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Sequential Changes of the Plasma-protein Pattern in Cases of Hepatitis A

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ABSTRACT

The level of 21 plasma proteins was followed in Hepatitis A for two months after onset of icterus. The mean concentration of α_1-antitrypsin, orosomucoid, haptoglobin, C-reactive protein (CRP) and α_1-antichymotrypsin increased uniformely during the first week of hepatitis A. Thus, they differ from that of inoculation hepatitis earlier described. The mean curve for IgM was higher in hepatitis A than the corresponding results for inoculation hepatitis during the first week of illness, but because of great inter-individual differences in concentrations IgM determinations can not be used to discriminate between the two diseases in a given case. IgA levels were slightly increased early in hepatitis A but no change in IgG levels was observed. Prealbumin was the best mirror of the patients' recovery or deterioration.

INTRODUCTION

The detection of plasma protein abnormalities is of value in the diagnosis and follow-up of hepatic disorders including hepatitis. As early as the nineteen-forties, Gray and Barron (8) showed that hepatitis is accompanied by a polyclonal type of hypergammaglobulininemia and this has since been confirmed by others (3,4,7). Wollheim (22) was the first to recognize a difference between hepatitis A and hepatitis B, namely, a substantial increase of IgM in most cases of hepatitis A but in only half of those of hepatitis B. This difference has been widely disputed (6,12,14,19).

Scattered observations have been reported on the variation of some proteins during the course of hepatitis. Belfrage (3) observed a low haptoglobin level in sera from patients with hepatitis B, but not in sera from those with hepatitis A. Müller and Müller-von Voigt (16) studied the variations in 16 individual plasma proteins in cases of liver disease and found a series of significant changes in patients with acute hepatitis. Their findings refer to single observations during the early phase of the disease.

We have previously reported on the sequential changes in the pattern of plasma proteins in hepatitis B (11). Our findings have been confirmed to a major extent (5,15,20,21) though results have been interpreted as applying to acute viral hepatitis in general rather than to hepatitis B alone.

The aim of the present investigation was to study the sequential changes in plasma proteins in patients with hepatitis A during an acute epidemic enabling the changes to be compared to those reported in hepatitis B (11).

MATERIAL AND METHODS

Patients: Thirty people aged 18-54 (mean 34) years were infected with hepatitis A in a factory where a point-source outbreak occurred. Accumulated evidence reported earlier (18) revealed that they were infected in the factory canteen. The epidemic was of short duration. The diagnosis was based on epidemiological evidence and anti-HAV determinations. None of the patients showed any serological evidence of hepatitis B. The clinical course of the hepatitis A infection was uneventful and all patients had normal levels of serum bilirubin and serum alanine amino transferase (S-ALAT) within three months of onset of their illness.

Blood sampling: The first blood samples were obtained within one week of onset of symptoms. The majority of samples were of serum with only a few plasma samples from the first week of the illness. Plasma samples were then taken at weekly intervals for at least ten weeks.

The following 21 plasma proteins were determined: Prealbumin, albumin, orosomucoid, α-lipoprotein, α-antitrypsin, α_1-antichymotrypsin, ceruloplasmin, α_2-macroglobulin, haptoglobin, hemopexin, fibronectin (earlier wrongly designated AHF), transferrin, C3, C4, plasminogen, prothrombin, properdin, immunoglobulin G, immunoglobulin A, immunoglobulin M and C-reactive protein (CRP). All the plasmaprotein analyses were performed by electroimmunoassay (13) with the modifications described earlier (10,17).

RESULTS

The protein pattern usually followed the same course in all patients, though it varied in intensity and in the duration of abnormal values.

The results of the determinations of α_1-antitrypsin, orosomucoid and haptoglobin are summarized in Fig. 1. They are plotted against the time after icterus was observed. Curves for the mean values are given in the figures.

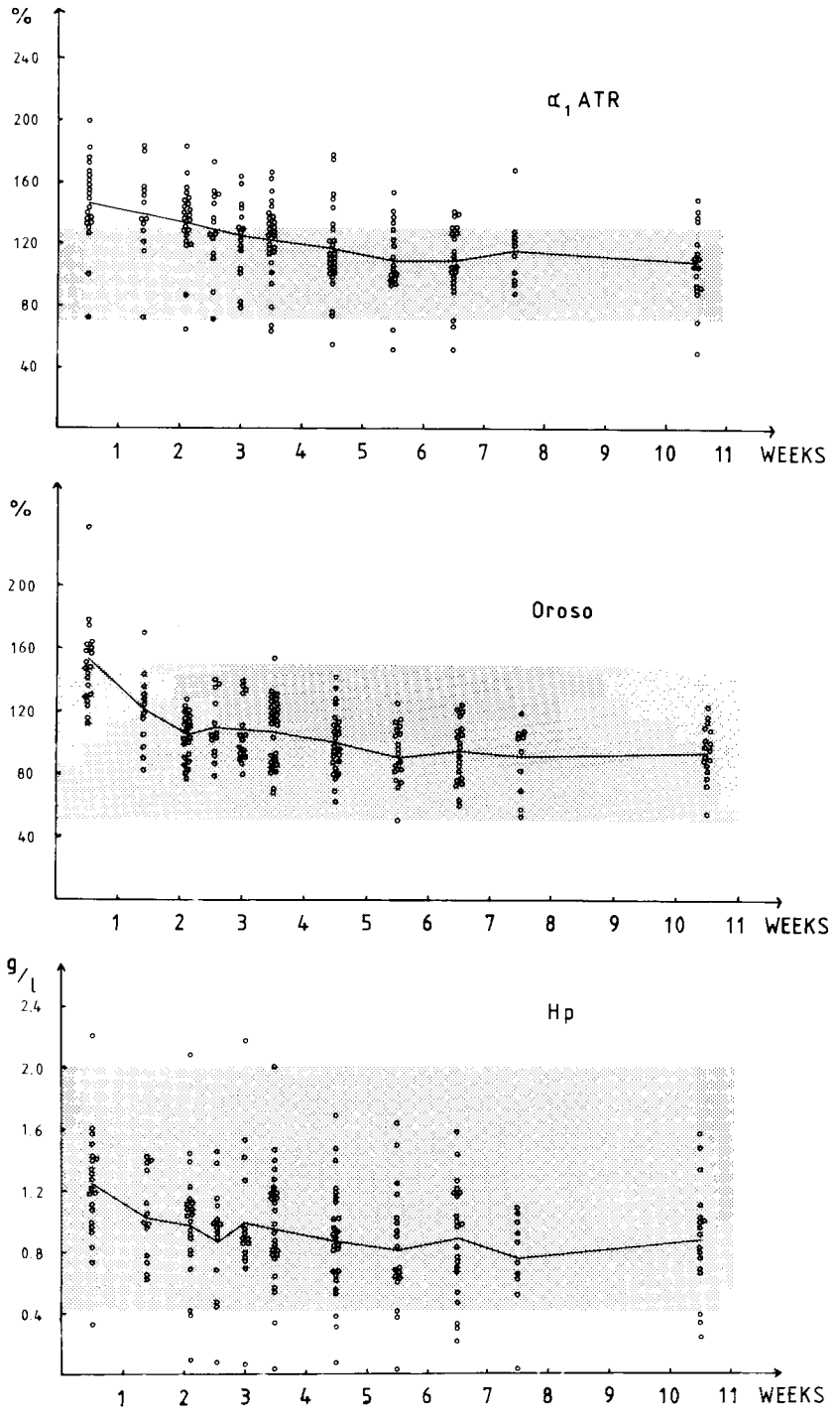

Fig. 1 Acute phase reactants (α_1-antitrypsin, orosomucoid, haptoglobin) during the course of hepatitis A. The normal (95 per cent) ranges are shaded and the mean value lines connected.

During the first 2-3 weeks a uniform rise of these three acute-phase reactants is noted. Then a gradual decrease of the mean concentrations of these three acute-phase reactants occurs over a period of 5 weeks. Having returned to the normal range the mean for α_1-antitrypsin, orosomucoid and haptoglobin remained normal during the rest of the period of observation.

α_1-antichymotrypsin - not shown in any figure - followed the pattern of orosomucoid very closely. Determinations of C-reactive protein (Fig. 2) were initially slightly to moderately increased but decreased considerably after the first two weeks.

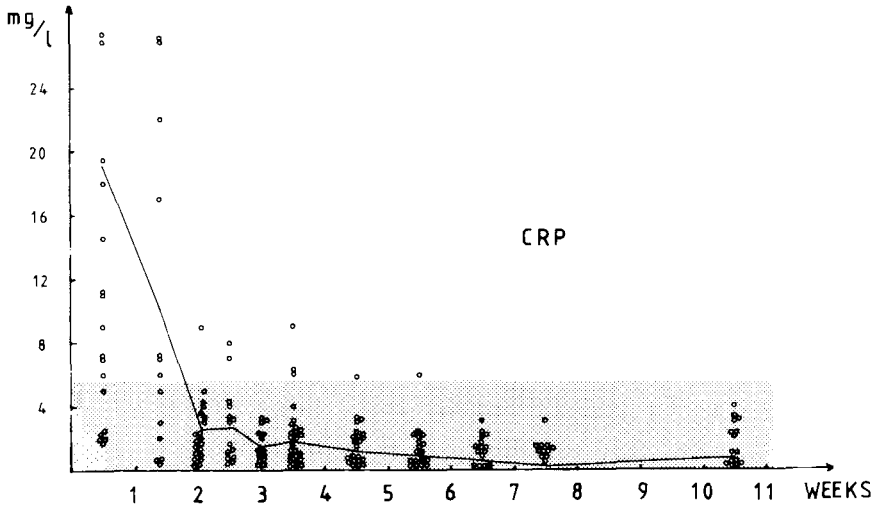

Fig. 2 C-reactive protein (CRP) during the course of hepatitis A.

Several proteins showed an initial fall in concentration with the lowest value around the 10-14 day of illness followed by a gradual return towards normal values. Prealbumin (Fig. 3), albumin, hemopexin and α-lipoprotein demonstrate this pattern. Starting from the normal range initially the mean serum albumin value reached its lowest point (36 g/l) during the second week and returned to the normal range after one month. The mean curve for hemopexin indicates values well below the normal range by the time the patient was hospitalized (78% of the normal mean). The mean curve reached its lowest point (63% of the normal mean) ten days after onset of the illness and returned to its starting level in the third week. The mean curve continued to increase gradually and reached its highest values (87% of normal mean) after 7 weeks and remained at that level during the rest of the period of observation.

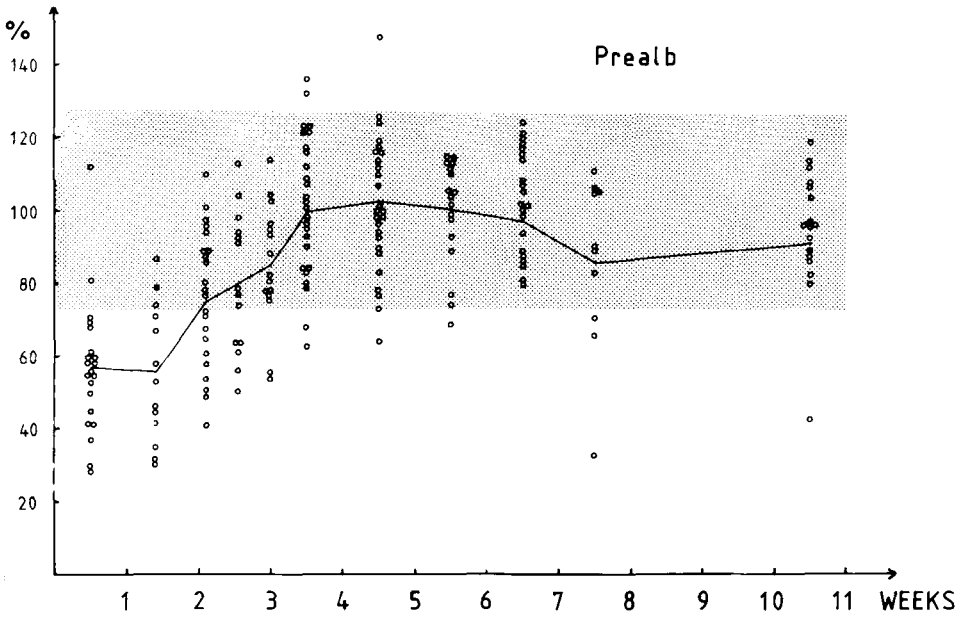

Fig. 3 Prealbumin during the course of hepatitis A.

Too few plasma samples were available from the first week of illness to allow any definite conclusions to be drawn about changes in prothrombin levels during this period. The mean concentration of prothrombin in plasma samples around day 10 was 80% of the normal mean. Thereafter the mean prothrombin level remained normal.

A third group of proteins including transferrin (Fig. 4), α_2-macroglobulin (Fig. 4), ceruloplasmin and properdin showed only minor changes and the mean curve remained essentialy constant within the normal range during the whole time of observation. The same appears true for plasminogen, fibronectin, C3 and C4, provided allowances are made for the paucity of plasma samples collected during the first week of the illness.

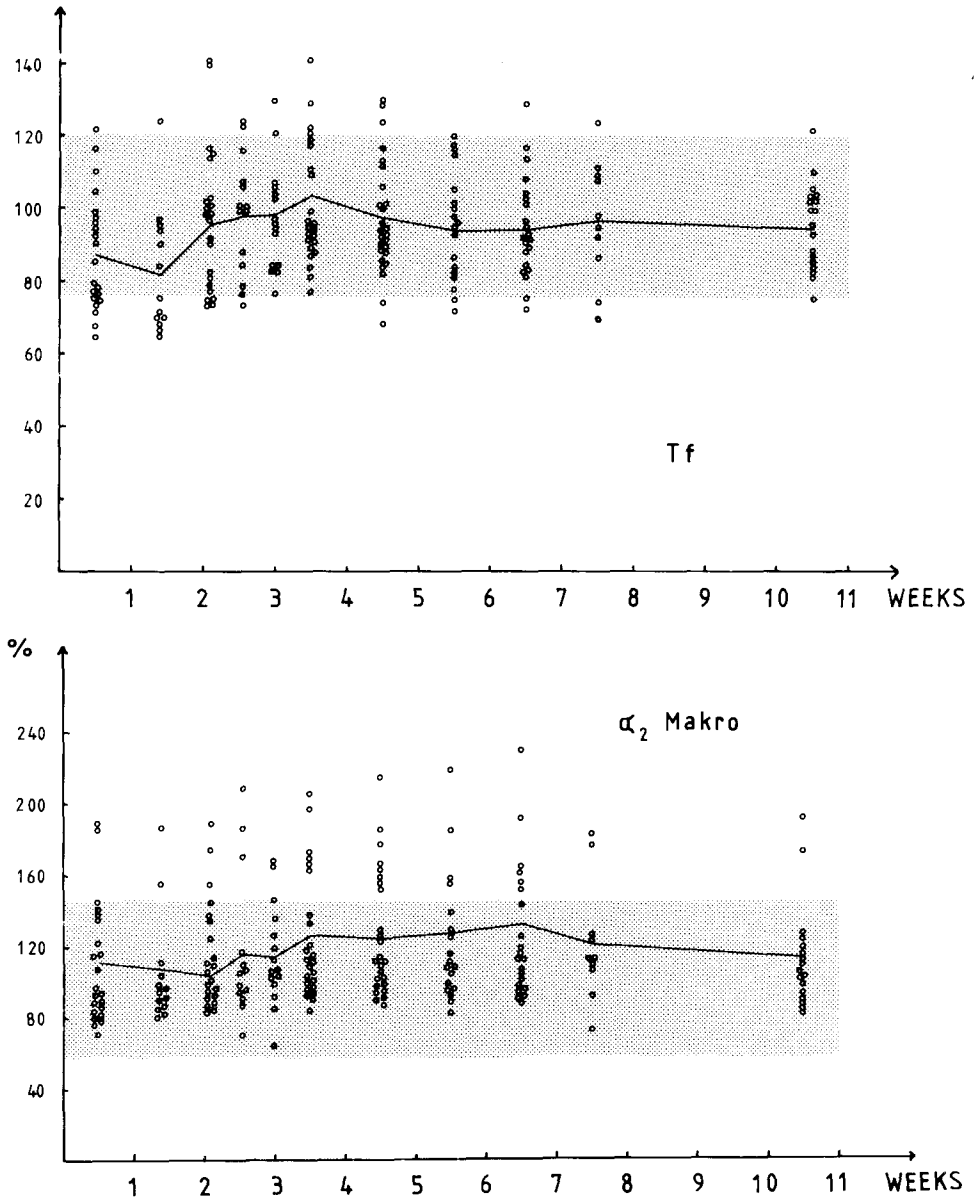

Fig. 4 Transferrin and $\alpha_2$macroglobulin during the course of hepatitis A.

The IgM values varied greatly between the different patients although the individual values followed the mean curve (Fig. 5). Most patients already had peak levels of IgM on admission, co-inciding with the appearance of jaundice. The values gradually returned to normal during the following months. The mean curves of levels of IgG and IgA were both within the normal range during the whole period of observation. A slight increase in IgA levels (Fig. 5) was, however, observed during the first two weeks of illness.

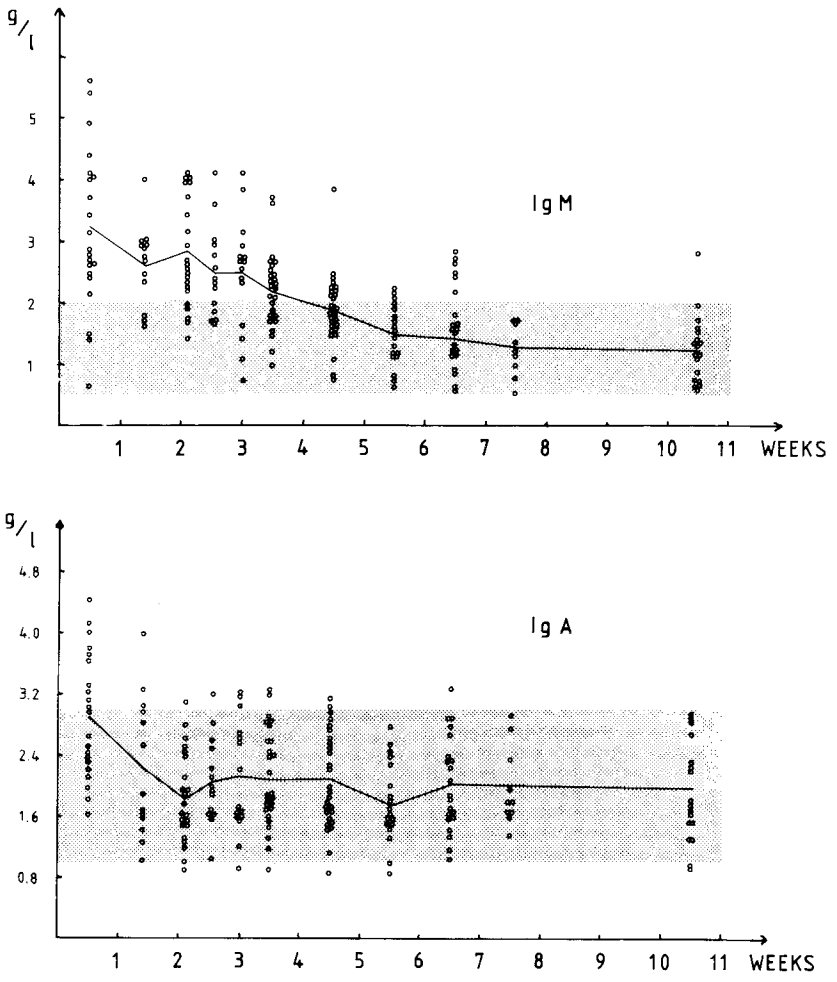

Fig. 5 Immunoglobulin M and A during hepatitis A.

DISCUSSION

The data presented are based on samples drawn from patients suffering from hepatitis A. None of the patients showed any serological evidence of hepatitis B. Thus, the data obtained merit a comparison of the sequential changes in pattern of plasma proteins in hepatitis A with those reported earlier for hepatitis B (11). Since the presentation of the hepatitis B series those sera have been checked for antibodies to hepatitis A as this test became available. No evidence of hepatitis A was found in those sera.

Much attention has been paid to the changes in the serum immunoglobulin concenteration in cases of hepatitis A and B. The IgM levels in hepatitis A reported here showed that the mean curve for IgM reached much higher values than the corresponding curve for hepatitis B. This is evident from the onset of the illness when the mean curve for IgM starts at 3.2 g/l compared to 1 g/l for hepatitis B (11). Substantial interindividual changes were seen in hepatitis A, i.e. there were just as many patients suffering from hepatitis A with an IgM value well above 4 g/l during the first week of illness as there were patients with an IgM value below 2 g/l. Thus, IgM values afford the clinician little, if any, diagnostic guidance in any given case.

In the course of hepatitis A we did not observe any change in IgG concentrations. Thus, our results confirmed those reported by Krugman, Giles and Hammond (12) and by Giles and Krugman (6) but not those of Lo Grippo, Hayashi and Sharpless (14), Bevan, Taswell and Gleich (4) or Wollheim (22). The slight increase in the IgA levels during the first two weeks of hepatitis A reported here was not observed for hepatitis B (11). After the initial minor increase the mean curve for IgA was almost identical for hepatitis A and B. This agrees with data reported by Wollheim (22).

No explanation can be offered for the marked reaction of IgM in many patients in the early phase of hepatitis A at the time when only a minor reaction is found in hepatitis B. Perhaps the peak in IgM levels in hepatitis A may coincide with the peak of virus shedding in this disease though it remains to be shown that the patients with the highest IgM values are those that shed the greatest number of virus particles.

The slight increase in plasma IgA levels during the first two weeks of illness in hepatitis A but not in hepatitis B remains unclear. Hepatic oedema with consequently increased portal venous pressure early in hepatitis A might be an explanation. The increased pressure in the portal vein affects the blood flow in the intestine. The IgA produced there might thereby be forced back into the systemic circulation.

The constant rise in the values of the acute-phase reactants (α_1-antitrypsin, orosomucoid, haptoglobin, CRP, and α_1-antichymotrypsin) which is characteristic of bacterial infections, traumatic lesions (2) and aseptic necrosis (10) is also demonstrated in the early phase of hepatitis A, as reported here. This contrasts to the findings in hepatitis B (11). Furthermore, in hepatitis A the harmonious rise of α_1-antitrypsin, orosomucoid and haptoglobin during the first week after the appearance of jaundice is a reaction of great regularity,

as shown in Fig. 6. In this figure the mean curves are given for these three acute-phase reactants during the first week of illness. The scales used are such that the values for these three proteins in healthy individuals will be around 100% for α_1-antitrypsin and orosomucoid and 1 g/l for haptoglobin. This profile is quite different from the one we have reported for hepatitis B (11), which is included in figure 6 for reference. Thus, the response of these acute-phase proteins may be used as a diagnostic tool for differentiation between hepatitis A and B, particularly in those cases when serological tests in these diseases have not given unequivocal results. These findings also stress the fact that the determination of one acute-phase reactant may not always suffice and much better information can be obtained if 2 or 3 acute-phase proteins are determined simultaneously.

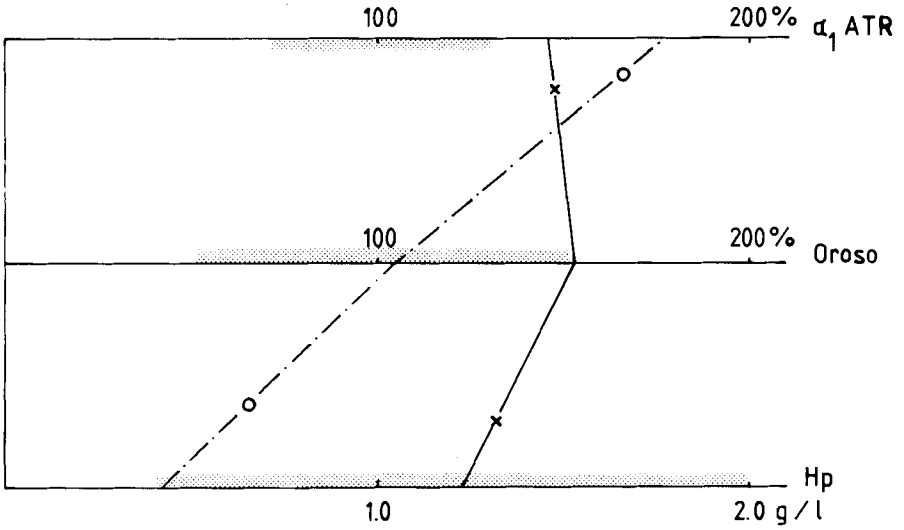

Fig. 6 Relation between individual values of α_1-antitrypsin, orosomucoid and haptoglobin during the first week of hepatitis A. The normal (95 per cent) ranges are shaded and the mean value lines (x - x) connected. The corresponding mean value lines for hepatitis B (0 - • - 0) is given for comparison. (The individual value obtained for hepatitis B have been reported earlier (11)).

The concentration of C-reactive protein may also assist in differentiation between hepatitis A and B early in the illness. Comparing the mean curve obtained for CRP in hepatitis A with that of hepatitis B arrived at earlier (11) significantly higher levels were seen in hepatitis A than in hepatitis B, confirming the results obtained by Hedlund (9).

The different results for the acute-phase reactants reported here compared to those reported for hepatitis B earlier (11) suggests that the pathology of the 2 types of hepatitis is quite different. The findings would be consistent with a pronounced cellular reaction with an increased activity of granulocytes or monocytes in hepatitis A but not in hepatitis B.

When monitoring the patients suffering from hepatitis A it is helpful to have a variable that reflects the clinical course of the disease. The S-ALAT, very often used in this respect, could provide erroneous information as levels may decrease instead of increase when the patient is gradually getting critically ill. The results of this study would seem to indicate that the prealbumin values were the best mirror of the patients' recovery or deterioration during the course of hepatitis A. This is in agreement with earlier reports (1,11,15,16,20,21).

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