THE TREATMENT OF HEPATITIS
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The treatment of chronic hepatitis is among the most current and attractive problems connected with hepatology, thanks to the fact that chronic hepatitis is probably the only affliction of the liver that can be favourably influenced by the properly directed use of medicaments. While only a short time ago, due to the lack of therapeutic means, the illness took its fateful course, the application of cortisone derivatives and immuno-suppressives led to a decisive turning point. The prerequisite for successful therapy with these medicaments is, on the one hand, a precise diagnosis, meaning an accurate definition of the form of hepatitis to be treated and, on the other, the determination of degree of activity of the illness. In view of the innumerable different forms of chronic hepatitis, a confusin picture emerges in the clinic. The following summary shows the essential forms encountered in practice.

1. HBs-Ag positive chronic active hepatitis 54%
2. HBs-Ag negative chronic active hepatitis ("lupoid") with immunological features 32%
3. HBs-Ag negative chronic active hepatitis (non defined form) 14%

The frequency of distribution of the individual forms can also be derived from the summary.

As far as the degree of activity in the treatment is concerned, a clear line of distinction must be drawn between chronic active hepatitis and chronic persistent hepatitis. Only the active form requires specific therapy.

In the case of chronic active hepatitis the following therapeutic principles enter into consideration:

1. Mono-therapy with cortisone
2. Mono-therapy with azathioprine
3. Combinational therapy: cortisone + azathioprine
4. Mono or combinational therapy with chloroquine
5. Mono-therapy with D-penicillamine
6. Therapy with interferon

I will first talk about mono-therapy with cortisones. The favourable effect of cortisones is substantiated scientifically by a number of studies.

In 1964 we were able to show statistically that the results of longterm treatment with prednisolone over an extended period are better than a shock treatment lasting only a few weeks.

In 1971 Cook at al. reported a significantly lower mortality rate coupled with a marked increase in the tendency of the bilirubin, IgG and albumin to return to normal values when using a long-term treatment with 15mg prednisolone. 86% of patients treated with prednisolone survived for more than two years while 66% of the untreated patients in the control group died in the same period.

In 1972 the Mayo-Clinic (Soloway et al.) presented a survey in which a comparison of biochemical and histological parameters showed a statistically substantiated improvement of the group treated with cortisone as against the control group. The period of survival was significantly extended.

I will now report on our own observations and results with cortisone therapy.

In the following Table 1 the results of cases treated by us between 1966 and 1975 are summarised. You can see, that we have separated the HBs-Ag positive from the HBs-Ag negative cases. The HBsAg negative group includes 32 cases of so-called lupoid hepatitis. The results were obtained on the basis of all biochemical parameters as well as the biopsic findings.

The statistical evaluation of our overall results permits the significant statement that the HBs-Ag
negative cases with hypergammaglobulinemia and immunological signs, in other words the cases of so-called lupoid hepatitis, are substantially more influenced by glucocorticoids than the HBs-Ag positive cases, as you can see in the next slide, where in the both upper rows the HBs-Ag positive patients are compared to the patients suffering from a lupoid hepatitis. In recent months this has also been repeatedly established in the U.S.. The average period of treatment of all our cases together was three years and 91 days, with a deviation from 18 months to 9 years. The average treatment doses ranged between 6g and 56.6g.

The next Table 2 shows the initial doses used. It can be seen that these are 60 or 50 mg in most cases. On the other hand, we even began in some cases with 15 mg and, in contrast, in others with 100 mg. In statistically evaluating the findings it appears to be of great significance that the best results were obtained in cases receiving in initial dose of 60 mg or 50 mg.

The next Table 3 shows the maintenance dose determined which, on occasion, was continued for several years. The lowest maintenance dose was 10 mg, the highest was 30 mg in four cases. Most frequently, in around a third of all cases, it was 15 mg, and in almost half of all cases it was 12 or 15 mg, as can be seen. Differences in the results of treatment, which were best with a maintenance dose of 15 mg, could not be statistically substantiated.

Based on our results the following guidelines for the treatment of chronic hepatitis emerge. The
indication give rise to cortisone therapy has to be effected with the utmost precision. The use of cortisone can only be justified in cases where the risks involved in this therapy can be considered as being less than those involved in the spontaneous course of a chronic active hepatitis. The clinical picture, the biochemical parameters, in particular GOT, GPT and gammaglobulin, and under certain conditions the immunological phenomena and the histological findings, must unambiguously demonstrate a chronic active hepatitis.

Of the cortisone derivatives we use only prednisolone. In the matter of dosage there are in principle two different approaches. One can either commence with a high dose which is then reduced in small steps along with the clinical improvement down to the maintenance dose, or one begins with a low dose which is the actual maintenance dose planned. “Maintenance dose” means the lowest possible quantity at which, under good clinical condition, the biochemical parameters continue to show a tendency to become normal and, from the histological viewpoint, the signs of activity are either in the process of reduction or have disappeared. We normally begin with 60 mg prednisolone. This initial dose is given for 3-6 days. After this we reduce in steps of 5-10 mg, in accord with the decrease of transaminases. When a dose of 25 mg is reached we reduce in steps of 2 mg until the maintenance dose is arrived at. The reduction in small steps is of such vital importance because, sometimes, the difference of 1-2 mg determinates whether or not a process is reactivated or continues to decline. Each case has its typical maintenance dose which is usually between 10 and 25 mg.

The maintenance dose must be continued until all of the parameters used for assessment clearly indicate that the inflammation process has been eliminated or at least has become steady. This is mostly the case only after a number of years, and seldom after treatment lasting less than two years. For this reason most authors hold the view that cortisone treatment must as a rule last for at least two years. This is following by the “slinking out”. A process of long duration which is best accomplished by reducing the dose by 1 mg, and at most 2 mg every 2-4 weeks. The biochemical parameters, in particular the transaminases and gammaglobulins, need to be continuously monitored. If these again rise, the “slinking out” must be stopped and the prednisolone dose again increased. A properly managed “slinking out” process is vital for the success of the treatment.

The criticism directed at cortisone therapy sheds light on the problems involved in it. The following are the points under discussion:

1. The view is widely held that the results obtained with cortisone therapy are not better than when chronic active hepatitis is allowed to take its spontaneous course, particularly in cases which are HBs-Ag positive. Against this it might be countered that controlled investigations have proven clearly that, in terms of survival, those treated come out markedly better. It should, however, be noted that no differentiation was made in the controlled surveys between HBsAg positive and HBs-Ag negative cases, or that the number of HBs-Ag negative patients dominated in a high degree at least in the report by the Mayo-Clinic and bei Williams.

It is therefore wholly thinkable that the longer period of survival of the cortisone group as a whole is due to the favourable results of the HBs-Ag negative cases contained in it. This assumption suggest itself in the light of our statistical returns an the reported observations in the U.S., according to which the HBs-Ag negative cases as well as those with immunological signs are significantly more strongly influenced than are the HBs-Ag positive cases.

2. On the next Table 4 our total collective -first row- has been separated into two groups: patients with lupoid hepatitis -second row- and patients without lupoid hepatitis -third row. As already discussed, you can easily recognize, that the patients with lupoid hepatitis show the best results significantly, whereas on the opposite the most unfavourable results are achieved within the group
Table 4. Chronic active hepatitis

Results of long term therapy with prednisolone (100 patients)

<table>
<thead>
<tr>
<th>No.</th>
<th>in remission</th>
<th>in remission and improved</th>
<th>unchanged and impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Total collective</td>
<td>100</td>
<td>38 %</td>
</tr>
<tr>
<td>II</td>
<td>Lupoid hepatitis</td>
<td>32</td>
<td>59 %</td>
</tr>
<tr>
<td>I - II</td>
<td>68</td>
<td>28 %</td>
<td>66 %</td>
</tr>
</tbody>
</table>

of patients, where lupoid hepatitis has been excluded.

Furthermore, the fact should be considered that the treatment of HBs-Ag positive cases produce HBs-Ag persistence and hence to the carrier condition, that means the already questionable success of this therapy is affected by initiation of the carrier condition. This is all the more serious when taking into account that in a number of HBs-Ag positive cases, even without treatment, HBs-Ag can no longer be detected in the blood after a sufficient lapse of time and that the course of the illness the spontaneously and gradually turns into a chronic persistent hepatitis. This possibility of a spontaneous favourable development might even be eliminated by administering cortisone. Fro this reason many authors today hold the view that the indication for mono-therapy with cortisone is only substantiated in HBs-Ag negative cases. With immunological features the indication for treatment of the HBs-Ag positive cases with cortisone mono-therapy, however, still to be regarded as controversial and by no means ultimately substantiated. A fundamental problem is posed by the further question as to whether the transition into hepatic cirrhosis can be prevented by cortisone therapy. In this regard there are up to now no reliable studies that even approximately would make an assessment of this problem possible.

3. A third point of criticism is the frequency with which relapses occur. The quota of relapses involved in discontinuation tests is high. In a study made by Mistilis only 30% remained in remission when cortisone treatment was discontinued. On the other hand in roughly half of the cases maintained remission was dependent on continued cortisone doses, which were administered for up to eight years. In practice, relapses occur when nor account is taken of this fact and the guidelines applied in setting the dosage are not adjusted in this behaviour.

The following are the most frequent mistakes made: the initial dose is reduced after too short a period of treatment and/or in steps which are too large; the maintenance dose is discontinued after too short a period “slink out” on discontinuing the treatment. Our relapse quota for the year 1955 to 1966 was 18.3%. In the ensuing years, from 1966 to 1975, when we had learned more about countering the relapse danger, the quota fell to 6.6%. Objections based on the frequency of relapses must therefore be largely rejected relapses mostly occur as a result of faulty treatment.

4. Another objection concerns the side effects of account of which it is thought, it is not possible to give the doses for as long a period as is necessary. The reply to this is that there are certainly unavoidable side effects, but that the risk of their occurrence can be reduced by taking specific precautionary measures and keeping a careful watch on the patient.

The majority of authors hold the view that the side effects, when compared to the increase in life expectancy arising form cortisone therapy, have scarcely any weight at all.
Treatment with azathioprine was introduced by Mackey in 1964. The functional mechanism is presumed to be immuno-suppressive. Controlled surveys taking account of the survival period are not available. German authors found out that azathioprine has a favourable influence of chronic active hepatitis. Against this it was demonstrated in a study by the Mayo-group (Baggenstoss et al.) that azathioprine is not superior to a placebo. Prednisone and a combination of prednisone and azathioprine were more successful than azathioprine alone and placebo therapy. However there is no doubt that after taking azathioprine a decrease in the transaminase activity and often also an improvement in the hypergammaglobulinemia come about. Opinions differ with respect to the influence on the histological process. The observation of improvements is countered by observations indicating no positive influence.

Moreover, the value of the treatment is limited by very often grave, an sometimes menacing side effects. In my view the domain of therapy with azathioprine lies in using it in combination with glucocorticoids.

The latter combination has proven to be succesful in many cases. It offers the advantage that effects can be obtained with small single doses of both pharmaceuticals together which would only come about with substantially higher doses of one of them alone. In this combination azathioprine has a "cortisone-saving" effect. The Mayo-Clinics controlled survey of 120 patients has shown that 50 mg azathioprine + 10 mg prednisolone produced the same good results as 20 mg prednisolone alone (see Table 5).

In general we proceed in such a way that we first try prednisolone alone. If the desired effect can be obtained only with relatively high doses of prednisolone, so that the maintenance dose is considerably more than 20 mg, we add azathioprine. Then it is often possible to keep the maintenance dose for both substances at a very low level. The combinational treatment is particularly suitable for HBs-Ag positive cases, since -as I said at the outset- the latter respond far less readily to cortisone than the immunologically characterised HBs-Ag negative cases.

Treatment with D-Penicillamine was introduced in Germany some years ago. D-penicillamine has an immuno-suppressive and Cu-mobilising effect. In addition it is impeding collagenisation. Several authors report astonish effects. Others, myself included, noted neither a positive effect nor a deterioration. Moreover, the side effects of the substance are very serious. For this reason I hold the view that D-penicillamine is not to be recommended for the treatment of chronic active hepatitis unless and until thoroughly controlled studies are available.

With chloroquine, whose action is similar to that of cortisone and whose effects can be proven by the discontinuation test, astonishing improvements can be obtained, both alone and also in combination with cortisone, as is shown by the following slide.

The first well-founded results with interferon were reported by Robinson 10 weeks ago at a symposium in Bethesda in the U.S.. This substance is formed by a virus-infected host cell and quite generally inhibits virus infections of cells. Robinson reported that in a series of cases the hepatitis-B-markers were eliminated and that the hepatitis progress stopped. In some cases, however, the HBsAg reappeared later. This might possibly open up a new way, and it remains to be seen whether or not this new mode directed directly against the HBs-Ag is the prelude.
to a new phase in the struggle against chronic hepatitis in the form of a new therapeutic principle.

Summary

The influencing of chronic active hepatitis by means of cortisone is, thanks to the significant extension of the period of survival, scientifically substantiated.

The so-called lupoid hepatitis is thereby significantly more favourably influenced than is HBs-Ag positive chronic hepatitis.

Azathioprine has the effect of reducing the cortisone dose, for which reason the combination cortisone + azathioprine is today most commonly applied in the treatment of HBs-Ag positive chronic hepatitis. The results obtained to date by this approach are encouraging. Further studies over an extended period are necessary in order to be in a position to form a well-founded assessment of this mode of treatment.