Diclofenac-Associated Hepatotoxicity: Analysis of 180 Cases Reported to the Food and Drug Administration as Adverse Reactions

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Diclofenac is a nonsteroidal anti-inflammatory drug approved in the United States in 1988 for the treatment of patients with osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis. To characterize the clinical, biochemical, and histological features and possible mechanisms of hepatic injury associated with its use, a retrospective analysis was undertaken of 180 patients whose cases were reported to the Food and Drug Administration from November 1988 through June 1991, as having had possible adverse reactions to diclofenac. Of the reported 180 cases, 79% were female, 71% were 60 years of age or older, and 77% had osteoarthritis. Sixty-seven percent of the cases were detected by symptoms and the remainder by abnormal laboratory tests. Seventy-five percent of the symptomatic patients (90 of 120) were jaundiced. Seven of the 90 icteric patients died. The biochemical pattern of injury was hepatocellular or mixed hepatocellular in 66% of cases. Only 8% had a pattern of cholestatic injury. The remainder, with modestly increased values of both transaminases and alkaline phosphatase, were considered "indeterminate," i.e., either mild hepatocellular or anicteric "cholestatic" injury. Sections of liver from 21 cases were available for study. Hepatic injury was apparent by 1 month after starting the drug in 24%, by 3 months in 63%, and by 6 months in 85% of cases. The latent period in 12% was 6 to 12 months, whereas in 3% it was greater than 12 months. A combination of rash, fever, and eosinophilia, all hallmarks of immunological idiosyncrasy (hypersensitivity), was not reported in any case; additionally, the long latent period in most of the patients led to the inference that the mechanism is probably metabolic idiosyncrasy. The data suggest that diclofenac-related liver injury is particularly likely to involve osteoarthritic females, presenting with jaundice 1 to 6 months after starting diclofenac, with injury that is predominantly hepatocellular and presumably caused by metabolic idiosyncrasy. (HEPATOLOGY 1995;22:820-827.)

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) approved in the United States in 1988 for treatment of rheumatoid arthritis (RA), osteoarthritis (OA), and ankylosing spondylitis[1] and in 1993 for the management of pain. The drug has been available in Europe since 1974. As is true of other NSAIDs, diclofenac has been associated with gastric hemorrhage, renal dysfunction, serious hepatic injury, and blood dyscrasia.[2-24] Despite the attributed[25] uniformity of NSAIDs with regard to adverse hepatic effects, there appear to be differences among them in the hepatic injury that they may provoke, including its character, presumed mechanism, estimated incidence, and clinical importance.[26-30] Accordingly, the characterization of the hepatic injury caused by individual NSAIDs seems warranted. A previous study, similar to the present one, focused on sulindac-associated hepatic injury.[31]

Approximately 60 cases of diclofenac-associated hepatic injury have been reported in the medical literature; most have shown acute hepatocellular injury.[2-21] Several have shown a pattern of chronic hepatitis.[14,16,22,23] The individual reports have varied in the completeness of the data and the light that they shed on factors affecting susceptibility to injury and its character. Accordingly, the effort was undertaken to define more fully the character of the injury and to search for factors affecting susceptibility among a large number of suspected cases of diclofenac-related liver injury reported to the spontaneous reporting system of the Food and Drug Administration (FDA). After follow-up to establish the validity of the data, the reports were used to characterize the biochemical pattern of injury, clinical features, and histological changes, as well as the mechanisms of injury.

MATERIALS AND METHODS

There were 434 reports of diclofenac-associated hepatic injury submitted to the voluntary reporting system of the FDA, directly or through the manufacturer, between November 1988 and June 1991. These cases were identified for review by using Coding Symbols for Thesaurus of Adverse Reaction Terms suggestive of hepatic injury.[30,31] As was done in the study of sulindac-associated injury,[31] the validity of the data

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; OA, osteoarthritis; FDA, Food and Drug Administration; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; ULN, upper limit of normal.

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TABLE 1. Cases of Diclofenac Hepatic Injury (n = 180)

Gender	
Females	142
Males	38
Age (yr)	
<40	8 (5%)
40-59	43 (24%)
>60	123 (68%)
Missing	6 (3%)
Indications for use of diclofenac:	
Osteoarthritis	139
Rheumatoid arthritis	22
Other	19
Ankylosing spondylitis	1
Psoriatic arthritis	1
Miscellaneous conditions	15
Unknown	2

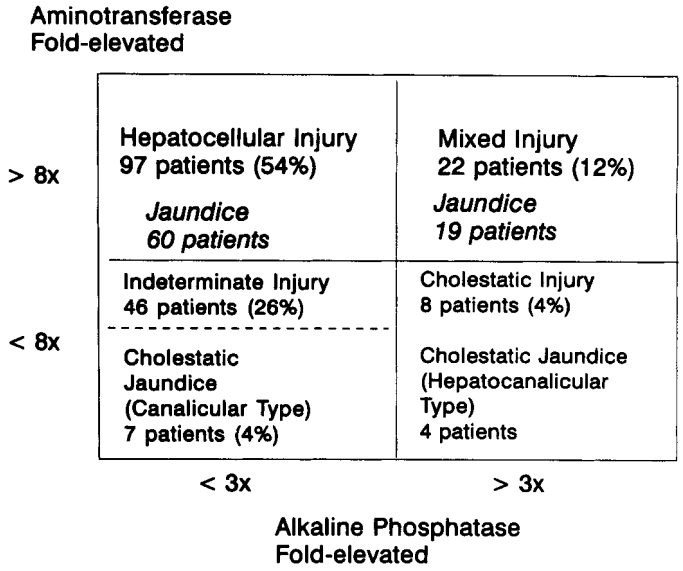

FIG. 1. Graphic presentation of criteria for types of hepatic injury. See text for description. Note that serum transaminase levels less than eight times the upper limit of normal with ALP less than three times the normal define canalicular cholestasis if there is jaundice or bilirubin values greater than 2.4 mg% or indeterminate injury if neither jaundice nor bilirubin value greater than 2.4 is present.

was established by written inquiry and telephone calls to the reporting physician by one of the authors (ATB). The manufacturer (Ciba-Geigy, Basel, Switzerland) also supplied available clinical information on cases on which it had data. Each case was reviewed by the authors to evaluate the validity of the relationship to diclofenac, to categorize the form of injury, and to deduce the apparent mechanism from the clinical features.

After elimination of 254 cases because of duplicate reporting, foreign sources, other possible causes for liver enzyme abnormalities, and inability to obtain adequate information, 180 cases remained for analysis (Table 1). Biochemical data to characterize liver injury (bilirubin, aspartate transaminase [AST], alanine transaminase [ALT], and alkaline phosphatase [ALP]) were available or solicited. They included the normal values for the respective laboratory, baseline levels, and values during the acute event and, when available, previous and subsequent values. The pattern of injury was classified as hepatocellular, cholestatic, mixed, or indeterminate (Fig. 1). Hepatocellular injury was defined by a peak transaminase increase of at least eight times the upper limit of normal (ULN) with an ALP value less than three times the ULN, and cholestatic injury was defined (hepatocanalicular type[32]) by an ALP value at least three times the ULN and transaminase values of less than eight times the ULN. "Mixed" injury was defined by transaminase increases greater than eight times the ULN accompanied by an ALP value of more than three times the ULN. The combination of transaminase increases less than eight times the ULN with ALP values less than three times the ULN was classified as cholestatic (canalicular type[32]) if jaundice was present or serum bilirubin levels were above 2.4 mg/dL and as indeterminate in the absence of these markers of hyperbilirubinemia. Serological tests that were available for review in most cases included hepatitis B surface antigen, antibody to hepatitis B core antigen (immunoglobulin M), and antibody to hepatitis A virus (immunoglobulin M). Results of a test for hepatitis C (Anti HCV) were available in only 19% of the patients.

Presumption of mechanism of injury was based on clinical criteria.[22] Presence of fever, with or without rash, and/or eosinophilia, if accompanied by abrupt onset during the first 4 to 5 weeks of treatment, was presumed to reflect immunological idiosyncrasy (hypersensitivity). Lack of clinical hallmarks of hypersensitivity and/or gradual development of the illness later than 5 weeks after starting the drug was presumed to reflect metabolic idiosyncrasy.

In attempting to identify the effect of age, gender, and indication for diclofenac therapy on susceptibility, the proportion of each in the reports was compared with the number of prescriptions for the respective category (information obtained from the IMS American, Inc National Prescription Audit and the IMS National Drug Therapeutic Index for the period from January 1988 to June 1991 [Table 2]). Proportions are expressed as percentages. Statistical significance was evaluated by the χ^2 test.

RESULTS

A total of 180 cases of hepatic injury were analyzed (Table 1). In 89% of the cases the drug had been taken for treatment of rheumatoid arthritis or osteoarthritis (Table 1), yet only 34% of the use of the drug was for these conditions, and 66% was for conditions other than

TABLE 2. January 1988 to June 1991 Drug Mentions for Diclofenac (in millions)

	OA	RA	OA + RA	All Others	Total
Female	3.52	1.27	4.80	8.15	12.94
0-59	0.86	0.66	1.52	4.62	6.15
60+	2.66	0.61	3.27	3.53	6.80
Male	1.48	0.58	2.07	5.29	7.36
0-59	0.45	0.32	0.77	3.45	4.22
60+	1.03	0.26	1.29	1.85	3.14
Total	5.01	1.86	6.86	13.44	20.30

NOTE. Source: National Disease and Therapeutic Index IMS American, Inc.

Abbreviations: OA, osteoarthritis; RA, rheumatoid arthritis.

TABLE 3. Diclofenac Hepatic Injury in Patients With RA or OA: Comparison of Expected With Observed Distribution of Cases According to Gender, Age, and Diagnosis

	Use (in millions)	Injured	Relative Risk
Gender			
Female	4.80 (70%)	132 (82%)	
Male	2.07 (30%)	29 (18%)	
Total	6.87	161	
Ratio (F-M)	2.32	4.55	2.0 ($P < .001$)
Age			
(missing)*		6	
≥60	4.56 (67%)	112 (72%)	
<60	2.29 (33%)	43 (28%)	
Total	6.85	155	
Ratio (≥60:<60)	1.99	2.6	1.3 ($P = .13$)
Diagnosis			
OA	5.01 (72%)	139 (86%)†	
RA	1.86 (28%)	22 (14%)†	
Total	6.87	161	
Ratio (OA-RA)	2.69	6.32	2.4 ($P = .001$)

Abbreviations: RA, rheumatoid arthritis; OA, osteoarthritis.

* The 6 missing values did not enter the corresponding calculations of ratios or percentages.

† Figure in parentheses refers to proportion of all patients with arthritis.

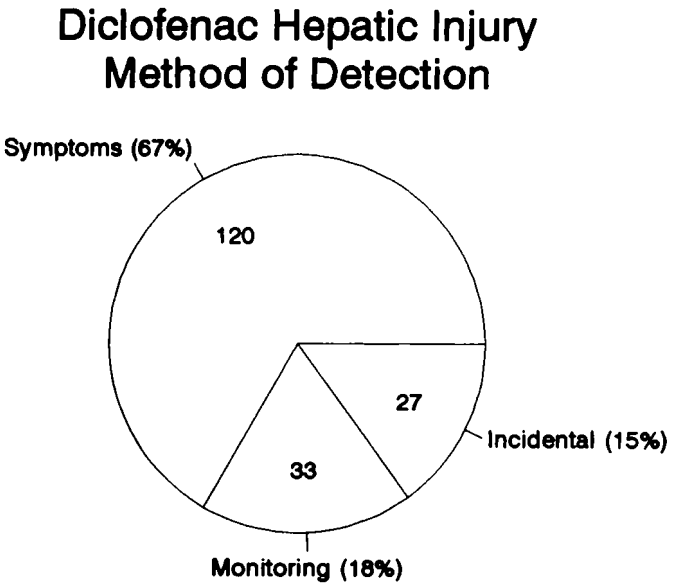

FIG. 2. Circumstances that brought cases to attention.

arthritis (Table 2). Although information regarding duration of use was not available, the variety of condition other than arthritis may be presumed to have been treated for short periods in contrast to the usual long-term treatment of patients with arthritis. Distribution by gender, diagnosis, and age for both cases and users is shown in Table 3. The ratio of females to males among cases with hepatic injury was 4.55 compared with the gender ratio of 2.32 among users, yielding a relative risk of 2.0 for females ($P < .001$, Table 3). Age appeared to have no identifiable effect. When the ratio of individuals aged 60 years or older to those under 60 years old was compared with the ratio among users, the relative risk was 1.3 ($P = .13$). The 6.32 ratio of osteoarthritis to rheumatoid arthritis among cases, compared with the 2.69 ratio among users of the drug, yielded a relative risk of 2.4 ($P < .001$; Table 3). The small number of cases with other diagnoses and the heterogeneity of the group precluded useful analysis.

Two thirds of the cases (120) presented with signs or symptoms. The remainder were identified by increased levels of AST and ALT noted by monitoring (18%) or as incidental tests (15%) (Fig. 2). Jaundice was present in 90 of the 180 cases (50%) (Fig. 3). It was the only complaint in 14 of the 90 icteric cases (17%) and was accompanied by anorexia, nausea, and/or vomiting in 58 of the 83 non-fatal icteric patients (70%). These symptoms also occurred in 21 of the 29 anicteric symptomatic patients (72%). Abdominal discomfort was recorded in 19 (16%) of the 120 symptomatic patients, and pruritus was noted in 15 of them (12%). Seven of the 90 icteric patients died, yielding a case fatality rate for icteric cases of 8%. There were no fatalities among the anicteric cases.

The duration of therapy before the detection of hepatic injury was under 6 months in 85% of all cases (<1 month [24%]; 1 to 3 months [39%]; 3 to 6 months [22%]). In 12% of all cases, the duration of treatment before the detection of injury ranged from 6 to 12 months. In 3% of all cases, more than 1 year had elapsed before evidence of hepatic injury was detected (Fig. 4).

Specimens of hepatic tissue were available from 21 cases. All but 6 disclosed hepatocellular injury (Fig. 5A through 5C). One case showed a mixed hepatocellular-cholestatic injury, and 2 cases showed mainly cholestasis with portal area inflammation and cholangitis (Table 4). Six of the cases of hepatocellular injury revealed changes of chronic hepatitis (Fig. 5D), 4 with consider-

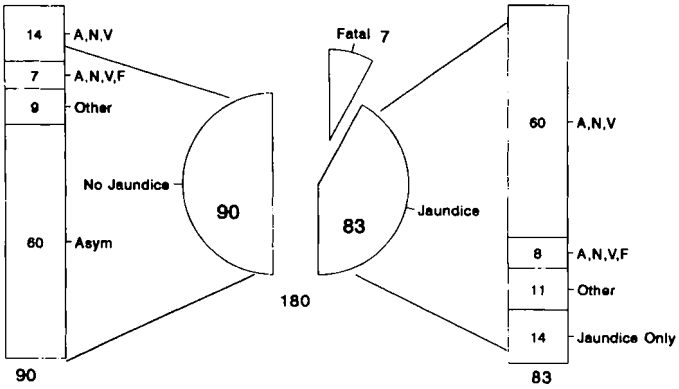

FIG. 3. Clinical manifestation of 120 symptomatic patients, 90 icteric patients, and 30 of the 90 anicteric patients. Abbreviations: A, anorexia; N, nausea; V, vomiting; F, fever; Other, abdominal pain, pruritus, and/or malaise; Asym, asymptomatic.

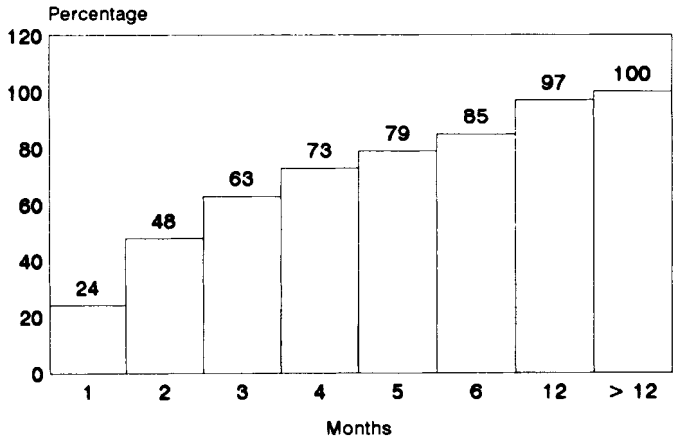

FIG. 4. Duration of intake of diclofenac before appearance of hepatic injury. Cumulative figures for onset of injury by end of each period.

able lobular injury and 1 with cirrhosis. Nine showed acute hepatocellular injury with spotty necrosis in 2 cases, zone 3 necrosis in 6 cases, and granulomatous inflammation in 1 case. In the remaining 3 cases, the injury was trivial or nonspecific.

Of the 180 cases, 119 (66%) had increased transaminase values to more than 8 times the ULN (Fig. 1). Among the 90 icteric cases, 88% (79 cases) had transaminase levels in that range. In three fourths of cases (60 patients) the pattern was that of hepatocellular injury with ALP levels less than three times the ULN; and in the remainder (19 patients) the injury was mixed with ALP levels more than three-fold increased (Fig. 1). Only 8 patients (4%) had ALP increases more than 3 times the ULN with transaminase values less than eight times the ULN (cholestatic [hepatocanalicular type] pattern), and 29% of all cases had transaminase and ALP values of the indeterminate pattern—either mild hepatocellular, i.e., anicteric (26%) or cholestatic (canalicular type) injury, i.e., icteric or bilirubin level greater than 2.4 mg/dL (4%).

Hallmarks of hypersensitivity were uncommon. None of the patients had fever, rash, and eosinophilia. Fever and rash were present in only 2 patients. Fever alone was recorded in 17 additional patients and rash alone in 5 others. Eosinophilia was observed in 7 other patients, all without fever or rash. Readministration of the drug led to prompt recurrence of abnormality in 1 of 19 patients tested. The remaining 18 developed increased ALT levels as early as 5 days and as late as 1 year after restarting the drug.

There were seven fatal cases; all had been jaundiced. Six of the fatal cases were female, six were older than 60 years of age, and all seven had osteoarthritis. Peak transaminase values were usually in excess of 1,000 IU/L, and bilirubin levels ranged from 13 to 25 mg/dL. The duration of therapy for the fatal cases ranged from 4 to 69 days (median of 24 days). An eighth patient with mild hepatic injury died of a complication of subclavian artery catheterization while under treatment for renal failure.

DISCUSSION

Attribution to diclofenac of the etiologic role in the hepatic injury of the 180 cases among the 434 cases reported to the FDA was based on excluding cases with other recognized possible etiology. Hepatitis A and B were excluded by serological tests in 96 of the patients (53%). Thirty-four patients (19%) had negative tests for hepatitis C. Although testing for hepatitis C is of limited help in diagnosis of acute hepatitis, there was little reason to consider that entity to be the diagnosis in the 180 cases, i.e., no history of recent transfusion or drug abuse. There were no reports of tests for human immunodeficiency virus.

The hepatic injury induced by diclofenac, reflected by the biochemical values, is mainly hepatocellular. The hepatocellular character of the injury is also reflected in the 8% case fatality rate for icteric cases since it is characteristic of drug-induced hepatocellular jaundice to have a case fatality rate in that range.[32] The histological character of the injury in the 21 cases with material for study also shows the main thrust to be hepatocellular. These observations are consistent with most other reports.[1-22] However, cholestatic injury also has been reported[13] and was found in 8% of our patients (Fig. 1), hepatocanalicular cholestasis in 4, and canalicular cholestasis in 7 patients. Chronic hepatitis has been reported by others[22,23] and was seen in 6 of the 21 patients with histology in this study.

The mechanism of injury appears to be idiosyncrasy rather than intrinsic toxicity of the drug, since the incidence is very low. In view of the rarity of hallmarks of hypersensitivity and the delayed development of injury (after more than one month of taking the drug) in most cases (76%), and the delayed response to rechallenge in all but one of the 19 patients who responded to the readministration, the inference of metabolic rather than immunologic idiosyncracy seems tenable.[32] Other observers also have drawn attention to the rarity of features of hypersensitivity.[18] Furthermore however, Shapiro et al[8] have reported signs of hypersensitivity in association with diclofenac injury. In these few cases, the mechanism may have been immunological idiosyncrasy (hypersensitivity) despite lack of other hallmarks.

The likelihood that metabolic idiosyncrasy may be the mechanism is supported by the observation that diclofenac can injure hepatocytes *in vitro*[33-36] and that inhibition of metabolism inhibits the injury.[36] Although the acyl glucuronide of diclofenac binds covalently to hepatocytes,[35,36] its role in causing hepatic injury is not clear.[33,35] Metabolic transformation of diclofenac involves formation of hydroxy derivatives of the benzyl nucleus.[35] In the process, reactive toxic metabolites could be formed. Recent studies by Boelsterli and Kretz-Rommel[37] have shown that diclofenac-treated hepatocytes carry antigenic determinants that can be recognized by T-cell and by B-cell/macrophage combinations from diclofenac-

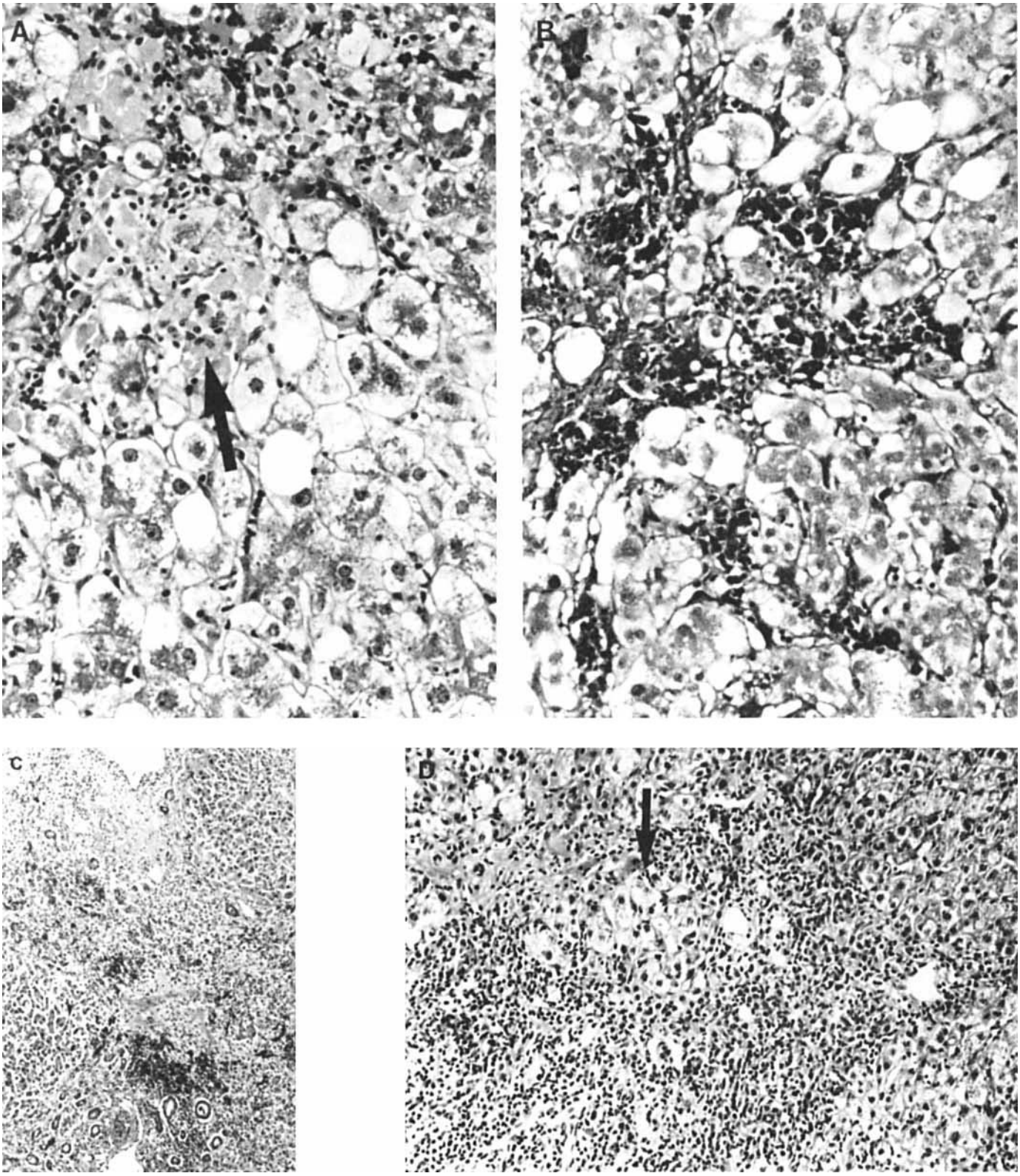

FIG. 5. (A) Biopsy section of case showing acute hepatocellular injury. There is drop out of cells in zone 3 (arrow). Adjacent, relatively spared liver cells show ballooning degeneration. (Hematoxylin-eosin; original magnification ×120.) (B) Same case showing zone 3 necrosis that is outlined by hypertrophied Kupffer cells containing lipofuscin (black). (Periodic acid-Schiff after diastases digestion, original magnification ×300.) (C) Autopsy section of case with massive necrosis. Almost all liver cells have dropped out and the residual stroma is congested. Note portal areas (top and bottom). (Hematoxylin-eosin; original magnification ×75.) (D) Biopsy section of case showing chronic hepatitis. A markedly expanded portal area is infiltrated with numerous inflammatory cells. The junction of the expanded portal area and adjacent parenchyma is ill defined (piecemeal necrosis). Note separated islet of hepatocytes (arrow). (Hematoxylin-eosin; original magnification ×150.)

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