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Management of Steatorrhoea of Cirrhosis of the Liver by an Indigenous Drug — Liv.52

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Our own study (Patney *et al.,* 1974) and several studies in the past (Fast *et al.,* 1959; Baraona *et al.,* 1962; Von Goidrenhoven *et al*., 1963 and Sun *et al.,* 1967) have amply confirmed that fat malabsorption occurs in 50-70% of cases of cirrhosis of the liver. The presence of steatorrhoea increases the malnutrition already present in these cases consequent to hepatocellular damage. The genesis of steatorrhoea in this condition however remains obscure although abnormal bacterial flora (Gorbach, 1971) and subnormal intraluminal concentration of conjugated bile salts causing impaired micellar lipid incorporation (Badley and Murphy, 1970) have been more recently blamed for its causation. The management of this condition has remained unsatisfactory. A correlation between the absorption function of the gut and hepatic function have been demonstrated (Siurala *et al.,* 1960; Summerskill and Mortel *et al.,* 1962).

Liv.52, an indigenous drug, is claimed to have a protective and regenerative effect on the hepatic parenchyma, to be a stomachic and a choleretic, with a salutary effect on liver glycogen and serum proteins along with diuretic and anabolic actions. In view of these, its easy availability and cheap cost, it was considered worthwhile to investigate Liv.52 in the management of this crippling complication of portal cirrhosis.

MATERIAL AND METHODS

A total of 72 cases of hepatic cirrhosis were investigated for the presence of steatorrhoea and out of these, 50 cases showed the evidence of its presence. The cases were taken for the study from the S.N. Hospital, Agra.

A detailed history was taken and clinical examination was done. Diagnosis was based on liver function tests and was confirmed in 23 cases by liver biopsy.

The following investigations were carried out in each case:

1. Complete haemogram — which included haemoglobin levels, total and differential leucocytic count, erythrocytic sedimentation rate, general blood picture, red blood cell count, packed cell volume and absolute values e.g. mean corpuscular haemoglobin (M.C.H.); mean corpuscular haemoglobin concentration (M.C.H.C.) and mean corpuscular volume (M.C.V.).
2. Liver function tests — consisted of serum bilirubin, serum proteins, albumin/globulin ratio, serum alkaline phosphatase, Van den Bergh reaction, thymol turbidity and flocculation, zinc sulphate turbidity and prothrombin time. All these tests were done using standard techniques (Varley 1969).
3. Ascitic fluid — was examined for total and differential cell count and protein content. The study included only those cases whose ascitic fluid was transudate on this examination.
4. Stool examination — was done for ova and cyst in each case.
5. X-ray abdomen — was done in each case to know the pancreatic calcification.
6. Liver biopsy — done by Van Silverman needle in 23 cases. It was successful in all at the first attempt.

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7. 3-days faecal fat estimation — was done after keeping the patients on a standard diet containing 75 g fat/24 hours at least 5 days before the test. Total faecal fats were estimated on 3 days' collection of stool by wet method of Vandekamer (1949).

Allocation of trial treatment with Liv.52

Treatment with Liv.52 was allotted on random basis to the cases of cirrhosis with steatorrhoea using random sampling tables.

The haematological examination and liver function tests were repeated after every 15 days and faecal fat estimation was repeated after a 30 days course of Liv.52 tablets in doses of 2 tablets three times a day.

OBSERVATIONS

Out of 72 cases studied for faecal fat excretion, 50 cases of hepatic cirrhosis had steatorrhoea. They showed a total faecal fat excretion of more than 6 g/24 hours. The incidence of steatorrhoea in cirrhosis, in this series was, therefore, 71.4%.

Out of 50 cirrhotic cases with steatorrhoea, 33 were males and 17 females. Their ages ranged from 17 to 60 years. Thirty out of the 50 cases were kept on Liv.52 tablets plus usual supportive treatment for a total period of 30 days and the remaining 20 cases were kept on the usual supportive therapy without Liv.52 and they served as controls.

Results of liver biopsy

In the test group (30 cases) 23 biopsies were done, out of which 18 showed the changes of post-necrotic cirrhosis and 5 showed the changes of diffused hepatic fibrosis (Figs. 1 and 2).

Results of the haematological examination

This study showed that there were significant improvements in haematological findings in both test groups (30 cases) receiving Liv.52 tablets with other supportive treatment and control group (20 cases) without Liv.52 only supportive treatments shown in tables 1A and 1B. The rate of improvement in haemoglobin levels is better in the test group (8.1 ± 3.01 to 11.64 ± 1.63 g%) in comparison to the control group i.e. (7.80 ± 2.12 to 10.73 ± 1.66 g%). (Fig 3).

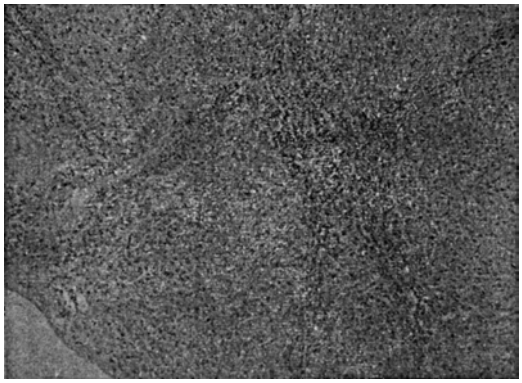

Fig. 1: Shows an area of fibrosis with normal architecture in the adjoining areas indicative of post-necrotic fibrosis.

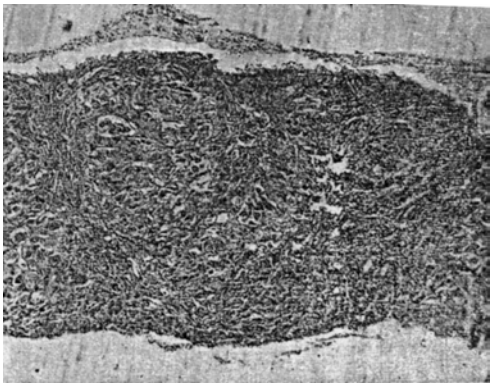

Fig. 2: Shows perilobular fibrosis with stand of fibrosis tissue spreading into the lobule – diffuse hepatic fibrosis.

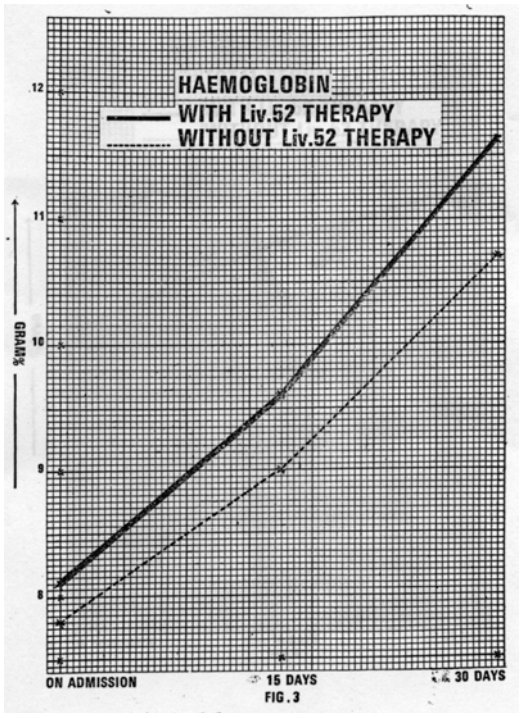

FIG. 3

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Table 1A: Mean results of haematological examination in 30 cases of hepatic cirrhosis before and after Liv.52 therapy									
Timing	Mean and S.D.	Hb (g%)	RBC mill/cmm	PCV (%)	TLC Cells/cmm	E.S.R.(mm)	M.C.V. (cu..mcrmol)	M.C.H. (Picogram)	M.C.H.C. %
On Adm.	Mean ± S.D.	8.1 ± 3.01	2.9 ± 1.20	27.73 ± 11.01	7780 ± 2.43	49.5 ± 15.34	92.6 ± 13.68	27.4 ± 15.90	28.95 ± 5.04
15 days	Mean ± S.D.	9.6 ± 1.90	3.3 ± 0.84	30.0 ± 5.04	9030 ± 1.87	36.6 ± 14.02	89.04 ± 5.96	28.59 ± 2.08	32.06 ± 1.73
30 days	Mean ± S.D.	11.64 ± 1.63	3.9 ± 0.78	35.00 ± 4.12	8950 ± 1.76	26.9 ± 11.32	89.06 ± 4.29	29.42 ± 0.92	32.8 ± 1.88

Table 1B: Mean results of haematological examination in 20 control cases of hepatic cirrhosis without Liv.52 therapy									
Timing	Mean and S.D.	Hb (g%)	RBC mill/cmm	PCV (%)	TLC Cells/cmm	E.S.R.(mm)	M.C.V. (cu.micrmol)	M.C.H. (Picogram)	M.C.H.C. %
On Adm.	Mean ± S.D.	7.80 ± 2.12	2.38 ± 0.73	19.25 ± 6.13	8660 ± 3.13	45.00 ± 13.9	80.4 ± 20.34	25.76 ± 3.37	30.12 ± 2.09
15 days	Mean ± S.D.	9.00 ± 1.66	3.06 ± 0.57	26.35 ± 5.34	8320 ± 1.41	35.25± 10.7	86.05 ± 6.37	26.03 ± 10.61	32.81 ± 0.99
30 days	Mean ± S.D.	10.73 ± 1.66	3.69 ± 0.47	33.45 ± 4.91	8450 ± 1.37	25.20 ± 7.4	88.62 ± 12.93	28.60 ± 1.49	32.67 ± 1.52

Results of liver function tests

On surveying the mean results of liver function tests in the Liv.52 group (30 cases) and control group (20 cases) in tables II A and II B there was marked improvement in test group on Liv.52 as compared to the control group. There was rise in the levels of total serum proteins (6.27 ± 1.11 g% to 6.87 ± 2.24 g%). Serum albumin (2.37 ± 0.66 g% to 2.83 ± 0.85 g%). Besides this, there was a fall in serum globulin levels (3.90 ± 1.72 g% to 3.30 ± 0.4 g%) and zinc sulphate turbidity (17.3 ± 1.60 to 11.1 ± 8.13 units) which clearly indicates that patients of the group on Liv.52 tablets showed a good response.

Table IIA: Mean results of liver function tests in hepatic cirrhosis before and after Liv.52 therapy in 30 cases									
Timing	Mean and S.D.	Serum Bilirubin (mg%)	Serum proteins (g%)			Serum Alk. Phosp. Units	Prothrombin time	Thymol turbidity (units)	Thymol flocculation	Zinc sulphate turbidity units
			Total	Albumin	Globulin					
On Adm.	Mean ± S.D.	1.34 ± 1.35	6.27 ± 1.11	2.37 ± 0.66	3.90 ± 1.72	20.83 ± 6.55	21.28 ± 4.23	5.9 ± 1.49	1.5 ± 0.56	17.3 ± 1.60
15 days	Mean ± S.D.	1.24 ± 0.80	6.65 ± 0.63	2.57 ± 0.64	3.88 ± 0.48	19.29 ± 5.50	19.73 ± 3.13	5.5 ± 1.62	1.5 ± 0.57	14.10 ± 4.81
30 days	Mean ± S.D.	1.09 ± 0.32	6.87 ± 2.24	2.83 ± 0.85	3.30 ± 0.49	17.58 ± 7.34	19.26 ± 2.15	5.2 ± 2.33	1.7 ± 0.99	11.1 ± 8.13

Table IIB: Mean results of liver function tests in 20 cases of hepatic cirrhosis in control subjects without Liv.52 therapy									
Timing	Mean and S.D.	Serum Bilirubin (mg%)	Serum proteins (g%)			Serum Alk. Phosp. Units	Prothrombin time	Thymol turbidity (units)	Thymol flocculation	Zinc sulphate turbidity units
			Total	Albumin	Globulin					
On Adm.	Mean ± S.D.	1.11 ± 0.31	6.33 ± 0.49	2.37 ± 0.69	3.96 ± 0.38	19.09 ± 5.18	20.05 ± 2.93	6.65 ± 2.61	1.72 ± 0.83	17.85 ± 4.30
15 days	Mean ± S.D.	1.02 ± 0.19	6.53 ± 1.10	2.48 ± 0.71	4.05 ± 0.58	19.40 ± 4.07	19.17 ± 2.28	6.75 ± 2.46	1.59 ± 0.59	14.55 ± 7.45
30 days	Mean ± S.D.	1.00 ± 0.23	6.50 ± 2.04	2.46 ± 0.83	4.04 ± 0.63	17.10 ± 3.59	18.94 ± 2.38	4.90 ± 4.13	1.75 ± 0.74	13.9 ± 2.56

The control group of 20 cases who were not on Liv.52 tablets showed some improvement in liver function tests. There was a rise in the total serum proteins (6.33 ± 0.49 to 6.5 ± 2.04 g%); serum albumin (2.37 ± 0.69 to 2.46 ± 0.83 g%); and also in serum globulin (3.96 ± 0.38 to 4.04 ± 0.63 g%). The increase in serum globulin was in contrast to the Liv.52 group where a fall was observed. There was a fall in zinc sulphate turbidity, too (17.85 ± 4.30 to 13.9 ± 2.56 units). The improvements however, were not to the same extent as in the Liv.52 group. (Figs. 4 to 7).

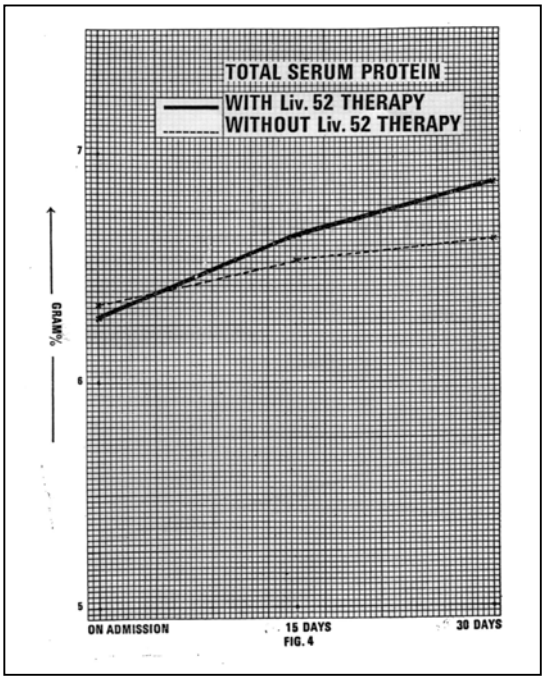

FIG. 4

Results of 3 days faecal fat estimation

By comparing tables III A and III B, it is evident that the Liv.52 group (test group of 30 cases) showed a very marked improved in their faecal fat excretion test. Their

fat excretion level came to normal i.e. from 10.75 g ± 4.12 to 6.36 g ± 1.24/24 hours.

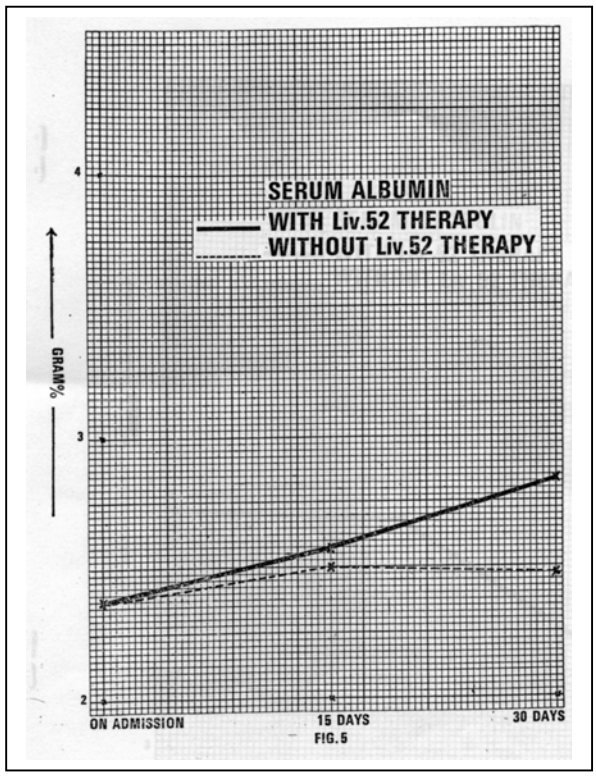

FIG.5

The 24 hours faecal fat excretion in the control group (20 cases) showed a very slight improvement in comparison to the test group on Liv.52 i.e. only 9.71 g ± 2.59 to 8.00 g ± 1.75 g/24 hours as shown in figure 8.

DISCUSSION

The present study had been undertaken to evaluate the role of Liv.52 in the management of steatorrhoea of cirrhosis of the liver. Several studies have now been done which have clearly demonstrated its beneficial and regenerative role on the liver parenchyma in portal cirrhosis (Patney *et al.,* 1973; Gupta *et al.,* 1972 and Prasad, 1974). Prasad has shown the effect of Liv.52 on regeneration of liver cells in tissue culture. He demonstrated that an explant from a cirrhotic liver grown in an organic culture containing Liv.52 exhibited regeneration of parenchyma cells with well maintained haemopoietic factors in addition to some division of cells. Thus Liv.52 stimulates mitotic activity of cells and so stimulates the liver cell regeneration and would thus correct all the secondary abnormalities consequent to liver parenchymal necrosis and degeneration.

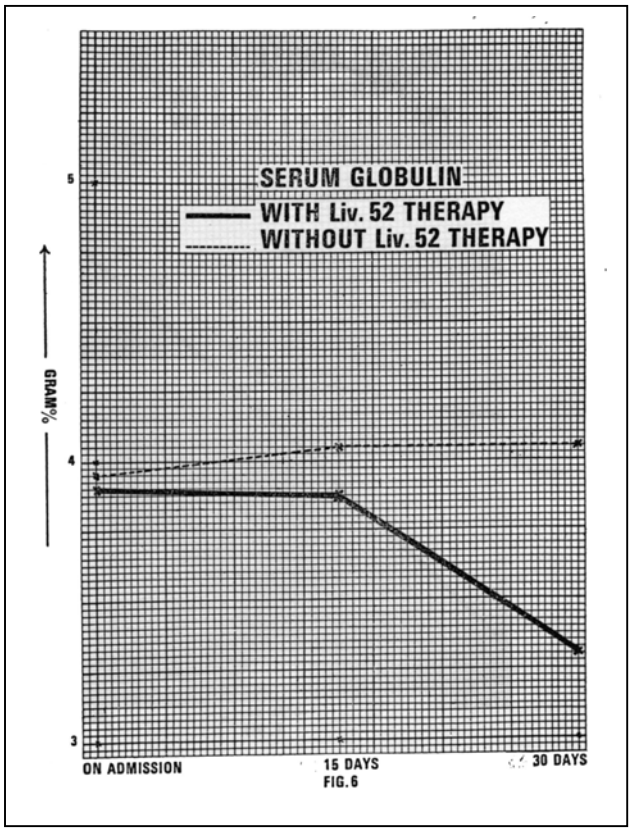

FIG.6

The genesis of steatorrhoea is still somewhat controversial. The possible mechanisms include (1) Malnutrition secondary to liver disease causing malfunction in the small intestine (Losowsky *et al.,* 1969). (2) Insufficient bile salt production to active normal micelle formation, necessary for the absorption of fat and fat-soluble substances (Badley *et al.,* 1970). (3) Presence of abnormal bacterial flora in the small intestine (Correia *et al.,* 1970). Several other explanations including a common underlying cause for both liver disease and malabsorption (Sobel and Wayne, 1963) liver disease — secondary to malabsorption, structural and functional change in the small intestine (Astaldi and Strosselli, 1960) portal hypertension (Gross *et al.,* 1950) pancreatic abnormality (Stinson, 1962) have not stood the test of time and are now not regarded as important contributory factors in its genesis (Losowsky 1969). The present findings of steatorrhoea in nearly 70% cases of cirrhosis of the liver is in keeping with several reports (Fast *et al.,* 1959; Baraona *et al.,* 1962; Sun *et al.,* 1967 and Von Goidrenhoven *et al.,* 1963), and confirms the general impression that steatorrhoea is a common complication of portal cirrhosis.

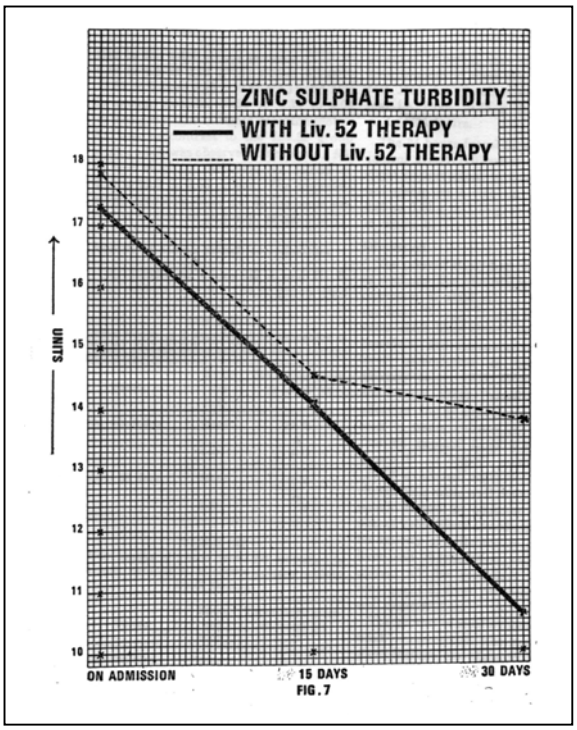

FIG. 7

The treatment of this complication of steatorrhoea in cirrhosis of the liver has been an unsatisfactory as that of portal cirrhosis itself but with the advent of Liv.52 therapy there is some enthusiasm in its treatment in view of its therapeutic actions as mentioned above.

In the present series 30 out of 50 cases of cirrhosis showing steatorrhoea were treated with Liv.52 two tablets thrice a day along with the usual treatment. Results have been compared with another 20 cases, who were treated only with usual supportive therapy. In all these cases the haematological examination and liver function test and faecal fat estimation were done on admission and repeated after 15 and 30 days of therapy.

The haematological picture in both these groups improved remarkably and it was because both of these were getting haematinics and a good diet but a perusal of figure 3 shows that patients on Liv.52 have an edge over the patients without Liv.52. The liver function tests showed improvement in both the groups but here again the test group on Liv.52 therapy showed a bigger margin of improvement. Mean serum albumin levels attained a higher figure and zinc sulphate turbidity showed a significant decrease in these as compared to control groups receiving only supportive therapy. (Figs. 4 & 6).

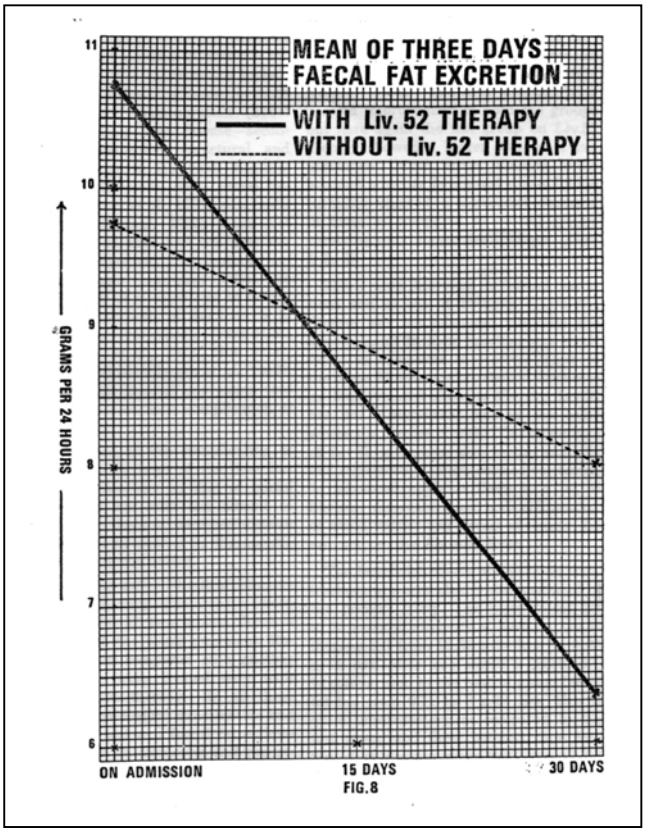

FIG. 8

There were however individual variations and 20 out of 30 cases where the disease was not advanced clinically the improvement in liver function was significant as compared to controls while in the other 10 advanced cirrhotics there was no improvement showing thereby Liv.52 has got a significant role in the cases where the disease is early. This advantage of Liv.52 is perhaps due to the anabolic and regenerative effects on the liver tissue. In advanced cirrhosis there is a lot of fibrosis, disorganisation and obliteration of blood vessels and Liv.52 obviously did not act on the fibrosed liver.

The beneficial effects of Liv.52 on steatorrhoea are very clearly demonstrated in the present study. The mean faecal fat in 30 cases of cirrhosis of liver on Liv.52 therapy fell from 10.72 g/24 hrs. to 6.36 g/24 hrs. after one month's treatment. In comparison, in the control group faecal fat fell from 9.71 to 8 g/24 hrs. This is quite unsatisfactory as compared to the test group and these patients thus continued to excrete more than normal fat with all its consequent results. When analysing

individual cases the difference is still more marked. While 20 out of 30 cases were cured of steatorrhoea in the test group on Liv.52; only 4 out of 20 in the control group returned to normal faecal fat excretion.

The present study thus, clearly demonstrates the significant beneficial effects of Liv.52 on liver functions and steatorrhoea of hepatic cirrhosis. How it reverses the steatorrhoea of liver cirrhosis, can only be theorised. The improvement in steatorrhoea in these cases of hepatic cirrhosis after Liv.52 is likely due to the anabolic and regenerating effects of Liv.52 on the hepatic cells and it also stimulates the secretion of bile salts from these cells, thereby increasing the concentration of conjugated bile salts in the intestinal lumen which are deficient in these cases of cirrhosis (Badley *et al.*, 1970) and thus more lipid micelle are formed and the absorption of fats improves.

SUMMARY

Out of a total of 72 cases of portal cirrhosis, 50 had evidence of fat malabsorption giving an incidence of steatorrhoea at 71.4%. A review of the modern literature showed wide lacunae in the genesis of steatorrhoea in cirrhosis of the liver. Its management, consequently, remains unsatisfactory.

Liv.52, in view of its anabolic, choleretic and stimulatory action on the regeneration of hepatic parenchyma was taken up for trial, by random allocation, for the management of steatorrhoea of cirrhosis of the liver. Out of the above, 30 cases were treated with 2 tablets Liv.52 t.i.d. with usual supportive treatment (Study group). The remaining 20 cases were kept on usual supportive therapy without Liv.52 (Control group) for a total period of 30 days. All these patients had complete haemogram, liver function test, and total faecal fat excretion estimation before the beginning of this treatment and 15 and 30 days after the treatment.

Mean haemoglobin levels in the study group improved from 8.1 ± 3.01 g% to 11.64 ± 1.63 g% as compared to the control group where it increased from 7.80 ± 2.12 to 10.73 ± 1.66 g%. The rate of this improvement is better in the study group. A survey of mean results of liver function tests also showed a marked improvement in the Liv.52 group as compared to controls.

In the Liv.52 group serum albumin rose from 2.37 ± 0.6 g% to 2.83 ± 0.85 g% and zinc sulphate turbidity fell from 7.3 ± 1.6 to 11.1 ± 1.83 units as compared to controls (serum albumin 2.37 ± 0.69 to 2.46 ± 0.83 g% and Zinc sulphate turbidity 7.85 ± 4.3 to 13.9 ± 2.56 units. The results are even more significant when comparing the effect of Liv.52 on faecal fat excretion. In the study group on Liv.52, the faecal fat excretion fell from 10.75 g ± 4.12 to 6.36 ± 1.24 g/24 hours as compared to the control group (9.71 g ± 2.59 to 8.0 g ± 1.75 g/24 hours). While 66.60% of the study group were cured of steatorrhoea, only 20% of the control group showed return to normal faecal fat excretion.

The mechanism of action of Liv.52 in this condition has been discussed.

CONCLUSION

Liv.52 is an effective agent in the management of steatorrhoea of cirrhosis of the liver curing nearly 2/3rd of the cases. In the rest when the disease is far advanced its beneficial effects are limited because of extensive, irreversible fibrosis and destruction of liver parenchyma.

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