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Foreign Body Giant Cell Reaction in Lungs, Liver and Spleen

A Complication of Long Term Haemodialysis

Burkhard Krempien* **, Jürgen Bommer, and Eberhard Ritz
University of Heidelberg, Department of Pathology (Head: Prof. Dr. Dres hc W. Doerr) and of Internal Medicine (Head: Prof. Dr. Dres hc mult G. Schettler), Heidelberg, Federal Republic of Germany

Summary. Accumulation of a foreign material in grotesque quantities was observed in the macrophages of lung, liver and spleen of a patient on maintenance haemodialysis. The material appeared in macrophages which were found either in groups or singly, without causing epitheloid cell reaction, necrosis or fibrosis. The material was non-isotropic, non-crystalline and did not stain with routine staining procedures. Transmission electron microscopy showed its presence within lysosomal membranes. The nature of the material and the mechanism of its incorporation into the patient remain unclear, but it is conceivable that incorporation is a consequence of longterm interaction of blood and foreign material during haemodialysis. The clinical consequences of such incorporation have to be established.

Key words: Haemodialysis – Foreign body reaction – Plastic material – Macrophages – RES

Introduction

During haemodialysis, the blood of uraemic patients interacts repeatedly with foreign material, i.e. cuprophane (or other) membranes, tubing, cannulas etc. A number of complications result from such interactions, e.g., disturbances of coagulation (Cannussi et al. 1978; Bjørnson et al. 1978), activation of the complement system (Craddock et al. 1975), leukocyte and platelet emboli into the lung resulting from interaction with dialysis membranes (Bischel et al. 1975), liver dysfunction upon exposure to some PVC tubing material (Neergard et al. 1971) and necrotising cutaneous dermatitis resulting from exposure to PVC tubing (Bommer et al. 1979).

* To Prof. Dr. G. Ule on the occasion of his 60th birthday

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Offprint requests to: Prof. Dr. B. Krempien, Pathologisches Institut der Universität, Im Neuenheimer Feld 220/221, D-6900 Heidelberg 1, Federal Republic of Germany

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The following case report describes another complication resulting from exposure of dialysis patients to foreign material. Such reactions are of clinical importance and also have implications for the manufacture of dialysis devices.

Case Report

V.L. (female) born 23. 5. 1919; renal disease: reflux nephropathy. In 1936 and in 1946, symptomatic urinary tract infection with pyelitis occured and subsequently, since 1946, continous proteinuria was found. During her first pregnancy in 1947, the patient had repeated episodes of urinary tract infection. An excretory urogramm in 1960 showed renal scarring with bilateral deformation of the parenchyma and the calyces. Elevated serum creatinine was first noted in 1967. The patient was subsequently maintained on antihypertensive therapy, low protein diet and forced diuresis. Terminal renal failure was reached in March 1971. She was put on maintenance haemodialysis and was dialysed first with a Scribner Shunt in the left lower limb and subsequently (from September 1971) with a subcutaneous AV-fistula in the left forearm. Later, fistulae were created in the right forearm and right upper arm. Neither a Scribner shunt nor a vascular prosthesis (Gore Tex or Impra) were implanted thereafter. At the time of admission, thoracic X-ray showed cardiomegaly and pulmonary congestion. Physical examination revealed no hepatosplenomegaly and no enlargement of peripheral lymphnodes. The patient was first dialysed with a Drake Willock machine (type 4015) with a DW blood pump (N 4504), using a Rhone-Poulenc RP 5 dialyser with silicon rubber tubing of Rhone Poulenc Company. From May 1977, the patient was dialysed with a Milton Roy (model B) machine and a Watson Marlow blood pump using Gambro Lundia Major dialysers and Gambro PVC tubing.

In May 1972, the patient developed HbS positive hepatitis with a peak increase of SGPT of 270 IU in June 1972 and prolonged cholestasis (alkaline serum phosphatase 280 IU with positive LPX). Transaminases had returned to normal values in August 1972 and by the same time liver and spleen were normal on palpation. Haematological values were unremarkable (leucocytes 6.100/µl and thrombocytes 120.000/µl). HbS remained positive until death.

The subsequent course of haemodialysis was uneventful until 1974 when splenomegaly, hepatomegaly and thrombocytopenia (60,000–80,000/µl) were noted for the first time. Hepatosplenomegaly increased progressively and at the time of death, the liver was 10 cm below the costal margin and the spleen was palpable in the pelvis. Because of progressive anaemia and thrombocytopenia, thrombocyte kinetic studies and erythrocyte kinetic studies with labeled cells were performed in 1978. Both studies showed marked sequestration in the spleen. Splenectomy was adviced, but the patient declined.

Because of progressive hyperparathyroidism with hypercalcaemia, elevated bone alkaline phosphatase and excessive immunoreactive PTH levels in the plasma, subtotal parathyroidectomy was performed in May 1976. Subsequently, the patient remained normocalcaemic on therapy with vitamin D_3.

Repeated thoracic X-rays were unremarkable with the exception of cardiomegaly.

Spontaneous bleeding (epistaxis, bruising of the skin) occured. In addition, progressive anaemia with high transfusion requirements and persisting leucocytopenia (2.500/µl) occured. The patient agreed to undergo splenectomy. X-ray and gastroscopy revealed marked pyloric stenosis.

In January 1979, splenectomy and pyloroplasty were performed. Postoperatively, the patient developed severe gastrointestinal bleeding and died during haemodialysis despite transfusion.

Results

Autopsy Findings

63 kg, 153 cm hepatosplenomegaly (liver 2,500 g; spleen 1,500 g). The hepatic surface showed a fine nodular transformation with slight capsular fibrosis. The spleen was firm on palpation and showed capsular fibrosis and no splenic infarction. Lungs and pleura were unremarkable on inspection. There was no evidence of pulmonary artery sclerosis. Haemosiderosis of all organs examined was noted. Other findings were non-contributory.

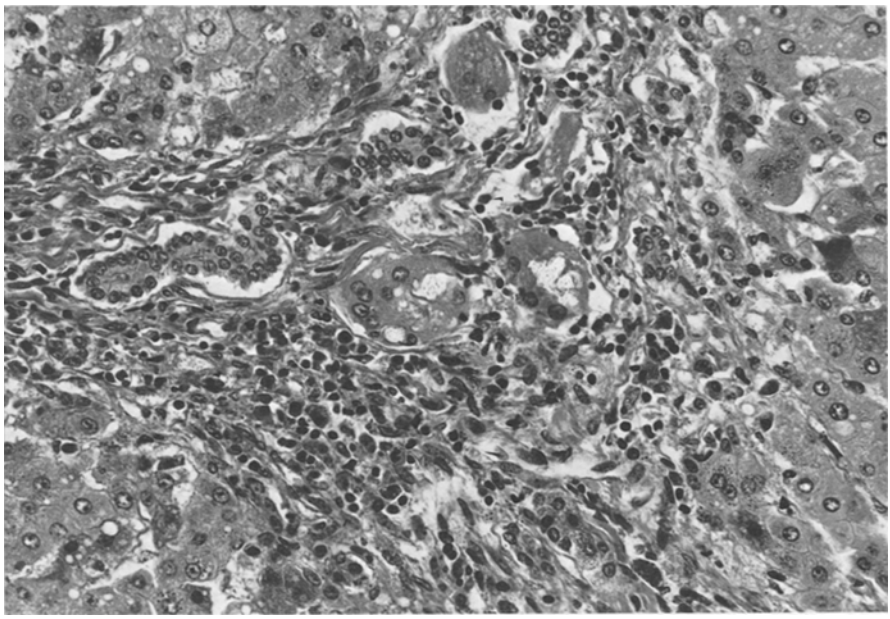

Fig. 1. Enlarged periportal field of the liver. Several foreign body giant cells with cytoplasmic inclusions of an unstained material. HE, enl. ×250

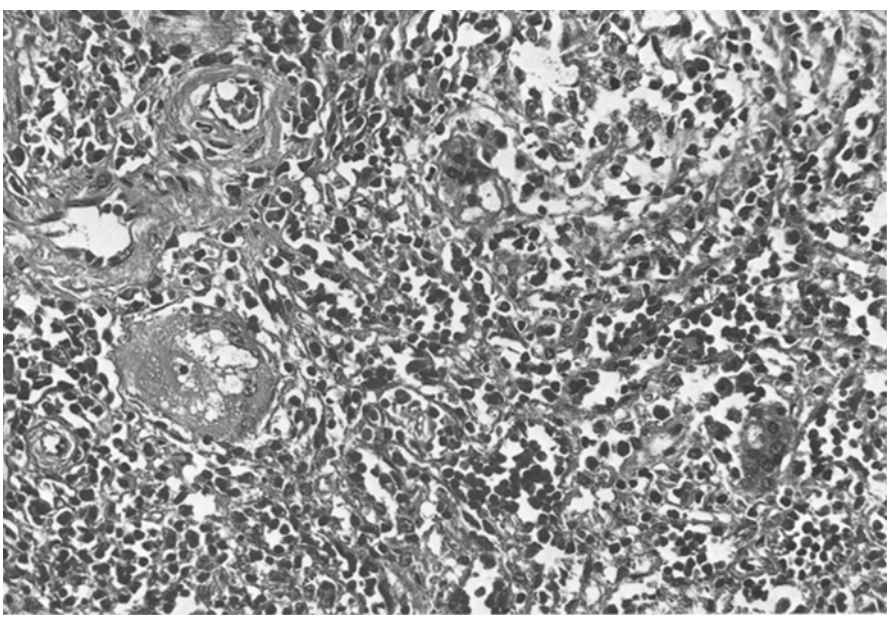

Fig. 2. Spleen: red pulpa with a group of giant cells, which contain similar inclusions as the giant cells of the liver. HE, enl. ×250

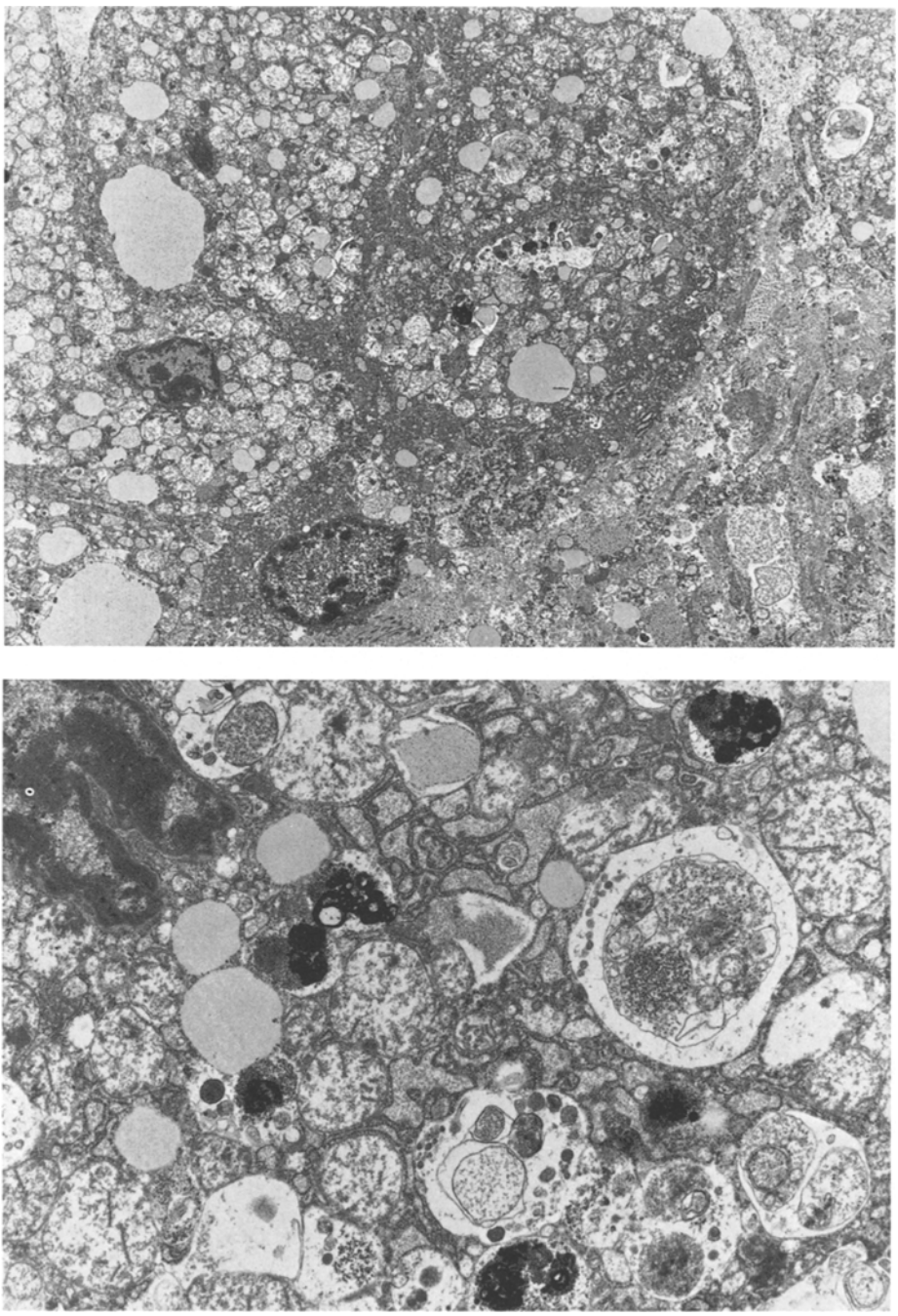

Fig. 3. a Giant cell of the liver with numerous lysosomal vesicles. Enl. ×5,100. **b** at higher magnification different structural properties of the content of these vesicles can be discerned: some vesicles are filled by a dense globular material; others contain delicate lamellae or a fine granular and homogeneous substance. Enl. ×18,600. Transmission electron microscopy, autopsy material

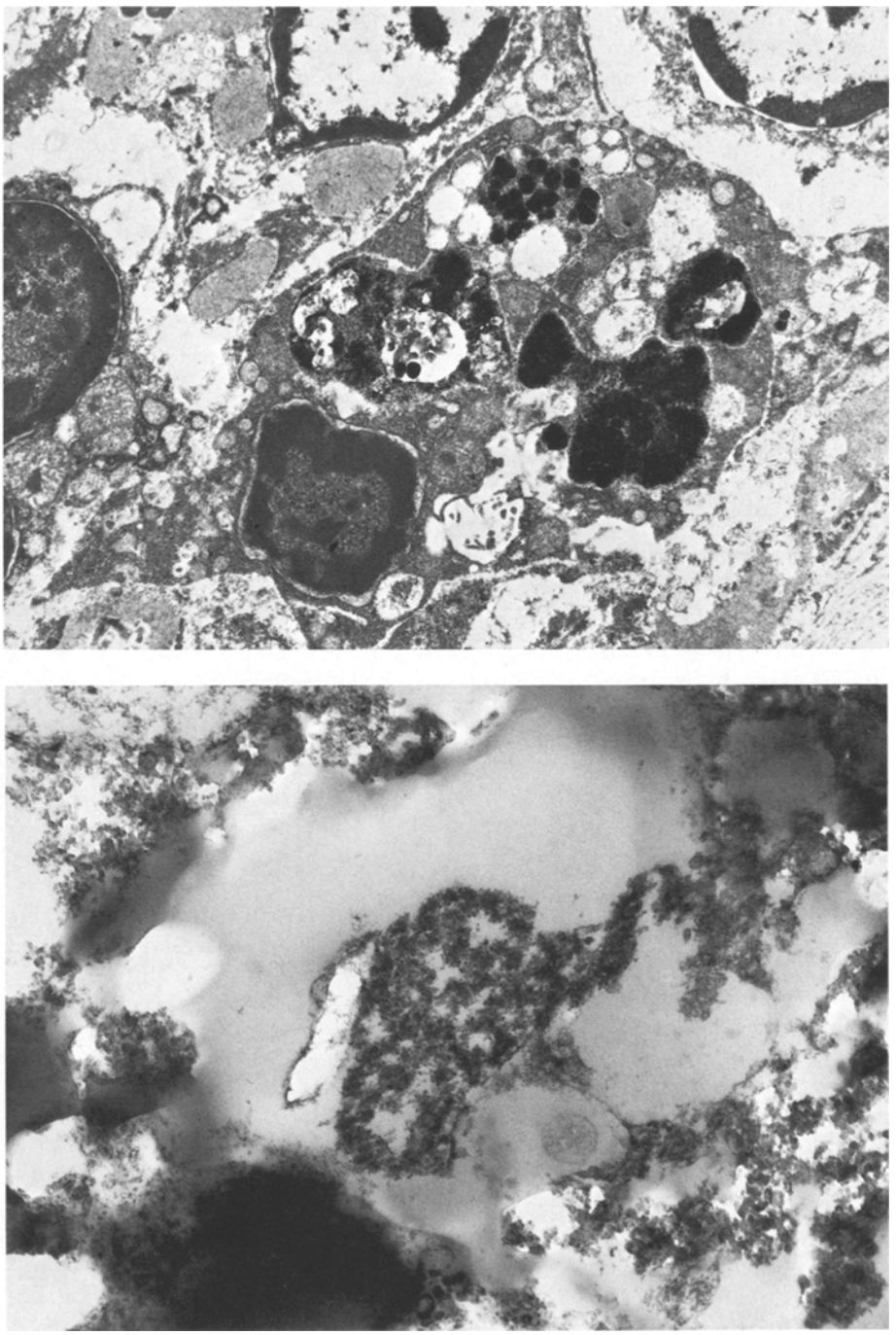

Fig. 4. **a** Spleen. Vesicles containing a globular or granular material. Enl. ×18,600. **b** At higher magnification often a fused appearance of such lysosomal inclusions can be seen. Enl. ×54,000. Transmission electron microscopy

Histological Findings

Lung. In the interstitium of the lung and in some places within the alveoli, scattered foreign body giant cells were observed. The interstitium was not increased in thickness. The pulmonary capillaries were patent and showed no evidence of microemboli. The cytoplasm of the foreign body cells contained inclusions measuring approximately 5–50 μ. The inclusions were irregularly shaped, non-refractile on polarisation microscopy and showed a non-crystalline, colourless, usually homogenous and occasionally slightly granular structure. There was no fibrosis or cellular infiltration adjacent to the foreign body giant cells. No foreign material was seen in lymphatic vessels but foreign body giant cells were noted in the mediastinal lymph nodes.

Liver. In the periportal fields, numerous foreign body giant cells were noted. No such cells were seen in the sinusoids and in the vicinity of the central veins. The giant cells occured either singly, as in the lung, or in groups, in contrast to what was observed in the lung. No evidence of fibrosis, necrosis, deposition of calcium or iron was found around these cells. In addition, extracellular foreign material was not observed. Around collections of foreign body giant cells there was, occasionally, infiltration of lymphocytes and histiocytes. Eosinophils were not observed. Epitheloid cells were never seen. In addition, the periportal fields were diffusely infiltrated with lymphocytes and the typical changes of chronic aggressive hepatitis were observed with destruction of the ground plate, piece meal necrosis, bile duct proliferation, septal fibrosis and micronodular cirrhosis with steatosis of liver cells (Fig. 1).

Spleen. In the red pulp, outside the sinusoidal lumen, there were numerous foreign body giant cells occuring singly or in collections of up to ten cells. In all respect their appearance resembled the findings in the liver, but the changes in the spleen were much more extensive (Fig. 2).

Other Organs. No foreign body giant cells or foreign material were demonstrable in brain, myocardium, pancreas, thyroid, adrenal glands, bone marrow and intestinal mucosa.

Transmission Electron Microscopy. Electron microscopy showed macrophages with numerous lysosomes which contained electron dense material of varying densitiy and occasionally granular appearance. As far as can be evaluated from autopsy samples the material included in foreign body giant cells appeared to be bounded within lysosomal vacuoles. In many sections, the foreign material had a lacquer-like appearance as if it has been smeared out. This may have resulted from partial solubilisation during standard procedure of preparation for transmission electron microscopy (Figs. 3a, b, 4a, b).

Discussion

The present case shows clearly that foreign material in large quantities may accumulate in several organs of patients on maintenance haemodialysis. It is

noteworth that no such material was observed in a number of organs (e.g., brain, myocardium, pancreas, intestinal mucosa etc) whereas is was prominent in organs which contain macrophages (e.g., lung, liver, spleen and lymphnodes). The pattern of accumulation of foreign material in parts of the reticulo endothelial cell system was uniform, but the sinusoidal Kupffer cells were devoid of such material. This is in contrast to what one observes after injection of foreign material (e.g., mica-crystals) into the portal vein, which causes accumulation of crystals in Kupffer cells. The finding that Kupffer cells do not contain foreign material, must not lead to the assumption that Kupffer cells are not involved in the accumulation process of the material. It is possible that Kupffer cells eliminate the foreign material in a soluble form from the blood, which then is stored in a visible form in macrophages of the periportal fields.

Extensive haemosiderosis and micronodular cirrhosis with aggressive hepatitis were present in the patient under study. Whether these conditions predisposed to subsequent foreign body induced hepatosplenomegaly must remain undecided. It is also conceivable that the grotesque extent of foreign body reaction in this particular patient is due to some predisposing metabolic abnormality, but again this must remain conjectural.

The investigations carried out to date do not permit definite conclusions with respect to the nature of the material and the mechanism by which it was introduced into the organism, but certain considerations are pertinent. The material found was isotropic under polarized light and did not show a crystalline structure. It was solubilized in part during preparation for electron microscopy which is suggestive, but not conclusive evidence that the material is organic in nature. The material was not stained with haematoxilin eosin, Masson Goldner or PAS. Furthermore, it did not exhibit an intrinsic structure, specifically, it did not contain microfibrils. Under transmission electron microscopy, the material had a glaze-like appearance. In our own studies we found that polytetrafluorethan (Gore Tex vascular prostheses) reacted similarly in preparation for electron microscopy. This analogy is compatible with the assumption that organic polymers are present.

The coarse granular aspect which was observed occasionally on light microscopy may represent cutting artefacts. The material was observed only in the intracellular position and – as far as can be judged from autopsy material – was included exclusively within lysosomal membranes of macrophages. The material appeared to be permanently sequestrated intracellularly within lysosomes without causing necrosis, fibrosis or cirrhotic transformation. No emboli of the material within capillaries of lung or extrapulmonary tissues were observed but the inherent unreliability of autopsy material and the sampling problem have to be considered.

It appears reasonable to assume that the material is related to the exposure of the patients blood to foreign material during haemodialysis. It is of interest that a foreign material with similar histological properties was observed in the early days of extracorporeal circulation for cardiac surgery (Prof. Doerr, personal communication). This material was never chemically characterized and was no longer observed after 1968. A preliminary analysis, using gas chromatography, showed a higher concentration of phthalate in liver and spleen of our

hemodialysed patient than in tissue specimens of controls. But sofar, we are unable to identify the chemical nature of the material which is visible within our histological sections.

It is unclear whether the material entered the patients circulation in soluble form or in particulate form as microemboli. One point which argues against microembolism is the fact that changes were less pronounced in the lungs when compared with the liver and the spleen. However, intra-alveolar material may have partly disappeared via mucociliary clearance of alveolar macrophages. In addition, no material was observed in other extrapulmonary organs, particularly the brain.

It is also possible that soluble material (plasticizers, unpolymerized mono- or oligomers, reaction products of ethylenoxide sterilisation etc) entered the blood stream and were taken up by macrophages either directly or after metabolism.

The clinical consequences of the accumulation of foreign material can be grave. As documented by the present case, advanced hepatosplenomegaly may cause thrombocytopenia, anaemia and leucocytopenia with considerable clinical complications. While no pulmonary dysfunction was observed in the present case, interstitial pulmonary disease may conceivable cause clinical problems. Remote dangers, i.g. potential carcinogenesis, cannot be currently assessed.

It will be of great importance to identify the substance involved. Because of possible clinical consequences, every effort should be made to prevent accumulation of foreign material in haemodialysed patients. It is obvious that this may necessitate changes in manufacture of dialysis equipment if the above complication occurs more frequently. Preliminary observations in this institute showed that analogous changes, although of less severity, can be observed in a sizable number of dialysis patients. The exact proportion of patients involved and the minimal duration of dialysis for the changes to occur will have to be worked out in future investigations.

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