FATAL HEPATIC NECROSIS; THE POSSIBLE ASSOCIATION WITH DIPHENYLHYDANTOIN AND MEPROBAMATE; A CASE REPORT

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Hypersensitivity to diphenylhydantoin had been well documented in the literature [2] The reactions, at times, may cause death to the patients (Bray, 1959; Watts, 1963). Exfoliative dermatitis, the most frequent reaction, may occur together with generalized lymph node enlargement and hepatosplenomegaly, a clinical syndrome mimicks malignant lymphoma morphologically [11,2].

Hepatic necrosis associated with diphenylhydantoin is extremely rare. In 1941, Mandelbaum described the first clinical hepatitis related to diphenylhydantoin therapy. The first fatal case was reported by Dubois in 1950, with detailed pathological description of the liver. Since then, two more autopsy cases were added, one by Gropper [6] and the other, by Crawford and Jones [3].

There have been no previously reported cases of massive hepatic necrosis attributed to meprobamate, alone or with dilantin treatment.

We present herein, a possible case of fatal hepatic necrosis associated with diphenylhydantoin and meprobamate treatment for epilepsy in Thailand.

Case Report

A 40 year-old, mentally retarded Thai man was first seen at the out-patient-department, Chulalongkorn Hospital, Bangkok, on 22 April, 1969 with a chief complaint of intermittent convulsions for over a year. The seizure occurred once or twice a month, and each episode was followed by certain period of unconsciouness.

He had retarded growth since childhood. He was able to stand up at the age of two. His mental development was slow and poor. During childhood he frequently had convulsion accompanied by hyperpyrexia. However, as he grew up the attack was less and less often and eventually it was absent until the present illness.

Three years prior to admission, he had a car-accident sustaining head injury.

After investigations including EEG, the clinical diagnosis was epilepsy. He was not hospitalized, but 300 mg./day of dilantin in divided dose was given for a short period of time and the medication was stopped because of fever.

On May 13, 1969, the patient came back to the hospital complaining of tremor of the extremities. No abnormal finding was found at the examination. Dilantin was continued together with meprobamate in a dose of 400 mg. twice daily. There

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was no history of injections or blood transfusion.

On july 8, 1969, the patient developed abdominal distress, mild jaundice and became stuporous. The drugs were not taken off. Tryptanol and vitamin B complex were added. Five days later, the patient became markedly icteric with mental confusion. He was then hospitalized.

The body temperature was 98.0°F on admission. Pulse rate was 96/min and the respiration was 22/min. The blood pressure was 126/90 mm. Hg. He was restless, dull and confused. There was deep jaundice. Liver and spleen were not palpable. Systemic examination was unremarkable except for slight increase in deep tendon reflexes, bilaterally.

Urinalysis revealed 3 plus bile in urine. The hemoglobin was 11 gm per cent. The white cell count was 9900 with 78 per cent neutrophils and 22 per cent lymphocytes. The BUN was 8.5 mg. per cent, creatinine, 1.5 mg. per cent and the SGOT was 1700 units.

He was treated symptomatically without improvement. He developed fever of 100.4°F soon after admission, and remained so until just prior to death. He died on the third hospital day.

At autopsy, marked jaundice of the skin and sclerae was noted. The skin throughout the body showed no rash or hyperpigmented areas. There was 200 ml. of yellowish and clear fluid in the peritoneal cavity. The liver weighed 430 grams, It was soft, dark greenish brown and the capsule was wrinkled. The cut surface, revealed mottling green and red interspersed by tiny grey nodules. (Fig. 1). The bile-ducts were thoroughly patent and not dilated. The spleen weighed 110 grams. It was soft and purplish red. Each kidney weighed 130 grams. They were firm, tan with yellowish hue. The substance bulged slightly on cutting. The brain was 1550 grams in weight, and showed no significant alteration on external examination and the cut surface except for the thickening of the leptomeninges at the base. Other organs were not remarkable. There was no enlargement of any lymph node in the body.

Histologically, the liver showed diffuse massive necrosis which was mainly centrolobular in distribution. In the majority of the lobules, there was less than one-fourth of the liver parenchyma at the periphery which was still normal in appearance. New lobules without central veins were infrequently encountered. In general the central veins were not dilated, and the basement membrane was still well observed. No red cells were present in these central veins. In the necrotic zones, there was complete destruction of the liver cells but the Kupffer's cells were still viable. The reticulum framework was irregularly disrupted or collapsed (Fig. 2). The only recognizible cells in these necrotic zones, besides the Kupffer's cells, were considerable number of leucocytes; chiefly, the lymphocytes and macrophages with only few neutrophils and eosinophils. The macrophages and the Kupffer's cells contain yellowish brown pigment which stained black in reticulum stain and showed negative staining reaction for iron. At the juxtaposition between the necrotic zones and the preserved peripheral zones, there was evidence of transitional cell changes from dying cells to normal cells.

The hepatic sinusoids were dilated in the immediate areas surrounding necrosis. They contained a certain number of lymphocytes and neutrophils.

Figure 1 : The surface of the liver shows mottling appearance. The liver weighs 430 grams. Note the wrinkled capsule.

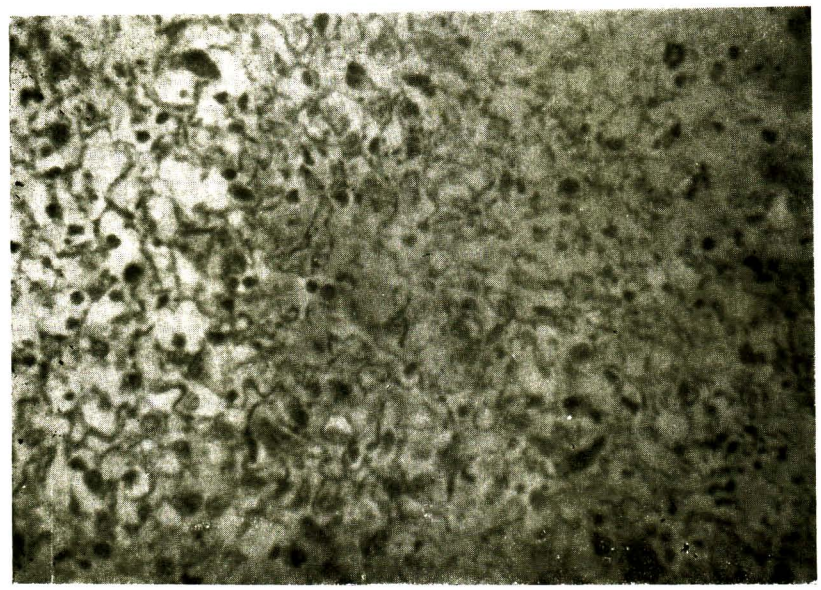

Figure 2 : The reticulum framework shows disruption and collapse. The Kupffer's cells are large and hyperchromatic containing numerous pigment granules. Wilder's reticulum stain x 100.

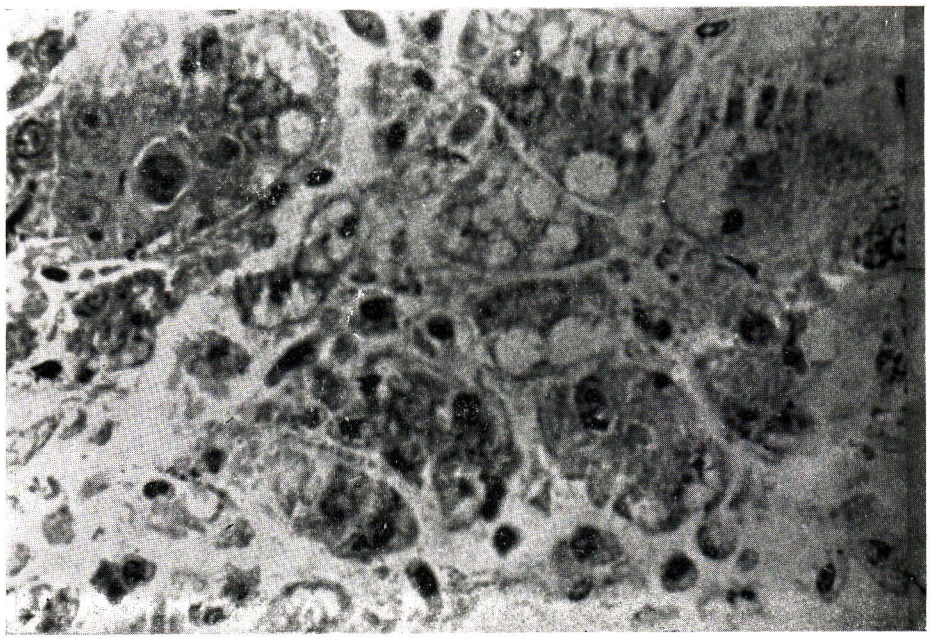

Figure 3 : The liver cells, in this picture, are very large containing numerous vacuoles, some in a morula-like manner. Intrahepatic cholestasis is shown in the left of the field. H & E x 400.

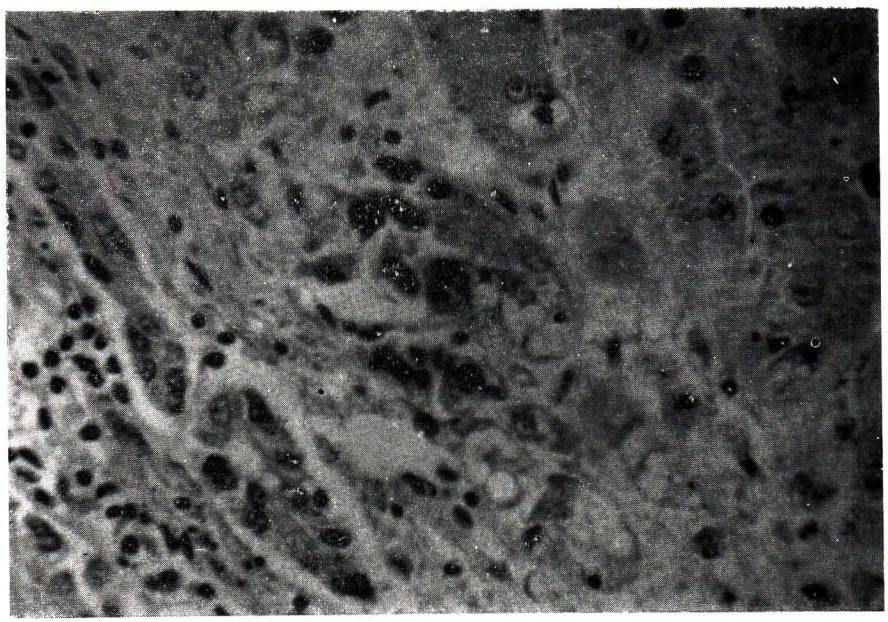

Figure 4 : The hepatocytes at the periphery of the lobules are enlarged containing numerous vacuoles in a morula - like manner. H & E x 430.

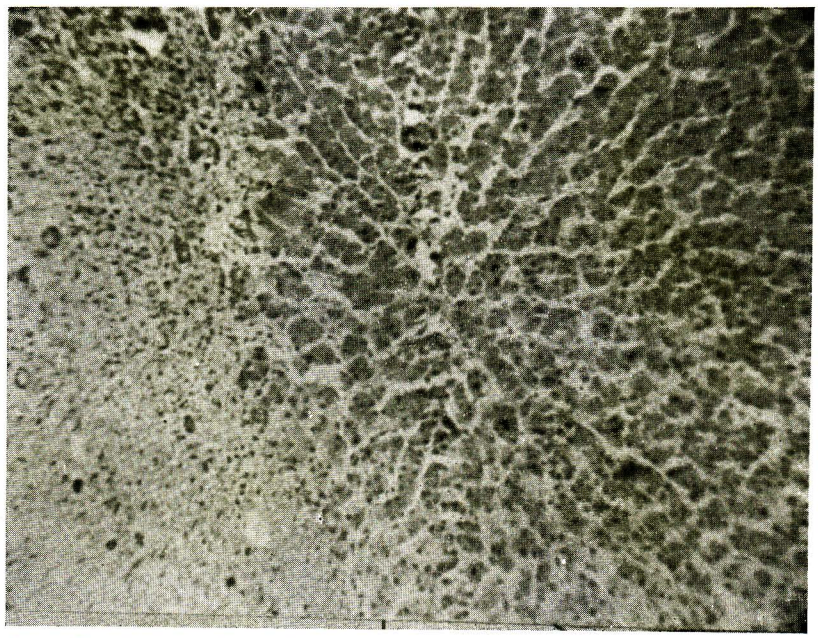

Figure 5 : A some what well preserved liver lobule showing centrolobular cholestasis. Note massive necrotic zone with evidence of ductulization of hepatic cells. H & E x 60.

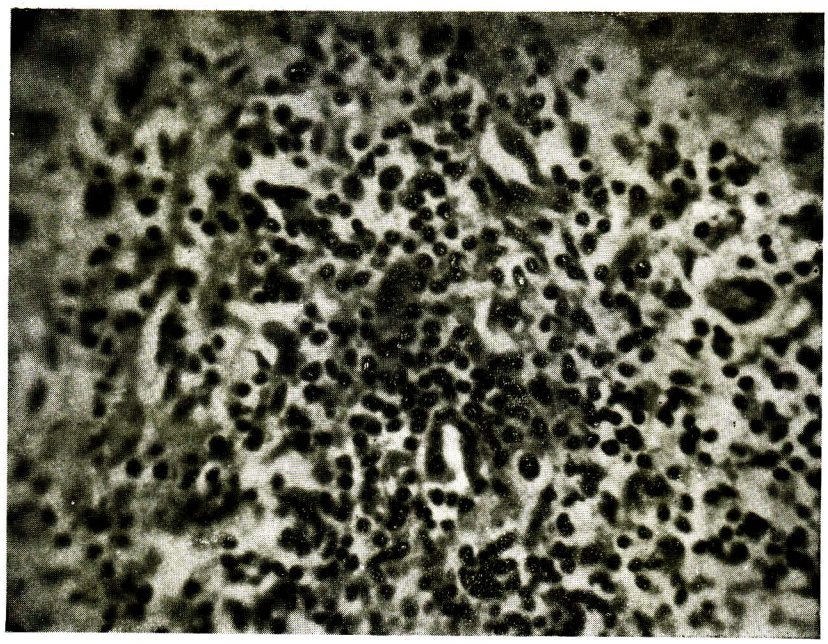

Figure 6 : The portal tract is intensly infiltrated by leucocytes comprising mainly of mononuclear cells, a few neutrophils and eosinophils. H & E x 400.

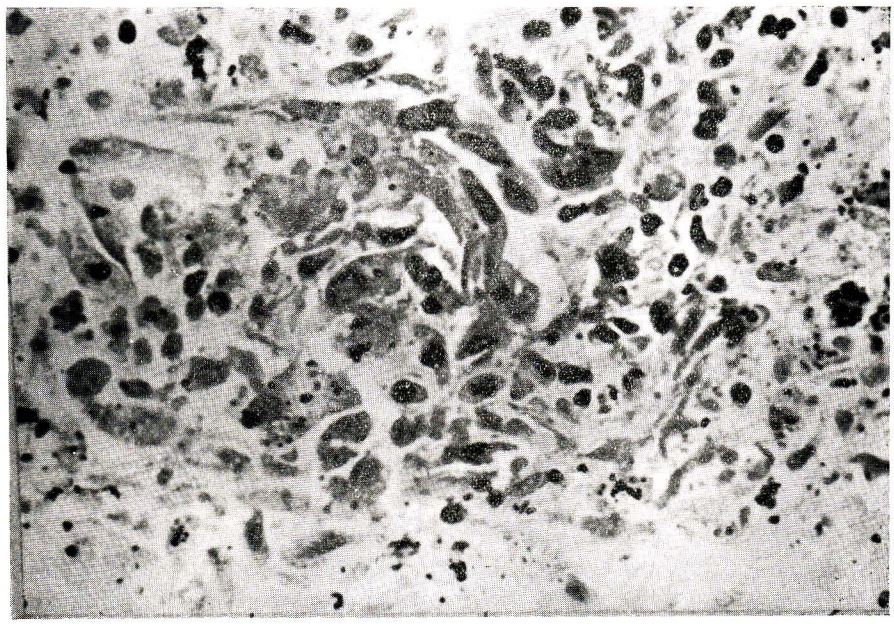

Figure 7 : a "granuloma - like" area in the mid - zone of a liver lobule. Noted pleomorphic giant cells and epithelioid cells shown in this picture. H & E x 439.

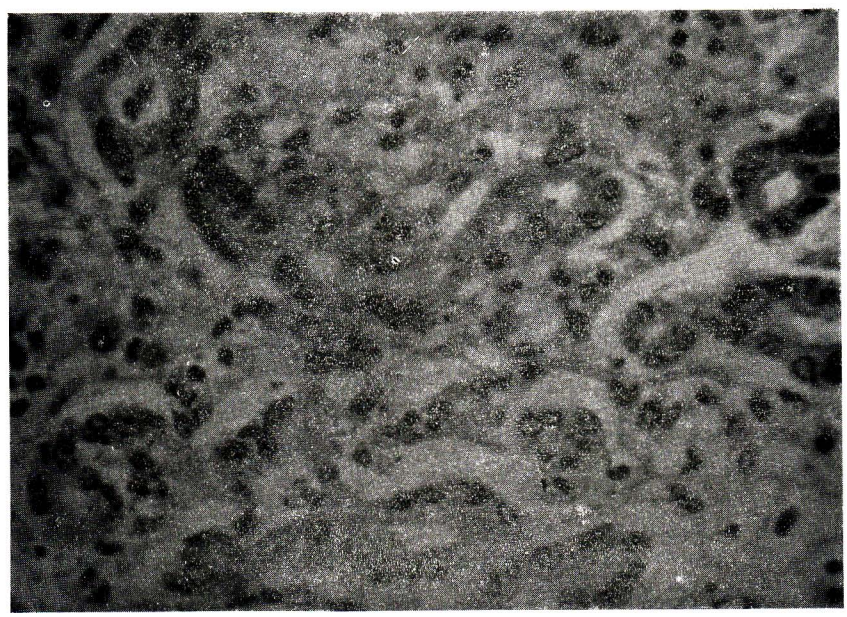

Figure 8 : Marked bile - duct proliferation in almost every portal tract. The cells are larger and occasionally pleomorphic. The lumens are mostly empty, but a few contain neutrophils. H & E x 430.

In the periphery, the liver cells were enlarged and many of them contain numerous large and small multiple vacuoles in morula-like manner. (Fig. 3, 4). No eosinophilic bodies were found in all sections examined. The cells in the new-formed lobules retained their normal features, except for their sizes which were enlarged.

Theer was mild to moderate intrahepatic cholestasis in the peripheral zones as well as in the neo-lobules. Bile-thrombi were scant and bile-lake was not found (Fig. 5).

The portal triads showed intense cellular infiltration. The cells were lymphocytes, large mononuclear cells and neutrophils. Eosinophils were also present in much smaller number. (Fig. 6). No pigment was present.

Occasionally, and especially, within the peripheral or mid-zonal portions of the necrotic areas, were small nodular necrosis surrounded by large hyperchromatic cells resembling "epitheloid cells," and large mononuclear cells. A few cells had multiple nuclei. No eosinophils were found in these "granuloma-like" areas. (Fig. 7).

The most striking feature in this case was the prominence of bile duct proliferation. Thie new buddings were present in almost every portal tracts in all sectiare examined. They were not ductulization from hepatic cells because large bile-thrombi were noted and they were solely in portal areas. Some areas were more extensive than the others. The ductular epithelium was large, polygonal with ample cytoplasm. The nuclei were centrally located. The lumens, in general, were dilated, containing bile-thrombi or leucocytes, but most were empty. (Fig. 8). The reticular framework was fine and undisturbed throughout the portal canals.

The splenic sinuses were dilated and contained large acidophilic mononuclear cells, few lymphocytes and neutrophils. The lymphoid follicles were not abnormal.

The kidneys showed congestion. The glomeruli were normal. There was slight blurring of the cut-line of the lining tubular epithelium, especially in the proximal convoluted tubules. Bile-casts and granular greyish casts were scantly seen in the distal segments. No accompanying cell damage was noted around these casts; and the basement membrane was intact throughout.

Comment:

When admitted to the hospital, the patient was considered to have drug-induced hepatitis, but the actual drug that cause the liver damage was not apparent. Coincidental viral hepatitis, though possible, was not entertained because of the absence of prodomal symptoms, such as fever, general weakness, and gastrointestinal disturbances such as loss of appetite and vomiting. The hemogram was within normal limit, except for mild relative lymphocytopenia which is unusual for typical fulminant viral hepatitis, In the latter, the opposite is rather a rule [3].

There were only two known drugs taken by the patient prior to the occurrence of jaundice, namely diphenylhydantoin, and meprobamate. There is no documented case in the literature of meprobamate massive hepatitis, or severe cholestasis either in man or animal. Although meprobamate is known to produce toxicity such as psychotic manifestation and epilepsy upon withdrawal of the medication, yet it is unlikely in this case that it can cause such massive lesion in liver. Tryptanol, another drug which was administered after jaundice had already developed, may or may not complicate the

picture of massive necrosis of the liver in this patient. However, the possibility could not be entirely excluded.

It is noteworthy that all three patients who died of hepatic necrosis associated with diphenylhydantoin were negroes. Another patient, reported by Saltzstein and Ackerman [12] inwhich the diagnosis of toxic hepatitis was rendered by needle biopsy of the liver, was also a negro.

The duration of medication until the time of development of clinical liver damage was 77 days in our patient. It was 200 days in Dubois [5] 65 days in Gropper's [6], 14 days in Saltzstein and Ackerman [12] and 17 days in Grawford's and Jones [3] patient.

Exfoliative dermatitis was present in all cases previously reported. It was not noted in our patient. However, this does not exclude the possibility of the skin lesion in our patient that might occur sometimes during the course of the medication, because of the fact that he was mentally retarded and was neglected. Generalized lymph node enlargement also was present in all except in Dubois[5] patient. No definite striking changes were observed in the lymph nodes is our case, although there was evidence of reticulum cell hyperplasia of the spleen.

Fever was present at the time of admission in all cases. The temperature ranged from 98.8°F in Dubois[5] cases to 103.6°F in Grawford and Jones child (1963). The duration of fever preceding jaundice was between 1 – 8 days in 3 cases. There was no fever on admission in our patient, but the temperature went up to 100.4°F four hours later and remained high until just prior to death.

The weight of the liver was 430 grams in our patient. It was 680 grams in Dubois[5] 1730 grams in Gropper's[6] and 325 grams in Grawford and Jones[3] 11 year old child. The gross appearance in our patient as well as in other inwhich the livers were small, did not differ from what would be expected from massive hepatic necrosis of any etiology. The liver was small, shrunken with wrinkled external surface; and the cut – surface was dark – green or greenish – brown.

Histologic changes in the liver had been previously described in four patients, including one patient reported by Saltzstein and Ackerman[12] inwhich the study was made only by needle biopsy. In all five cases, including our, certain important similar features stand out.

Massive necrosis of the liver which tends to be centrolobular in distribution. This was an outstanding feature in all cases except that reported by Saltzstein and Ackerman (1959). The reticular framework is collapsed (Dubois,[5] Crawford and Jones,[3]. In many areas, in our patient, the lobular pattern was completely disrupted. Hemorrhage was not prominent. In general, this type of lesion is indistinguishable from "viral hepatitis type" of drug reaction such as in isoniazid or halothane hepatitis; neither nor it can be differentiated from a fulminant type of viral hepatitis.

Moderate to severe cholestasis with bile–thrombi were also observed in all cases except in Saltzstein and Ackerman's[12] patient. In our case, intrahepatic cholestasis was not marked compare to so – called "drughepatitis epatitis type" of reaction chlorpromazine induced reaction[7, 11] Bile – thrombiare present at random and no bile lake found.

Periportal inflammatory cell infiltration was noted in all cases. The cells were neutrophils, eosinophils and lymphocytes[3, 5, 11] No description concerning inflammtory infiltrate was given in Grop-

per's report[6]. Judging from the accompanying photomicrograph, the cellular infiltrate was quite heavy and predominantl present throughout the periportal areas as well intralobularly. In our patient, similar reaction was discernable, but mononuclear cells were more prominent than neutrophils and eosinophils; intralobular distribution is scant. In addition, granuloma-like foci were occasionally observed. They were located mainly close to the portal tracts. This reaction has never been previously described.

Budding of bile-ducts was the most striking feature in our case. The new-formed bile channels were lined by large polygonal or cuboidal cells having ample cytoplasms and occasionally showing pleomorphic nuclei typical of active regenerating cells. The lumens were sometimes, dilated and contain bile. Among the four cases previously described, only in Crawford and Jones[3] patient showed this type of changes. The lesion may, sometimes, be seen in viral hepatitis of longer duration[13] but it is not a feature of "acute yellow atrophy" viral hepatitis.

Bile duct proliferation is not a feature in both viral hepatitis and in "viral-hepatitis type" of drug reaction.[11,13] is a constant feature in drug induced hepatitis type of reaction[11]

Other features of interest was the presence of vacuoles in the liver cells in our case. The vacuoles were small, fine and conglomerate within enlarged hepatocyte in a morula-like manner, similar to steatosis in tetracyclin reaction[7, 11] In Saltzstein and Ackerman[12] patient, the liver cells also showed necrosis and vacuolization of unknown nature. Intrahepatocytic vaculoase were reported to the bmoste striking changes in sensitized rats challanged by intravenous injection of specific antigen and hence, hypothesized to be characteristic of immunological liver damage[10]

In direct hepato-toxic drug reaction, sometimes, fatty degeneration is prominent[11, 13] This feature is not present in viral hepatitis even in the fulminant type. This type of lesion and, infact, other lesions in our patient as well, are very similar ot Labrea hepatitis, which is known to occur only in the Amazon river basin; and thougth to be caused by a virus[4]

Another feature which was emphasized be Dubois[5] in his report, and also was noted in our case, is the presence of the gradual call death and transition from normal cells. Lucke[8] stressed the absence of dying cells and evidence of reticular framework destruction in viral hepatitis, except in rare fulminant cases. Onthe contrary, in Crawford and Jones[3] patient, the junction between collapsed central areas and the intact cells at the periphery was sharp and transition from coagulation necrosis to normal was not observed.

Acidophilic bodies which are commonly found in viral hepatitis. was rarely found in "drug-induced hepatitis" or in "viral-hepatitis type" of drug reaction[11] These bodies were not present in our case.

Dilatation of hepatic sinusoids or of perisinusoidal area were observed by both Dubois[5] and Gropper[6] We noted sinusoidal dilatation to be present only around areas of massive necrosis, probably as the result of liquefaction necrosis of cells. Gropper the nearby hepatic[6] noticed brown pigment in Kupffer' cells which was also inconspicuously prominent in our case. The nature of the pigment is not known. Lipofuscin pigmentary

change has been mentioned in drug's reaction[7] especially from direct hepato-toxicity (Sherlock, 1968).

It is postulated that diphenylhydantoin may produce immunologic type of drug reaction[2, 3, 6, 11,] rather than direct toxic insult to the tissue. Exfoliative dermatitis, cosinophilia and sporadic selective occurrence of hepatic damage seem to favor hypersensitivity type of reaction. The absence of cosinophils in our patient, is an evidence against sensitivity reaction. The presence of cosinophils in the portal tracts may also be found in any type of hepatic injury. Intracytoplasmic vacuoles have been shown to be lysosomal in nature by Papadimitriou and Blackwell (1967) and were believed to be evidence of immunological liver damage.

Granulomatous inflammatory process in the liver associated with diphenylhydantoin has never been noted before, although it was mentioned by Popper and his colleaques[11] in their report. The granuloma-like lesion in our case, may represent immunologic reaction to drug metabolites or to the damaged liver cells induced by diphenylhydantoin, despite the absence of the afore mentioned criteria which are regarded to be suggestive of hypersensitivity. Immunofluorescence study would be helpful of establish the hypersensitivity etiology in our patient's lesion. It is noteworthy to recall the reticuloendothelial proliferation in diphenylhydantoin reaction in lymph nodes which, sometimes, so prononunced that it mimicks malignant lymphoma[1, 12]

Direct hepatotoxicity of the drug action is not likely. In such possibility, cases of liver damage should be commonly found in both men and experimental animals; and the development of the tissue damage after injury should be much more rapid.

Another explanation proposed by Popper et al[11] is the possibility of genetic variation in metabolism of the drug. Individual genetic code may be prone to be damaged in some susceptible racial stock. The tendency of diphenylhydantoin hepatic necrosis in non-caucasian race, therefore may be of importance.

Summary

A fatal massive hepatic necrosis associated with diphenylhydantion and meprobamate administration in a 40 year-old Thai man was reported. The clinical manifestation of hepatic damage occurred 77 days after the beginning of therapy. It is possible that drug reaction produced death in this patient and the most probable responsible drug is diphenylhydantion although meprobamate toxic reaction could not be entirely excluded. A review of literature and brief pathogenesis are discussed.

Acknowledgement: The authors are indebted to Dr. Somsak Dechakaisaya Professor and Head of Department of Pathology for his permission to study and report this case.

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