At the time of referral she was probably taking in excess of 40 mg prednisone a day. She was afraid to leave her home and her telephone in case she might require urgent medical help, but there was no evidence to suggest that bronchospasm had actually been present recently in any appreciable degree. Intermittent asthmatic attacks, two necessitating admission to hospital, had occurred since the age of 12 years. She had had psychiatric inpatient treatment six months before because of anxiety symptoms. She was the youngest of six children, and her parents were elderly. She had left school with a poor academic and attendance record, and had subsequently failed to persist in any training or occupation for long. She had not made stable friendships and an illegimate pregnancy had been terminated one year previously.

Physical examination showed definite Cushingoid features with plethoric moon-shaped facies and acne, bruising on both legs (without any clear history of physical trauma), and peripheral muscle wasting. Height was 5 ft 5 in (165 cm), weight 8 st 3 lb (52 kg) (92% average body weight), B.P. 135/85 mm Hg. No other physical abnormalities were noted on clinical assessment. Routine blood and urine investigations were unexceptional. Chest radiograph showed increased transverse cardiac diameter. *X*-ray picture of hands, tibiae, and fibulae showed definite osteoporosis. The peak expiratory flow rate was 440 l./min (this being normal for her age and height). The patient refused further metabolic investigations.

The diagnosis was thought to be one of secondary Cushingoid state (due to an addictive dependence on prednisone) and bronchial asthma. In view of her distressed state she was admitted immediately to a psychiatric ward. Prednisone was gradually withdrawn over a period of four weeks. She became very anxious as this was being done, but her symptoms eventually subsided in the ward setting and medication with salbutamol (2 mg tablets four times a day as well as by inhaler) and diazepam 5 mg three times a day was continued. She was advised to stop smoking. Her dependence on prednisone was discussed with her at length. When discharged after four weeks she was free from bronchospasm and was no longer receiving steroid medication. Subsequent follow-up proved to be very difficult because she avoided outpatient appointments and changed her family doctor regularly. On at least one occasion she persuaded her new doctor to give her prednisone before he knew the full facts of her case and at a time when she did not have severe bronchospasm. She also sought further supplies of steroids at a hospital accident department soon after her discharge from hospital.

Comment

This patient developed an intense dependence on prednisone after its use in treating her bronchial asthma. It is likely that this dependence was predominantly psychological in nature. In view of the danger that psychological dependence may eventually dominate the clinical picture, it is wise to review the psychiatric history before any patient is given long-term steroid therapy.

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Alpha$_1$ Fetoprotein and Antialpha$_1$ Fetoprotein in Acute Viral Hepatitis

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Alpha$_1$ fetoprotein (α_1FP) is known to occur in infants and adults with hepatocellular carcinoma and malign teratoma (Kew *et al.*, 1971), but its presence in other hepatic disorders seems uncommon. While studying cryoprecipitates in acute viral hepatitis and chronic active hepatitis we found that some consisted of α_1FP, and so we decided to look for a theoretical immune response to this antigen.

Patient and Methods

The patient, a woman aged 26, was a technical assistant in our laboratory who often gave blood for use as a normal control. One sample had been stored at −20°C for three months. She became ill, with malaise, headache, mild fever, and asthenia. One week later jaundice developed and the first serum sample was collected. Serum enzyme activity was as high as 1,500 mU/ml for both transaminases and 500 mU/ml for lactic dehydrogenase; serum bilirubin was 4 mg/100 ml. She was confined to bed without further treatment. She was discharged from hospital after 40 days, when the clinical and biochemical findings had returned to normal. Blood samples were taken weekly throughout the illness, starting on the seventh day (see table), and sera stored at −20°C until tested.

Results of Tests on Weekly Blood Samples Taken Throughout Illness

Serum Sample No.	When Taken	Latex Fixation	Hepatitis-associated Antigen	Hepatitis-associated Antibody	α_1FP	Anti-α_1FP	Cryoprecipitate
1 ..	1 week	1/640	+	−	+	−	+
2 ..	2 weeks	1/640	+	−	+	+	+
3 ..	3 weeks	—	+	−	+	+	+
4 ..	4 weeks	—	−	−	+	+	−
5 ..	5 weeks	—	−	−	+	+	−
6 ..	6 weeks	—	−	−	+	−	−

Paper and agar-gel electrophoresis and microimmunoelectrophoresis were performed on an LKB apparatus. Antisera to whole human normal serum, to purified IgG, IgA, and IgM, and to kappa-chains were prepared in rabbits and rendered monospecific by absorptions. Antisera to IgD and lambda-chains were obtained commercially.

Antigammaglobulin factors were looked for by the latex fixation test as described by Singer and Plotz (1956). Lupus erythematosus cell formation was investigated by the classical technique of Hargraves (1954). Antibodies to nuclei, non-organ specific cytoplasm—that is, components—smooth muscle, gastric parietal cells, renal tubules and glomeruli, and bile canaliculi were studied by an indirect immunofluorescence technique using cryostat sections of mouse organs. Goat antisera to human immunoglobulins were prepared in our laboratory and labelled with fluorescein isothiocyanate 12·5 µg/mg protein, according to Nairn (1968). Hepatitis-associated antigen and antibody were investigated by countercurrent electrophoresis in 0·85% 0·05 M agarose-veronal pH 8·2 in the same LKB apparatus.

α_1FP and anti-$\alpha_1$fetoprotein (anti-α_1FP) were looked for by Ouchterlony's immunodiffusion method, Mancini's single

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radial immunodiffusion, and countercurrent electrophoresis in 0·85% 0·05 M agarose-veronal pH 8·2, using commercial (Hoechst) α_1FP and anti-α_1FP rendered monospecific by absorption with normal human serum. Cryoprecipitates were looked for by storing sera in capillary tubes at 4°C. When present they were isolated and washed at least 10 times with 0·15 M NaCl until the supernatant was free of protein when read at 280 nm in a Beckman spectrophotometer. The precipitates were soluble at 37°C (Arana *et al.*, 1971).

RESULTS

All tests performed on samples of serum obtained before the onset of hepatitis were normal. Unfortunately there was not enough serum to be able to look for hepatitis-associated antigen or antibody. No autoantibodies were found by immunofluorescence in any of the subsequent samples. The latex fixation test became positive (see table) after one week of symptoms, and still showed a titre of 1/640 by the second week. Thereafter no antiglobulin activity could be shown. All lupus erythematosus cell preparations were negative. Hepatitis-associated antigen was present until the third week, but hepatitis-associated antibody was never found.

Much cryoprecipitate appeared in the second week. Isolated and thoroughly washed, it proved to be a mixed cryoglobulin consisting entirely of α_1FP and IgMK. It was free of both hepatitis-associated antigen and antibody. Anti-α_1FP activity could not be found in the IgMK, but neither did this show antigammaglobulin or any other antibody activity. IgG, IgA, and complement could not be detected in the cryoprecipitate. An M-component was detected in the serum agar-gel electrophoresis, in the slow gamma region, which corresponded with an inflexion in the IgM precipitin line on immunoelectrophoresis performed with rabbit antisera specific to human μ-chains. The M-component persisted in sample 6, when cryoprecipitation had already subsided two weeks earlier.

α_1FP was present in all the samples. Anti-α_1FP was shown in sample 2 both by Ouchterlony's diffusion in agarose and by counterelectrophoresis. Detectable amounts persisted for four weeks. Serum complement levels were not determined owing to technical difficulties.

Comment

Acute hepatitis was diagnosed in this patient on the clinical and biochemical findings, and these pointed to serum hepatitis. A transient positive latex fixation test is not surprising, since anti-gammaglobulins and other autoantibodies in sera of patients with hepatic disorders and viral diseases have been widely reported (Capra *et al.*, 1969; Walker and Doniach, 1968). Cryoprecipitates in sera of patients with hepatic injuries, including acute viral hepatitis, are not uncommon. A hepatitis cryoprecipitate containing a monoclonal immunoglobulin has already been found in our laboratory. The coexistence of IgMK and α_1FP suggests the possibility of an immune complex precipitate. Anti-α_1FP activity, however, could not be detected in the isolated cryoglobulin, but this could have been owing to lack of sensitivity in the methods used.

The presence of α_1FP in acute viral hepatitis is rare (Sauger *et al.*, 1971), but we believe that naturally occurring human anti-α_1FP has never been reported before. Since α_1FP is a normal component in the human fetus, the appearance of antibodies with this specificity may be regarded as a loss of tolerance. Thus, according to current postulates (Allison, 1971), acute viral hepatitis could be seen as an illness that may resolve completely when occurring in a normal B/T-cell system or progress towards chronic hepatic disease when surveillance is lost or somehow unbalanced (Mackay, 1968; Sherlock, 1970). The mechanism by which autologous α_1FP behaves as an antigen eliciting autoantibodies could be the bypassing of the T-cell system control caused by the viral aggression. The follow-up of this patient and purification of serum fractions will be of great interest.

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