large extent this attitude must have been influenced by the fact that there have been no reports in which the adenovirus has actually been demonstrated in, as opposed to cultured from, the liver, and only few reports in which other suggestive morphological evidence was present. Zuckerman (1970) goes so far as to say that ". . . all the adenovirus strains tested so far in tissue culture produced marked cytopathic effects and virus inclusions were readily identified with the light microscope. No such observations have yet been made in liver biopsy specimens (or specimens of liver obtained post mortem) with viral hepatitis". Presumably this statement was meant to apply only to instances of "viral hepatitis" of the infectious hepatitis type, since there have been at least three instances published of liver necrosis with intranuclear viral inclusions which, however, are not listed by Zuckerman (1970). In all three instances adenovirus was isolated from the liver as well as from other organs. In 1969 Dvořáčková, Vortel and Hroch reported 12 instances of the "encephalitic syndrome with fatty degeneration of viscera", known in English-speaking

Fig. 6. Electron micrograph of virus infected liver tissue taken at low power to show the extent of virus multiplication. In two of the three cells shown the nuclear membrane has ruptured and virus has been released into the cytoplasm. ×8730

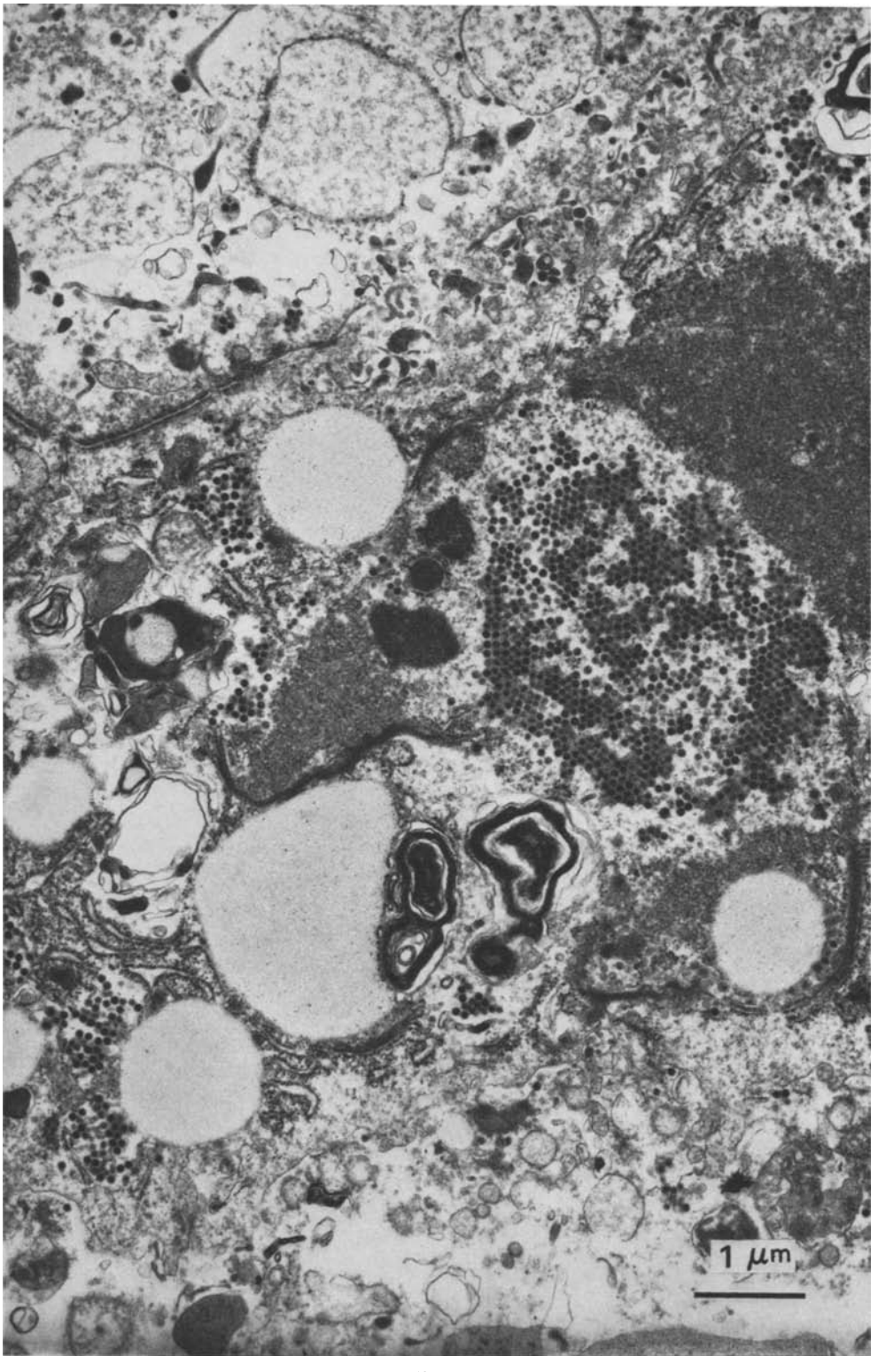


Fig. 7

medicine as "Reye's Syndrome". In four of these cases eosinophilic and amphophilic nuclear inclusions, similar to inclusions reported in the bronchial epithelium of patients with adenoviral pneumonias, were seen "in *some* (our italics) of the liver cells", and "small areas of necrosis of liver cells with slight inflammatory reactions" were present. In only one case (No. 8) of this series, however, was adenovirus type 3 isolated from the liver, conjunctiva and tonsils. Moreover, the authors themselves state that the possibility of contamination by a persistent adenovirus of lymphoid tissues could not be excluded, although they were inclined to consider the presence of intranuclear inclusions in the liver as evidence in favour of an active infection by adenovirus. In view of the fact that adenovirus could not be isolated in the other instances showing apparently similar inclusions, it is difficult to evaluate this case properly which, therefore, must be considered as questionable. Little doubt, however, can be entertained concerning the other two instances, both of whom showed very similar findings. In 1964 Benyesh-Melnick and Rosenberg reported the isolation of adenovirus type 7 from an infant dying with viral pneumonia and presenting widespread dissemination of the causative agent. The authors stated that in the liver there were areas of necrosis, and intranuclear inclusions, similar to those seen in some other viral diseases such as herpes simplex, were clearly recognized. Two years later Wigger and Blanc (1966) presented a similar case in whom widespread necrotizing bronchial lesions, perhaps typical of adenovirus infections, were accompanied also by widespread, but focal, areas of liver necrosis and the development of intranuclear inclusions in the liver, as well as in other cells of the body. Adenovirus type 2 was isolated from the liver as well as from brain, heart, lung and trachea. The description of these two cases closely parallels some of the findings in the instance presented here which, however, differs by virtue of the fact that in our case definite pathological changes were found only in the liver. The liver was also the only organ in which the characteristic intranuclear inclusions were seen despite a careful search for them in other tissues. This striking restriction of significant pathological changes to the only organ presenting cytological evidence of actual viral infection, despite the isolation of the virus from other, histologically not affected organs, strengthens the suggestion advanced here that the liver necrosis seen was indeed the result of an infection by adenovirus.

This suggestion receives further support by the fact that the virus actually was demonstrated in the inclusions by electron microscopy. Both the appearance of individual particles and their characteristic pseudocrystalline arrangement closely conformed to the standard ultrastructural description of adenovirus. This, then, appears to be the first instance in which the virus has actually been demonstrated in the nuclear inclusions of a severely damaged and, moreover, exclusively affected human liver. Interestingly enough, however, these electron microscopic findings perhaps can now also be closely correlated with the appearance of the inclusions on light microscopy, for observation with the oil immersion lens clearly showed the presence of an internal structure in some of the viral inclusions which perhaps be-

Fig. 7. Intranuclear inclusion with crystalline arrangement of virions. The nuclear membrane is broken and cytoplasmic membranes show degenerative changes. ×16200

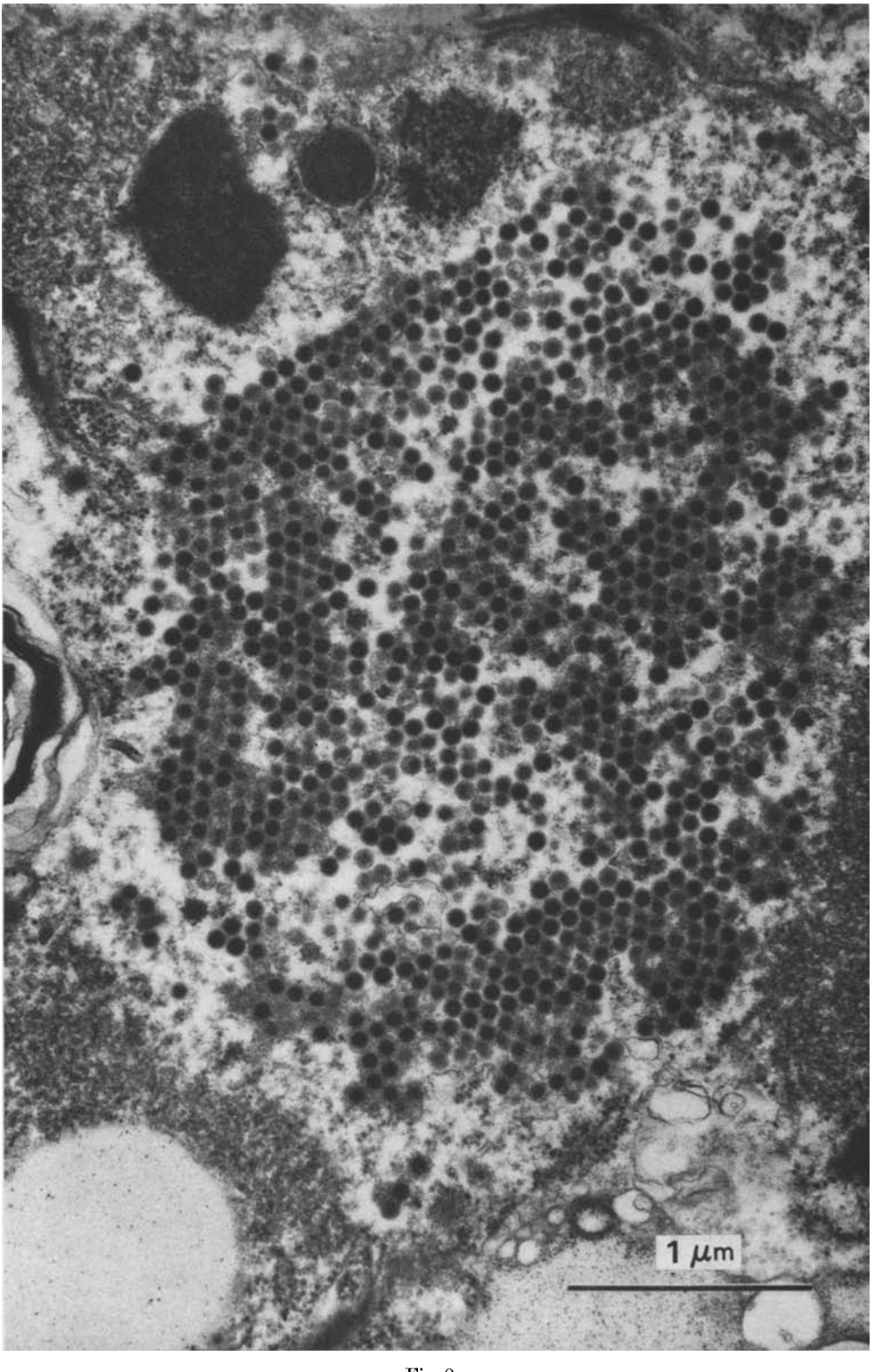


Fig. 8

comes understandable in the light of the typical ultrastructural pseudocrystalline arrangement of the adenovirus. A comparison of Fig. 5c with Fig. 6 illustrates this point. The appearance is similar to that shown in Plate II of Zuckerman's (1970) monograph on "Virus Diseases of the Liver", in which he depicts the "characteristic honeycomb appearance of a huge mass of inclusions" in cultures of human embryo hepatocytes infected with prototype adenovirus 3. This observation, therefore, offers the intriguing possibility of distinguishing with the light microscope on morphological grounds the inclusions of adenovirus infections from other viral disease for which they can be mistaken. Benyesh-Melnick and Rosenberg (1964) stated that "on a cytological basis it is difficult, if not impossible, to distinguish between the inclusions resulting from herpes simplex, from varicella and from adenovirus. Isolation of the virus has been the only means of identification". Kusane, Kawai and Aoyama (1958), however, thought they could "readily" distinguish the inclusions of adenovirus from those of the herpes virus, which were more eosinophilic and had a clearer contour. It is doubtful whether the degree of eosinophilia of an inclusion can be used as a distinguishing feature, since it may well be merely a question of the age and the stage of development of the inclusions. Wigger and Blanc (1966) also thought that"... the parenchymal lesions in the liver bear a striking resemblance to those produced by herpes simplex and varicella virus except for the morphology of the inclusions", but did not give any criteria which would allow this cytological distinction to be made. Despite some searching through the literature we have not found such criteria published elsewhere either. Hence the tentative suggestion is advanced here that one of the characteristic features to be looked for would be the "golfball surface" appearance of the inclusions shown in Fig. 5, which, until proved otherwise, may be considered as signifying the inclusions of adenovirus infection.

As far as the electron microscopic findings are concerned it may be worthwhile to mention here that Zuckerman, Bird, Dunkley and Love (1969) described an essentially similar morphological picture in cultured human embryo hepatocytes inoculated with San Carlos viruses. This group of viruses, isolated during an outbreak of infectious hepatitis, is closely related to adenovirus, but possesses minor differences in antigenic structure. In certain of the infected cells lamellar bodies, comparable in size and appearance to those seen by us in the infected liver cells, were observed. Inclusions of this type, which may consist of viral protein, may be characteristic for certain types of adenovirus. Adenovirus type 2 usually produces in vitro regular solid crystals; since different types of crystals are usually not found together, the virus isolated in the present study may not be entirely typical.

An additional feature of great interest was the thymic dysplasia with absent Hassall's corpuscles and generalized lymphoid hypoplasia found at necropsy here. No immunological studies have been undertaken in this patient, but an absence of immunoglobulins was demonstrated in the second, male, sibling in whom this feature was specifically looked for because of the characteristic findings in the first sibling. Both the morphological and clinical signs in these two infants, therefore,

Fig. 8. Enlargement of intranuclear inclusion to show the virion structure. Almost all virions are "full", i. e. contain nucleic acid. ×36400

allow the conclusion that we are dealing with the inherited thymic dysplasia of the type known by earlier workers as "Swiss agammaglobulinemia" (Haworth, Hoogstraten and Taylor, 1967; Sell, 1968; Waldmann, 1969; Duic, Crozier, Lynch and McClure, 1970). The significance of this conclusion emerges when it is realized that in the two cases of hepatic necrosis with adenovirus inclusions described by Benyesh-Melnick and Rosenberg (1964) and Wigger and Blanc (1966) a similar type of thymic dysplasia was present. It is well known that adenovirus infections in children frequently, though not exclusively, manifest themselves only by upper respiratory involvement (Sterner, 1962; Herrmann, 1968; Angella and Connor, 1968) and that, on the other hand, thymic dysplasias will in general predispose to more widespread, more severe, and more bizarre infections. The question which now arises concerns the part which the thymic dysplasia played in the unusual, and unusually severe, manifestations of the infection by adenovirus described here and in the other two published instances. Since this is the third time in which an association of thymic dysplasia ("Swiss type") and liver necrosis by adenovirus has been observed, one may well be justified in asking whether this association is purely accidental or whether there does exist a causal relationship which determines this curious manifestation of a generalized disease. This is the more pertinent if it is realized that in the case presented here the liver appeared to have been the predominant, perhaps even the only, organ affected. Until such time that it can be conclusively shown that the liver is also involved in normal infants with adenovirus infection, the possibility cannot be excluded that we are dealing with an unusual course of events significantly influenced by the abnormal immunological state of these children with thymic dysplasia. It may well be that the failure so far to demonstrate the adenovirus in the liver, on which Zuckerman (1970) has commented, may be determined by the presence of an adequately functioning immune system, whereas its inadequacy may lead to the liver necrosis (with or without dissemination) seen here and in the other two cases discussed. The analogy to the relation of "Hechts' giant cell pneumonia" and the commomly known infection by measles readily springs to mind. It is possible, therefore, that study of future instances of this syndrome of thymic dysplasia and liver necrosis caused by adenovirus will throw some light on the mechanism determining the course of infection by this agent, and lead to a better understanding of the factors which determine the manifestations of this common pathogen.

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