ACTIVE CHRONIC HEPATITIS: Part 2*

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TREATMENT

THE belief that an immunological mechanism is involved in the chronic inflammatory process in the liver led to the use of corticotrophin and corticosteroid therapy for active chronic hepatitis as early as the 1950's (Waldenström 1950, Bearn, Kunkel and Slater 1956, Mackay, Taft and Cowling, 1956). However disagreement over the indications for treatment, doubts about its real value and concern about possible side-effects continued until the 1960's when gradually a consensus developed in favour of treatment (Page, Condie and Good 1964, Mackay, Weiden and Ungar 1964, Mistilis and Blackburn 1967). In a prospective trial the Copenhagen Study Group for Liver Diseases (1969) analysed the effects of prednisone in a dose of at least 10 mg daily given to 169 patients with cirrhosis and showed that the death rate in female patients without ascites was significantly lower than in the control group. It was assumed that prednisone exercised its beneficial effect in "patients with 'active' cirrhosis particularly at the early stages." This conclusion was confirmed in a second report (1974) on the effect of prednisone in improving the survival of female patients with compensated non-alcoholic cirrhosis. The controlled prospective trial of corticosteroid therapy in active chronic hepatitis by Cook, Mulligan and Sherlock (1971) also clearly showed that corticosteroids were of value in improving life expectancy in the active phase of the disease, during the first two or three years. The realisation that the end result of continuing aggressive hepatitis was almost invariably cirrhosis and that many cases of cryptogenic cirrhosis probably represented the late stage of unrecognised active chronic hepatitis (Sherlock 1974) give hope for long-term benefits from effective treatment.

Criteria for Treatment

Summerfield, Ammon and Baggenstoss (1974) proposed that treatment should be given to patients with—

1. histologically proven subacute hepatitis regardless of clinical or biochemical features,
2. histologically confirmed active chronic hepatitis with "clinically evident and serious deterioration in liver function or with disabling symptoms",

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3. active chronic hepatitis with a continuing 10-week elevation of serum GOT to x 10 normal or above, or x 5 normal in association with serum gamma-globulin x 2 normal,

4. active chronic hepatitis in whom the beneficial results of treatment seemed likely to outweigh its deleterious effects, keeping in mind the potential of relatively mild active chronic hepatitis to deteriorate or progress to cirrhosis.

Sherlock (1975) considers that treatment should probably also be given to patients with histologically proved active chronic hepatitis and a six month history of liver disorder even though symptoms may be absent or mild and biochemical tests only modestly impaired. It seems unlike that Plotz would agree (1975).

In the Liver Clinic at the Royal Victoria Hospital it has been our policy since the early 1960's to treat positively all patients in whom a firm diagnosis of HBsAG negative active chronic hepatitis was made because of the very evident immediate benefits and the subsequent improvement in the quality of life resulting from corticosteroid and corticotrophin therapy.

**Mechanisms of action**

Uncertainty continues as to the relative importance of the differing modes of action of the immunosuppressive drugs corticotrophin, the corticosteroids, azathioprine and 6-mercaptopurine used in the treatment of active chronic hepatitis i.e. their effects on humoral and cellular immunity and any coexisting anti-inflammatory properties. Their intermediate metabolism in the liver is also of considerable importance. In patients with active liver disease the conversion of prednisone to the biologically active corticosteroid prednisolone is known to be impaired (Powell and Axelsen 1972). The fall in serum albumin levels with resulting reduction of prednisolone binding is however responsible for higher plasma levels of unbound circulating prednisolone. Whether in treatment it is preferable to maintain fairly constant levels of unbound steroid in the plasma or to produce very high levels intermittently, for example by the use of alternate day double-dose regimes (Powell and Axelsen 1972) remains a matter for discussion.

The conversion of azathioprine to 6-mercaptopurine, its active metabolite, may be seriously impaired in the presence of parenchymal disease of the liver so that little immunosuppressive activity may be found in the blood. This may well explain the poor results following its use alone in the treatment of active chronic hepatitis (Mistilis and Blackburn 1970, Whelan and Sherlock 1972, Murray-Lyon, Stern and Williams, 1973).

**Schedules of Treatment**

Many different therapeutic programmes using prednisone, prednisolone and azathioprine have been proposed. In that favoured by Mistilis and Blackburn (1970) prednisone was commenced in a dose of 60 mg per day together with azathioprine 25 – 50 mg daily. Over a period of six weeks the daily dose of prednisone was gradually reduced to 10 mg while that of azathioprine was increased
to between 50 and 100 mg. They found it desirable and often possible later to slowly and completely withdraw corticosteroid therapy while continuing to give azathioprine in a daily dose of between 25 and 150 mg. They emphasised the need for flexibility in both drug and dosage schedules, pointing out that patients may require an increase in azathioprine dosage or the addition of steroids to suppress exacerbations of the disease. They recommended that carefully controlled treatment should be continued until the disease was quite inactive.

The Copenhagen Study Group for Liver Diseases recommended the administration of prednisone in a daily dose of 15 – 20 mg for the first few months then, depending upon the needs of the individual patient, gradually reducing to a maintenance dose of little more than 10 mg per day. Male patients with compensated non-alcoholic cirrhosis, when compared with the control group, did not show any significant benefit from treatment and it was recommended that routine treatment of such patients with steroids should not be undertaken but should be the subject of further investigation.

Cook et al (1971) commenced treatment with 15 mg of prednisolone daily and reduced the dose whenever biochemical tests of liver function became normal or if serious side-effects developed. They suggested that corticosteroid therapy should be adjusted, on the basis of serum total globulin and albumin levels, during the first two or three years of the illness and should not be discontinued unless this was made necessary by severe toxic effects, until both serum albumin and total globulin concentrations were within the normal range.

Summerskill et al (1974 and 1975), on the other hand, recommended the use of fixed schedules of daily dosage in preference to “dose titration” upwards or downwards depending upon clinical response, changes in liver function tests, etc. Patients treated with prednisone alone received 60 mg daily for one week, 40 mg daily for one week then 30 mg daily for two weeks before reaching a maintenance dose of 20 mg daily. Patients on the combined treatment programme received azathioprine 50 mg daily together with prednisone 30 mg daily for one week, 20 mg daily for one week, 15 mg daily for two weeks and then a maintenance dose of 10 mg daily. The aim of treatment was a complete remission followed by the gradual withdrawal of both drugs over a six weeks period.

In the Liver Clinic at the Royal Victoria Hospital the initial and maintenance doses of the various agents were determined by the condition of each patient and “dose titration” upwards or downwards was employed. Prednisolone was used in preference to prednisone and the initial daily dose, which varied between 20 and 90 mg, was usually 40 to 45 mg. After two weeks, and provided the response was satisfactory, the dose was reduced to 30 mg daily for one to two weeks, then to 20 mg daily for two weeks and 15 mg daily for approximately four weeks. After further gradual reduction of dosage over a variable period of time a maintenance dose was reached which differed considerably from patient to patient, the range being 2.5 – 20 mg with an average of 7.5 mg per day.

In 1970 treatment with corticotrophin was commenced with the aim of preserving adrenal responsiveness in the hope that when a complete remission of the
disease occurred treatment could then more safely be withdrawn. In addition it was considered likely that the incidence and severity of side-effects would be less than with prednisolone. The plasma cortisol response to corticotrophin stimulation in patients with active chronic hepatitis was found by McCann (1973) to be essentially similar to that in asthmatics in whom injection of 40 units of Acthar gel at 10 p.m. caused a rise in mean plasma cortisol to 46 micrograms/100 ml. at seven hours with return to pre-treatment levels within 24 hours. Random estimations of plasma cortisol levels in patients with active chronic hepatitis receiving treatment with Acthar gel confirmed this pattern. Although no fixed regime of treatment with corticotrophin was used there was a modest degree of uniformity. Most patients received intramuscular injections of Acthar gel between 10 and 11 p.m. on five to seven successive evenings and a number received 40 units morning and evening over this period. Then followed reduction to 40 units on three evenings per week for perhaps two or three months when the dose was further reduced to 40 units twice weekly and this was continued for an average of nine months. Maintenance doses ranged from 20 units once a week to 40 units three times weekly, an average dose being 30 units twice weekly. Patients were shown how to give their own injections and this made possible the late evening administration of Acthar gel to cause maximum adrenocortical stimulation during the normal resting phase of the gland.

Response to Treatment

The effects of corticotrophin and corticosteroids were exactly similar in those patients, the great majority, who responded favourably to such treatment. Within 24 hours fever disappeared and a sense of wellbeing began to replace the malaise which was such a prominent feature in over one-third of the cases. Fatigue gradually lessened and energy returned. With the exception of acne, skin rashes rapidly faded and arthralgia disappeared. Vomiting was quickly controlled, appetite gradually returned and after two or three weeks nausea and abdominal discomfort had gone. Within two or three days of commencing treatment jaundice began to lighten but it took several weeks or months for it to disappear completely. Hepatic tenderness was gone within the first week and usually enlargement of the liver and spleen resolved within seven or eight weeks but a few patients had persistent hepatomegaly and splenomegaly. In three women normal periods were re-established two months, four months and twelve months after the commencement of treatment but in the fourth amenorrhoea continued for the remaining eight years of her life.

Serum albumin was the biochemical parameter showing the earliest return to normal, on average within two to three months, evidence of the stimulus to albumin synthesis caused by corticotrophin and corticosteroids and also of the restoration of liver cell function resulting from effective treatment of the hepatic disorder. It took an average of three to four months for the ESR to return to normal and four to five months for restoration of the serum bilirubin, pseudocholinesterase and alkaline phosphatase levels. In the majority of patients, whether treated with corticosteroids or corticotrophin, the SGOT had returned to the normal range in six months whereas the SGPT took on average nine months. Gammaglobulin levels remained elevated for approximately two years.
The aim of treatment, according to Summerskill et al (1974), is complete remission characterised by absence of symptoms, return to all normal activities, disappearance of chemical and immunochemical abnormalities associated with active chronic hepatitis and resolution of the histological hallmarks of the disease. A persisting elevation of SGOT to less than twice normal is regarded as being consistent with remission, as is the presence of residual or inactive hepatitis characterised by round cell infiltration of the portal tracts with minimal or no hepatic cell necrosis. They point out that these chemical and histological abnormalities are indistinguishable from chronic persistent hepatitis to which a proportion of patients with successfully treated active chronic hepatitis are thought to remit.

In the Royal Victoria Hospital series, unlike that reported by Summerskill et al, histological evidence of remission by serial liver biopsies was not sought partly because of a disinclination to extend the routine use of a painful and invasive procedure and partly because of the known variability in the appearances of different areas of the liver. It was for this reason that Cook et al did not attempt the evaluation of serial biopsies in assessing the effects of corticosteroid therapy in their patients.

Seventeen of our forty patients experienced a complete remission characterised by disappearance of all symptoms, signs and biochemical abnormalities of active chronic hepatitis. This occurred in less than one year in only nine patients, in one to two years in two patients, in two to three years in three patients and in three to four years in two patients, the average overall being 19 months. In nine patients persistent slight elevations of ESR, gammaglobulin, transaminases or alkaline phosphatase indicated that their response fell short of complete remission. Another six patients showed a good clinical response to treatment but improvement of only some of the disturbed liver tests. In seven patients a degree of symptomatic improvement followed the institution of treatment but the clinical and laboratory findings were largely unaffected. These and the one patient in the series who showed no response whatever resemble Summerskill’s “treatment failures” amounting to approximately 20 per cent of all patients. Persistent jaundice or even subclinical elevation of serum bilirubin, continuing very high serum alkaline phosphatase levels and unremitting hypergammaglobulinaemia are the usual indicators of an unresponsive and progressive disorder which almost certainly has already progressed to cirrhosis.

**Complications of Treatment**

Twenty-five of the 40 patients experienced complications, details of which are shown in the Table, but in only seven were they severe (Treadwell et al 1964). Two patients developed vertebral osteoporosis and one of them sustained collapse of several of the vertebral bodies in the lower dorsal and lumbar regions. Pre-existing diabetes was aggravated in two patients and in one of them it was necessary to discontinue treatment with corticotrophin and rely solely on azathioprine. A third patient developed mild persistent diabetes which was readily controlled by diet alone. One of 2 patients with ulcer-type epigastric pain suffered perforation of a chronic duodenal ulcer and required emergency surgery.
Complications of treatment in 40 patients with active chronic hepatitis

| Complication                        | ACTH (22) | Prednisolene (15) | Betamethasone (3) | Total (40) |
|-------------------------------------|-----------|-------------------|-------------------|------------|
| Facial mooning                      | 6         | 8                 | 1                 | 15         |
| Hirsutism                           | 6         | 1                 |                   | 7          |
| Thinning of scalp hair              |           | 2                 |                   | 2          |
| Acne caused or aggravated by treatment | 3   | 4                 |                   | 7          |
| Excessive weight gain               | 2         | 2                 |                   | 4          |
| Hyperglycaemia                      | 5         | 2                 |                   | 7          |
| Persistent                          |           |                   | (1)               |            |
| Transient                           |           |                   | (3)               | (1)        |
| Diabetes worsened                   |           |                   | (2)               |            |
| Bruising                            | 3         |                   |                   | 3          |
| Vertebral osteoporosis              | 1         |                   | 1                 | 2          |
| Muscle aching                       | 4         |                   |                   | 4          |
| Hypertension                        | 1         |                   |                   | 1          |
| Oedema                              | 3         | 3                 |                   | 6          |
| Ascites                             | 2         |                   |                   | 2          |
| Insomnia, tension or hallucinatory state | 1 | 1                 |                   | 2          |
| Dyspepsia                           | 1         | 1                 |                   | 2          |
| Fungus infection                    | 3         |                   |                   | 3          |

The other complications, while of concern to the sufferers, were inconvenient or unsightly rather than dangerous. Patients with chronic liver disease, particularly women, are especially sensitive to corticosteroids and corticotrophin and suffer side-effects more frequently and severely than do patients on similar dosage for other conditions. However withdrawal of treatment because of complications was rarely necessary and we share the view that complications of treatment are far outweighed by its benefits.

Relapses

During the period of follow-up at the Liver Clinic ranging from four months to 13 years 26 of the 40 patients have undergone a total of 58 relapses. Thirty-five of these occurred during the course of treatment with corticotrophin or one of the corticosteroids. Sixteen followed reduction of dosage below that required to maintain complete or stable partial remission. In 4 other instances it was considered that patients had been kept on too low a maintenance dose for some time before symptoms of the relapse developed. Intercurrent infections such as influenza, tonsillitis, otitis media, bronchitis, pneumonia, gastroenteritis and pyelitis appeared to be responsible for precipitating seven relapses though two patients were probably also receiving inadequate maintenance doses of prednisolone. One patient developed a florid lupus erythematosus rash following prolonged exposure to the sun. No cause was found for the remaining seven relapses.
Twenty-three of the 58 relapses occurred at intervals of from one week to several years after treatment with corticotrophin or corticosteroids had ceased. In those instances in which the relapse was probably due solely to premature withdrawal of treatment symptoms commenced within three months in 12 out of 23 and within one year in 19 out of 23. This corresponds to the experience of Sherlock (1974) and Summerskill (1974). In four instances however the relapses occurred 2, 2½, 4 and 12 years after all treatment had stopped. Intercurrent infection, usually involving the respiratory tract, probably played an important part in precipitating four of the 23 relapses while prolonged exposure to sunlight during the long hot summer of 1975 twice caused relapses typical of systemic lupus erythematosus without evidence of liver cell damage.

The great majority of the relapses were purely hepatic in type (44 out of 58). Some of these took the form of an acute illness closely resembling virus hepatitis with fever, sickness, deep jaundice and hepatic enlargement and tenderness. Some were insidious in onset with fatigue, debility, an indifferent appetite, loss of weight and ultimately darkening of the urine and overt jaundice. The remaining six patients with hepatic relapses were all symptomless but were found to have developed appreciable disturbances of their liver tests when they attended the Liver Clinic for routine reassessment.

The symptoms in six of the 58 relapses were characteristic of episodes of systemic lupus erythematosus and included a florid skin rash, polyarthralgia, tachycardia and occasionally pyrexia but there was no disturbance of the liver tests. The remaining eight relapses were of mixed type with skin rash, polyarthralgia and features of active hepatitis.

The inherent tendency to reactivation at any stage during the whole course of active chronic hepatitis is exemplified by the timing of the 58 relapses that occurred in the 26 patients who experienced relapses. Nineteen relapses occurred during the first two years of the illness, 12 between the third and fifth years, 15 between the sixth and tenth years and no less than 12 between the eleventh and sixteenth years. Of the 26 patients who suffered relapses eight did so within the first year of their illness, 15 within the first two years and 21 by the end of the fifth year but for the other five patients their first relapse still lay one to five years ahead.

Response of Relapses to Treatment

Many of the relapses responded quickly to the recommencement or augmentation of corticosteroid or corticotrophin therapy in full dosage but there was inevitably a proportion of treatment failures. Seven of the original twelve patients who had had a complete remission and had subsequently relapsed again achieved a complete remission as a result of a second course of treatment but five failed to do so, though they also became symptom-free and regained reasonable health. Often the only clinical signs during the inactive phase of the disease were mild facial venectasia and slight firm, painless enlargement of the liver. Mistilis and Blackburn (1970) noted that in some patients the only biochemical evidence of liver disease was a slightly reduced serum albumin level and varying degrees of
BSP retention but we would feel that in many there is also a degree of hyper-gammaglobulinaemia and in some a modest increase in SGPT. Relapses occurring later in the course of the disease usually showed an increasingly delayed response to treatment and eventually overt clinical signs of liver cell failure appeared. Many if not all of the patients in the later stages of the disease have cirrhosis and its complications often necessitate hospital admission.

**Mortality**

During the years 1961–1975 eight of the 40 patients with active chronic hepatitis died and four further deaths have occurred during the first six months of 1976. Two patients died during the second year of their illness, one each during the fifth, sixth and seventh years, two during the eighth year and one each during the ninth, twelfth, thirteenth, fourteenth and nineteenth years after the onset of active chronic hepatitis. Six patients with macronodular cirrhosis, portal hypertension and liver cell failure died in hepatic coma which in two patients was precipitated by pneumonia. One patient with macronodular cirrhosis and liver cell failure died of septicaemia. Uncontrollable diabetic ketoacidosis caused the death of a patient with advanced cirrhosis and chronic hepatic encephalopathy. One patient died of pulmonary embolism three weeks after a successful transection of the oesophagus for varices. The other three deaths were due to cerebral thrombosis, coronary thrombosis and acute left ventricular failure respectively.

**Discussion**

Since 1950 the concept of active chronic hepatitis has gained general acceptance and its importance as a major cause of cryptogenic cirrhosis has been recognised. The wide pathological and clinical spectrum of the disease has been established and the conspicuous immunological changes have been noted. Treatment with a variety of immunosuppressive and anti-inflammatory agents has been shown to result in striking symptomatic improvement and restoration to normal of many of the clinical findings and biochemical indices of the liver disorder. Prospective controlled trials have proved that effective treatment results in improvement in both the quality and length of life. In most centres treatment with one of the corticosteroids, usually prednisolone, is commenced in moderately high dosage which is then quickly reduced to maintenance levels and adjusted to the clinical, biochemical and haematological responses of the individual patient. These responses are the criteria usually employed in judging that a satisfactory remission has occurred. Treatment is then continued in the smallest dose that will control the disease process. If troublesome side-effects of treatment arise it may be possible to reduce the dose of prednisolone further by adding azathioprine in low dosage (50 mg per day). Sherlock (1974) recommended that therapy should be continued for six months after the liver tests have returned to normal, then slow withdrawal of prednisolone should be attempted while the patient is closely observed for signs of relapse. Steroid therapy does not induce permanent remission and it is the experience of most centres that even after two or three years' treatment the majority of patients will relapse after it is withdrawn, usually within the first year. Most patients require lifelong treatment (Murray-Lyon and Eddleston 1973).
The discovery that during a complete remission resulting from successful treatment the histological abnormalities of active chronic hepatitis may disappear or revert to those of chronic persistent hepatitis led Summerskill and his colleagues (1974) to adopt a much more aggressive approach to treatment. The use of moderately high fixed maintenance doses of prednisone (20 mg/day) for prolonged periods inevitably caused a higher incidence of serious complications of treatment but this was regarded as an acceptable price to pay for the improved prospects of achieving a complete clinical, biochemical, immunochemical and histological remission. Combined treatment with moderate fixed doses of prednisone (10 mg/day) and low dose azathioprine (50 mg/day) was found to be equally effective with fewer and less severe side-effects. Both of these regimes of treatment caused histological remission significantly more frequently than did prednisone used in the alternate day double-dose regime. In spite of these encouraging results however, relapses following the gradual withdrawal of treatment still occurred in approximately 50 per cent of patients.

Treatment with corticotrophin has proved very satisfactory and despite the fact that patients have been receiving or giving themselves injections regularly for long periods there has been no patient resistance to the treatment. Fewer serious complications occurred in the group of patients treated with corticotrophin than in those receiving corticosteroids and the presence of a fully responsive adrenal cortex is reassuring. Ultimately the treatment of choice will be that which, without causing an unacceptably high incidence of serious side-effects, offers the best hope of preventing or delaying the development of cirrhosis.

**Summary**

The responses of 40 patients with HB\(^5\)AG negative active chronic hepatitis to treatment with corticosteroids, mainly prednisolone, or corticotrophin have been observed and evaluated at the Liver Clinic over a period of from four months to 13 years. In the great majority marked symptomatic improvement and disappearance or modification of the clinical features of active hepatitis occurred together with biochemical evidence of decreased liver cell necrosis, increased excretory capacity and improved synthetic function. The responses to corticotrophin and corticosteroids were indistinguishable except for differences in side-effects. Seventeen of the patients underwent complete remission, and in another fifteen patients remission, though incomplete, was clinically satisfactory. Numerous relapses occurred both while treatment was being given and throughout the years following its withdrawal.

The intensity of continuing liver cell damage is greatest during periods of activity of the disease with consequent encroachment on hepatic functional reserve and increasingly severe architectural distortion resulting in cirrhosis and the development of portal hypertension. Having established a firm diagnosis therefore the principal aim of management must be to attempt with effective treatment to promote a complete remission as quickly as possible then, by careful review and reassessment, to foretell and forestall any subsequent tendency to relapse. Prolonged treatment is essential and only after all clinical, biochemical and haematological features have returned to normal should its very gradual withdrawal be
contemplated. Further relapse calls for recommencement of treatment in full dosage and there is a strong case for lifelong therapy unless the most stringent criteria for complete remission including serial liver biopsies are adopted.

Among the most effective regimes of treatment available at present are prednisolone and the combination of prednisolone and low dosage azathioprine, the latter having the advantage of fewer and less severe side-effects. It is anticipated that combined treatment with Acthar gel and low dosage azathioprine would be equally effective and may have an even lower incidence of side-effects while also preserving adrenal responsiveness. The ultimate choice will depend at least partly on the personality and constitution of the patient, the presence of other diseases such as severe diabetes, hypertension, duodenal ulcer and major psychiatric illness and also on the availability and cost of corticotrophin.

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