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Hepatic Glomerulonephritis

Characteristics of Hepatic IgA Glomerulonephritis as the Major Part

Yasushi Nakamoto[1], Hiroyuki Iida[1], Kenichi Kobayashi[1], Kazuhiro Dohi[1], Hiroshi Kida[1], Nobu Hattori[1], and Jugoro Takeuchi[2]

[1] The First Department of Internal Medicine, School of Medicine, Kanazawa University, Japan
[2] The Second Department of Internal Medicine, Tokyo Medical and Dental University, Japan

Summary. Glomerular lesions associated with hepatic disease were evaluated. Among 752 consecutive patients with hepatitis and cirrhosis, nephritic urinary changes appeared in 1.0% of chronic hepatitics and 9.2% of cirrhotics, but none in patients with acute or subacute hepatitis. Kidney tissue was obtained from 141 cases, of which 59 underwent immunofluorescent studies. Except for a few with possibly coincidental glomerulonephritis, the main glomerular pathology was mesangial depositive or proliferative lesions with frequent circumferential mesangial interposition. The highest incidence (up to 69.2%) occurred in liver cirrhosis. The glomerular immunohistology was not necessarily homogeneous. In acute or subacute hepatitis, IgG or IgM, if present, was dominant. The more chronic the course the liver disease followed, the more frequently significant IgA deposition emerged, occurring in 60.5% of cirrhotics. The IgA positive cases often disclosed paramesangial dense deposits, which is one of the characteristics of primary IgA nephritis. Hepatic IgA nephritis exhibited a lower nephritogenicity and a proneness to show mesangial interposition when compared with primary or purpuric IgA nephritis. The possible origin of glomerular IgA associated with liver disease is discussed.

Key words: Hepatic (cirrhotic) glomerulonephritis – IgA – Mesangial interposition – Paramesangial dense deposits

Introduction

Glomerular alterations associated with hepatic cirrhosis were first noted by Horn and Smetana (1942), followed by Baxter and Ashworth (1946). Their nature has been disputed. One group have considered them to represent glomerulonephritis (Patek et al. 1951, Fisher and Hellstrom 1959, Fisher and Perez-Stable

Offprint requests to: Yasushi Nakamoto M.D., The Third Department of Internal Medicine, School of Medicine, Akita University, 1-1-1 Hondo, Akita, Akita 010, Japan

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1968) while another has termed the morphological picture cirrhotic or hepatic glomerulosclerosis, assuming an endocrine or metabolic origin (Bloodworth and Sommers 1959; Sakaguchi et al. 1965; Salomon et al. 1965) or on the basis of the lack of mesangial cell proliferation (Wehner and Andler 1973). Acute alcoholic or viral hepatitis has also been shown to have associated glomerular changes (Eknoyan et al. 1972).

Since 1970, immunohistological evaluations have been performed (Manigand et al. 1970; De Werra et al. 1973; Callard et al. 1975; Nochy et al. 1976; Berger et al. 1977). They revealed a dominant participation of IgA in the form of immune complexes, thus favoring the view that this is glomerulonephritis. However, these studies were mainly concerned with alcoholic liver disease and certain geographical areas or racial groups. The present report describes some observations of glomerular pathology in a variety of liver diseases and types of cirrhosis in Japan and also delineates the morphological characteristics by both histological and fluorescent microscopic findings.

Materials and Methods

All the patients were admitted to the First Department of Internal Medicine, Kanazawa University Hospital between July 1962 and September 1979. Urinalyses on admission were reviewed in 752 cases; 31 of subacute or fulminant hepatitis, 179 of acute hepatitis, 293 of chronic hepatitis and 249 of liver cirrhosis. Nephritic urinary changes were defined as proteinuria, haematuria of more than 5 red cells in a high-power field, red cell casts and/or significant cellular and granular casts and nephrotic changes included proteinuria of more than 3.5 g per day.

Kidney tissue was obtained from 141 out of 752 cases; 18 of subacute or fulminant hepatitis (all by autopsy), 6 of acute hepatitis (all by renal biopsy), 13 of chronic hepatitis (10 by biopsy, 3 by autopsy) and 104 of hepatic cirrhosis (14 by biopsy, 90 by autopsy). The diagnosis of liver disease, hepatoma and type of cirrhosis in the subjects with renal biopsy was determined by liver biopsy, peritoneoscopy and arteriography. Average daily alcoholic intake in the history was determined and found to be than 85 g per day in 81 cases, between 86 and 144 g per day in 9 and more than 145 g per day in 14. The cirrhosis was classified as postnecrotic (21 cases), posthepatitic (68) and septal (15). This is a common pattern of frequency in Japan. 38 cases of cirrhosis were complicated by hepatoma.

As controls, kidney tissue was taken from 67 autopsied cases without hepatic or renal diseases. All the kidney specimens were processed routinely, and stained with haematoxylin and eosin (HE), periodic acid Schiff (PAS), Heidenhain's azocarmine aniline blue (Azan) and Jones' periodic acid methenamine silver (PAM). Glomerular histology was divided into (1) no appreciable change, (2) mild to moderate mesangial proliferation, (3) moderate to marked mesangial proliferation with local circumferential mesangial interposition (CMI), (4) moderate to marked mesangial proliferation with diffuse CMI (MPGN), (5) membranous nephropathy (MN), (6) crescentic glomerulonephritis (RPGN) and (7) acute diffuse proliferative and exudative glomerulonephritis (AGN). By mesangial proliferation is meant mesangial widening of the matrix or cell increase, or both.

59 out of the 141 patients underwent immunohistological studies, using fluorescent-labeled monospecific antisera for human IgG, IgA, IgM, C_3 and fibrinogen (Behringwerke, West Germany) as previously described (Nakamoto et al. 1978). Positive and negative controls were run simultaneously. Immunofluorescent findings were classified according to the predominant immunoglobulin class. When two classes were of equal dominance this was noted.

Circulating levels of IgG, IgA, IgM, C_3 and C_4 were measured by the radial immunodiffusion method (Behringwerke, West Germany) in 35 patients among those 59 who had an immunofluorescent study.

Hepatitis B surface antigen (HBsAg) in serum was examined by radioimmunoassay (Abbott Laboratories, USA) in 58 cirrhotics.

Statitistical analysis was performed by chi-square test or Fisher's exact probability test.

Results

Urinalysis Data. The incidence of nephritic urinary changes in chronic hepatitis and liver cirrhosis was 1.0 and 9.2%, respectively. This difference was significant ($P<0.001$). The nephrotic syndrome was also observed in 0.3% and 1.6%, respectively. In acute, subacute or fulminant hepatitis, there was no case with nephritic or nephrotic urine, although isolated transient proteinuria or a few red cells were seen in some instances.

Glomerular Histology. Table 1 shows light microscopic findings, omitting the cases with no change. MN, RPGN and AGN (non-streptococcal) in one case each of chronic hepatitis, and RPGN in one cirrhotic appeared to have the same time of onset as the liver diseases. The last case was eventually found to be associated with HBsAg, and will be discussed separately. In the 3 subjects with chronic hepatitis, it was uncertain whether the development of both diseases was coincidental or might have had a common denominator.

The majority remaining had a definite history of antecedent liver disease. In these cases, the glomerular lesions developed mainly from the mesangial area to the subendothelial space, and were observed most frequently in the cases with cirrhosis of the liver. The incidence in cirrhotics, excluding the case with RPGN mentioned above, was 72 out of 104 cases (69.2%), one-fourth

Table 1. Glomerular lesions associated with hepatic diseases

	No. of cases	Mild to moderate mesangial proliferation	Moderate to marked mesangial proliferation		Membranous nephropathy (MN)	Crescentic glomerulonephritis (RPGN)	Proliferative and exudative glomerulonephritis (AGN)	Total
			with local CMI	with diffuse CMI (MPGN)				
Subacute or fulminant hepatitis	18	2 (0)	0	0	0	0	0	2 (0)
Acute hepatitis	6	2 (0)	0	0	0	0	0	2 (0)
Chronic hepatitis	13	2 (0)	1 (0)	0	1 (1)	1 (1)	1 (1)	6 (3)
Liver cirrhosis	104	30 (2)	33 (9)	9 (7)	0	1 (1)	0	73 (19)
Total	141	36 (2)	34 (9)	9 (7)	1 (1)	2 (2)	1 (1)	83 (22)
Control	67	6 (0)	3 (0)	0	0	0	0	9 (0)

( ): Cases with nephritic urinary changes.

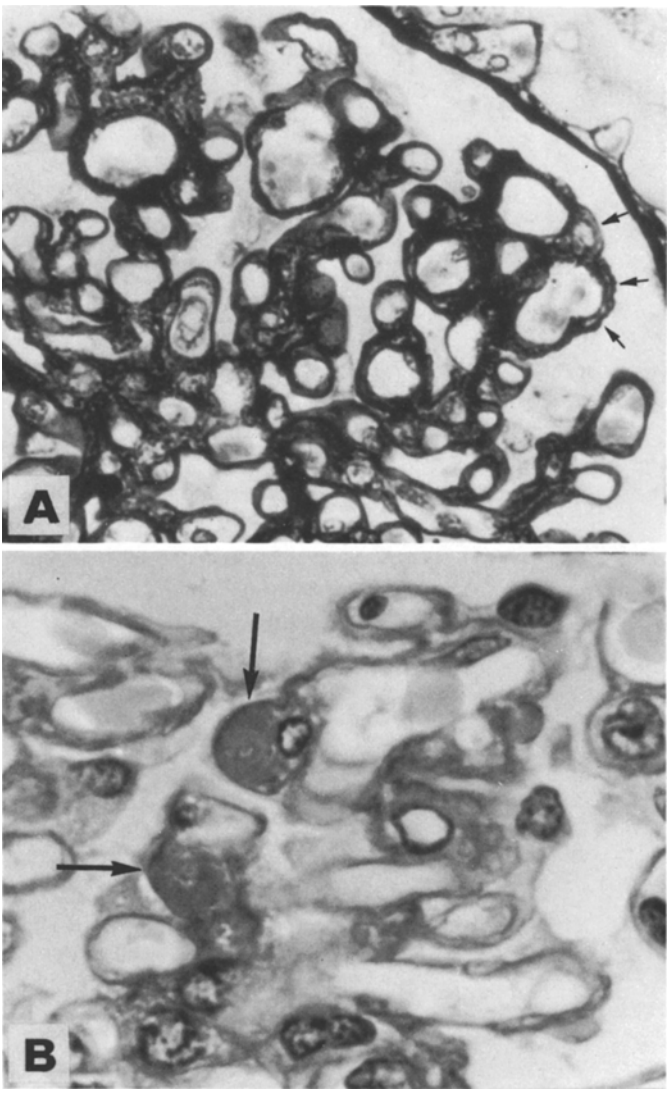

Fig. 1. A Circumferential mesangial interposition making a double structure of peripheral capillary walls *(arrows)* is seen. One can also note mesangial thickening due mainly to matrix increase and partly to mild cell proliferation. This is from a case of hepatic cirrhosis without nephritic urine, ×500, PAM. **B** Paramesangial dense deposits *(arrows)*, identical with those in primary IgA glomerulonephritis, are shown, from a cirrhotic with normal urine, ×1,000, PAS

of which displayed nephritic or nephrotic urine. When confined to the autopsied patients, it was 66.7%. The figures had a statistical significance ($P<0.001$) against the control (13.4%). The lesions in both hepatitics and cirrhotics presented the following aspects. (1) The frequency of nephritic urine increased in a manner which corresponded to the severity of glomerular lesions. (2) The cases accompanied by nephritic urine tended to show some degree of mesangial

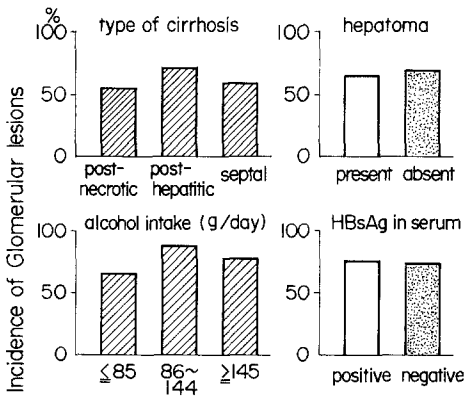

Fig. 2. The incidence of glomerular lesions in cirrhosis of the liver was compared with type of cirrhosis, daily alcohol intake, and the presence or absence of hepatoma and HBsAg in serum. There were no significant correlations

Table 2. Glomerular immunofluorescent findings (1)

	No. of cases examined	No. of negative cases	No. of positive cases				
			IgG	IgA	IgM	C_3	fibrinogen
Subacute or fulminant hepatitis	7	3	2	0	2	3	1
Chronic hepatitis	9	2	5	3	1	4	5
Liver cirrhosis	43	12	21	28	19	23	13
Total	59	17	28	31	22	30	19

cell proliferation. In those without it, mesangial thickening was usually due to matrix increase, with rather scanty cell proliferation, but there was no histological distinction between those with and without nephritic urine. (3) Local and diffuse CMI (Fig. 1A) occurred more often in those with liver disease, especially in cirrhotics ($P<0.001$ versus the control). One could not distinguish moderate to marked mesangial proliferation with diffuse CMI encountered exclusively in hepatic cirrhosis from the so-called membranoproliferative glomerulonephritis (MPGN). (4) Particularly in cirrhotics, paramesangial dense deposits (Fig. 1B) were present in 25.0% of the cases. Foamy paramesangial deposits which probably represented foamy degeneration of these deposits were also observed in an additional 6.7%, amounting to 31.7% in all. (5) Of 104 patients with liver cirrhosis, only 13 (12.5%) exhibited segmental sclerosis and/or adhesion, of which ten cases had nephritic urine. (6) There was no instance of membranous nephropathy in cirrhotics.

In order to determine possible contributory factors in the development of these glomerular lesions, the type of cirrhosis, alcoholic intake and the presence of hepatoma and HBsAg were evaluated. The incidence of glomerular pathology was not influenced significantly by these factors (Fig. 2).

Immunohistology. Table 2 shows the result of immunofluorescent studies in the glomeruli. All positive immunofluorescence was diffusely distributed in an essentially granular fashion. Reactivity for three classes of immunoglobulin, C_3 and

Table 3. Glomerular immunofluorescent findings (2)

	No. of cases studied	No. of positive cases	IgG dominant	IgA dominant	IgM dominant	IgG = IgA	IgG = IgA = IgM	IgG = IgM
Subacute or fulminant hepatitis	7	2 (28.6)	0	0	0	0	0	2 (28.6)
Chronic hepatitis	9	6 (66.7)	3 (33.3)	3 (33.3)	0	0	0	0
Liver cirrhosis	43	32 (74.4)	3 (7.0)	23 (53.5)	3 (7.0)	1 (2.3)	2 (4.7)	0
Total	59	40 (67.8)	6 (10.2)	26 (44.1)	3 (5.0)	1 (1.7)	2 (3.4)	2 (3.4)

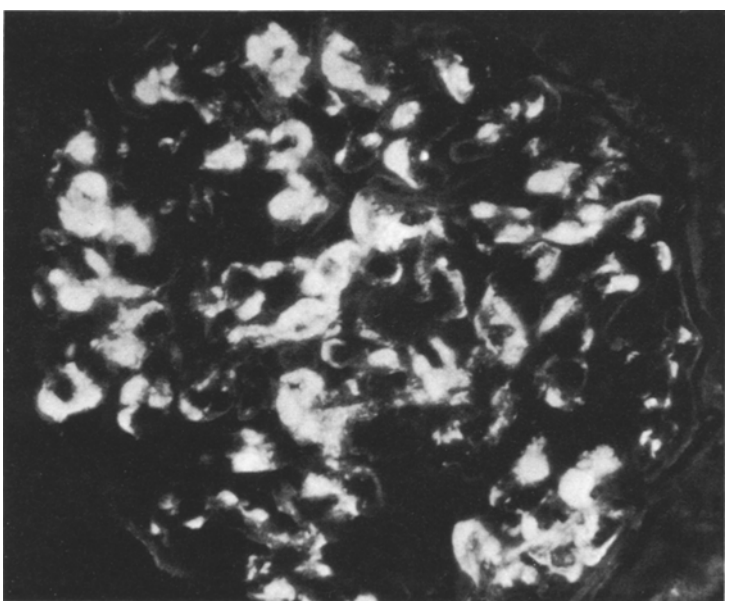

Fig. 3. IgA dominant immunofluorescence from a case of liver cirrhosis with normal urine. IgA is diffusely distributed from the mesangial area to the subendothelial space in a granular fashion. In this case, less intense IgG, IgM and C_3 were also present. $\times 400$

fibrinogen (-related materials) was positive in various frequencies. Isolated C_3 was positive in 2 cases of fulminant hepatitis, and fibrinogen alone in one with chronic hepatitis and RPGN. All other positive C_3 and fibrinogen were associated with immunoglobulin(s). Table 3 presents immunofluorescent patterns classified as mentioned above. A pattern of IgG dominant or equal to IgM seemed to be a little more frequent in subacute or fulminant hepatitis and some of chronic hepatitis than in hepatic cirrhosis, although the number of positive cases is small. In contrast, IgA dominant fluorescence (Fig. 3) began

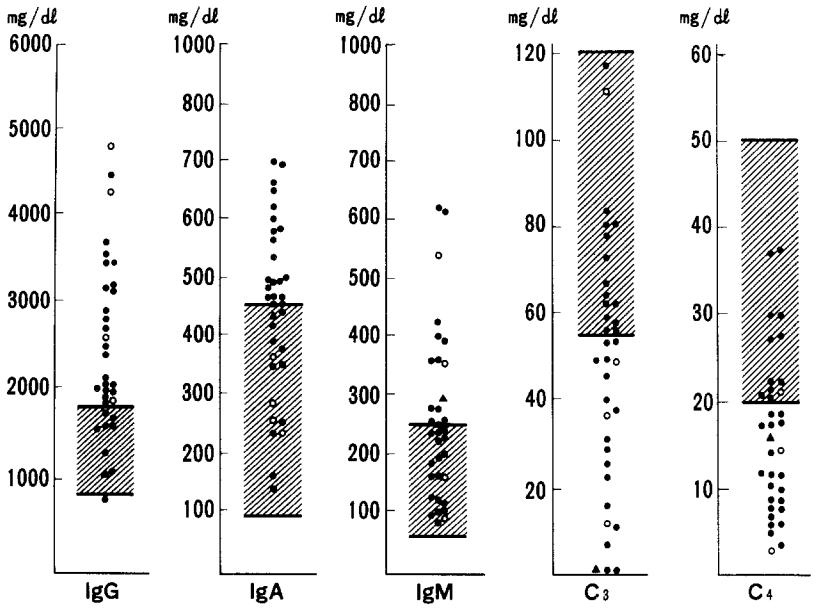

Fig. 4. Circulating levels of immunoglobulins and complement components. Shaded area; normal range, solid circle; liver cirrhosis, open circle; chronic hepatitis, solid triangle; subacute or fulminant hepatitis

to appear in chronic hepatitis and predominated in cirrhotics (53.5%). If those with IgA equal to IgG and/or IgM are included as described elsewhere (Nakamoto et al. 1978), significant IgA deposition was found in up to 60.5% of cirrhotics and in 81.3% among the immunoglobulin-positive cases. IgA alone was seen in 6 cases. Dominant IgM occurred only in cirrhotic patients, but, like IgG, occupied a smaller part. The cases with MN, RPGN or AGN mentioned above disclosed IgG or IgM in dominant pattern or staining with fibrinogen alone, all without accompanying IgA.

The effects of type of cirrhosis, alcohol intake and the presence of hepatoma and HBsAg were examined. As in the light microscopic findings, these factors did not show any relation to the immunofluorescent patterns.

Serum Immunoglobulins and Complement Components. There were polyclonal elevations of IgG, IgA and IgM in 73.5%, 57.1% and 44.1%, respectively (Fig. 4). All cases with increased IgA levels had cirrhosis of the liver. On the other hand, levels of C_3 and C_4 were reduced in 57.1% and 65.7%, respectively. In addition, even within normal limits, all but a few were below the median of normal. However, no correlation was seen between these levels of immunoglobulins and complement components, and the presence or pattern of glomerular immunofluorescence.

Discussion

Despite the dispute on the nature of glomerular lesions associated with liver disease (Patek et al. 1951; Fisher et al. 1959, 1968; Bloodworth and Sommers

1959; Sakaguchi et al. 1965; Wehner and Andler 1973), the glomerular pathology on close review can be judged to be essentially the same, and can be described in contemporary usage as mesangial depositive or proliferative changes with frequent capillary wall thickening, owing to mesangial interposition. Immunofluorescent evaluations have revealed significant IgA in a frequency of 56 to 80% of the cases studied (Manigand et al. 1970; De Werra et al. 1973; Callard et al. 1975; Nochy et al. 1976; Berger et al. 1977). In a larger series by Berger et al. (1977) with a total of 100 cirrhotics composed of 90 alcoholic, 2 posthepatitic, 2 haemochromatosis and 6 cryptogenic, 61 cases showed granular deposits of IgA as the main immunoglobulin in the glomeruli. The present results are essentially consistent with these studies, in spite of different geography, food habits and race. We also found the immunohistology to be uninfluenced by type of cirrhosis, alcohol intake, hepatoma or HBsAg. The present study, however, indicated that hepatic glomerulonephritis is not necessarily homogeneous. In addition to the patients with MN, RPGN and AGN, there were a few cases of liver cirrhosis with different pathogenetic mechanisms as judged from the glomerular immunofluorescence. Moreover, subjects following a less chronic course, e.g., acute or subacute hepatitis, as in the cases reported by Eknoyan et al. (1972), tended to show IgG or IgM dominant pattern. On the other hand, the more chronic the course, the more frequently an IgA dominant pattern appeared, forming a major part of the cirrhotic group. The histological aspects observed mainly in cirrhotics were those seen in patients with significant glomerular IgA deposition. Paramesangial dense deposits, known to be one of the characteristic lesions in primary IgA glomerulonephritis (Morel-Maroger et al. 1972; Ueda et al. 1977; Nakamoto et al. 1978) were seen exclusively in the IgA deposited cases. Thus, the IgA-positive glomerular alteration in cirrhotics and some chronic hepatitics appears to be one type of IgA-associated immune complex glomerulonephritis.

However, with regard to hepatic IgA glomerulonephritis, there seem to be some features different from primary IgA glomerulonephritis and Schönlein-Henoch purpura nephritis. It has been observed that there is a large discrepancy between the frequency of nephritic urinary changes and that of positive light and fluorescent microscopic findings (Patek et al. 1946; Bloodworth and Sommers 1959; Callard et al. 1975). Although nephritic urine is more often excreted as the glomerular lesions progress, abundant IgA deposits sometimes induce neither abnormal urine nor cell reaction. Wehner and Andler (1973) noted a paucity of mesangial cell proliferation by morphometry, and Berger et al. (1977) were impressed by a low frequency of segmental sclerosis. The present study observed this change in only 12.5% of cirrhotics, as compared to 25% or more in primary or purpuric IgA glomerulonephritic (Nakamoto et al. 1978). A lower nephritogenicity, therefore, appears to be one of the characteristics of hepatic IgA glomerulonephritis.

Another feature is a high incidence of circumferential mesangial interposition (CMI). Overall, 42 out of 104 cirrhotics (40.2%) had local or diffuse CMI. In hepatic IgA glomerulonephritis, CMI may be more prone to develop instead of mesangial cell increase. Persistent hypocomplementaemia or C_3 deficiency has been postulated to predispose to the development of MPGN, in which CMI is one of the histological hallmarks (Peters et al. 1973; Pussell et al. 1980).

A defective solubilisation of immune complexes by hypocomplementaemia was also demonstrated to occur (Miller and Nussenzweig 1975; Takahashi et al. 1976). A tendency toward hypocomplementaemia in liver disease as seen in our study has been ascribed to a depleted synthesis by the liver (Ruddy et al. 1972; Kourilsky et al. 1973), together with an increased consumption (Teisberg and Gjone 1973). Hypocomplementaemia may, thus, be related to the frequent appearance of CMI in hepatic glomerulonephritis, but this awaits further confirmation.

The origin of IgA deposited in the glomeruli of patients with chronic liver disease remains uncertain, but it has been shown that the diseased liver contains a significant amount of IgA. Mori et al. (1967) demonstrated the presence of IgA in Kupffer cells, endothelial cells of the sinusoids and infiltrating cells in the interstitium of the liver by immunofluorescence. They also observed that IgA was specifically elevated in the liver homogenate of cirrhosis and hepatic fibrosis. In contrast, Kater et al. (1979) recently claimed that continuous IgA deposits along the sinusoidal wall of the liver were specific for alcoholic hepatic disease. In any case, IgA in both kidney and liver has been found to be devoid of the secretory piece (De Werra et al. 1973; Whitworth et al. 1976; Kater et al. 1979). Since dietary and bacterial antigens (Bjørneboe et al. 1972; Triger et al. 1972) enter into the systemic circulation via a number of portacaval shunts in cirrhosis of the liver (Popper 1977), it is possible that IgA is conveyed from the liver. In fact, Kater et al. (1979) described an alcoholic man in whom IgA was detected in the capillaries of both skin and gut and the glomerular mesangium, in addition to the liver. The question may be raised whether IgA is produced in the liver (Cohen et al. 1960) or is carried on the portal blood into the liver. This may be answered by measuring IgA-associated immune complexes in the portal vessels. However, the influence IgA has on liver disease remains to be explored.

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