The fulminant hepatic failure surveillance study
Brief review of the effects of presumed etiology and age of survival

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Fulminant hepatic failure is a rare[1] but serious clinical syndrome usually manifest by acute onset of progressive jaundice, shrinking of the liver and hepatic coma.[2] The Fulminant Hepatic Failure Surveillance Study was organized to determine the etiology, clinical patterns, pathological changes and results of treatment and to report back to the participating physicians. Patients eligible for the study are those who develop hepatic failure with manifestations of hepatic coma[3] within eight weeks of the onset of an illness and who are presumed to have had normal liver function prior to that illness. The participating physicians undertake to send reports on all their patients who fulfil these criteria. We now have reports on over 600 patients which are being analyzed. The trends seem similar to those in the first 286 patients we studied who had shown hepatic coma and were unresponsive to painful stimuli (stage IV coma).

Table I shows that presumed diagnosis and age have a significant influence on survival. Thus survival in the under 15-years age group is 34.2%; in the 15 to 44-years age group it is 22.1% and in the over 45-years age group it is 5%. Etiology is of some importance and best correlates with age in infectious and serum hepatitis but in presumed halothane-associated hepatic failure the overall survival is low in every age group. Presumed halothane-associated hepatitis[2-4] occurs in about 80% of the patients after the second exposure to halothane and may thus be a preventable disease, and yet accounts for 20% of all the deaths in the Fulminant Hepatic Failure Surveillance Study. The age and etiology can also assist in deciding which patient may be suitable for more heroic treatment such as cross-circulation or transplantations.

The results of treatment are also influenced by age as shown in Table II. When standardized for age to eliminate the effect of differences in age distribution, the survival of patients with exchange transfusion is 20% and of those who have not had the procedure it is 10%. This is not a controlled study and simply shows the trends in survival following these procedures. A controlled study is being planned.

Complications[1-3,5] such as respiratory failure, renal failure, and gastrointestinal bleeding were frequently encountered in patients in fulminant hepatic failure and explained most of the deaths in stages II and III hepatic coma. Survival was related to complications. Twenty-five per cent of the 284 patients had no complications and of these 36% survived, whereas only 11% survived if complications were present, and in these also survival was age-and etiology-dependent. Complications are to be expected in those patients in whom the liver is less likely to regenerate, yet patients in stage IV coma recovered from both renal and respiratory failure. Two of 20 patients with severe renal failure associated with hepatic failure, survived.

Prognosis seems to depend on the ability of the liver to regenerate and on the skill of the physician to maintain these patients until this regeneration occurs. There is great need for both prevention of hepatitis and for improving the high mortality in this disease. The Fulminant Hepatic Failure Surveillance Study has given us a better understanding of this clinical syndrome.

I wish to acknowledge the contributions of the organizing group, Drs. T. C. Chalmers, C. S. Davidson, L. Gottleib, L. Lipworth, H. Popper and S. J. Saunders and the participating members who made the study possible.

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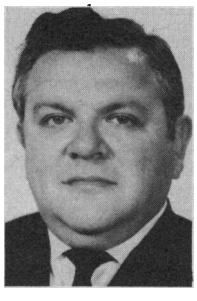

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Discussion

DR. KRUGMAN: The studies on the natural history of viral hepatitis which I have discussed during the past two days were carried out in collaboration with Dr. Giles and Dr. Hammond. Approximately 14 months ago we took a 2 ml. aliquot of our MS-2 serum out of the deep freeze, thawed it at room temperature, poured it into a 50 ml. Erlenmeyer flask and added 18 ml. of sterile distilled water to prepare a 1:10 dilution. The flask was placed on a hot plate and was removed after the solution had been boiled for one minute. After cooling at room temperature for 25 minutes the serum was used for a study which has been described in detail in a recent publication (*J Infect Dis* 122:432, 1970). The results revealed that boiled MS-2 serum was not infectious but it was antigenic. In a more recent study we demonstrated that viral hepatitis type B (MS-2) was prevented by active immunization with this inactivated MS-2 serum preparation. Two inoculations at four-month intervals were

Table I
284 patients in Stage IV hepatic coma: Age, etiology and survival

	0-14 yrs. P	0-14 yrs. D	15-44 yrs. P	15-44 yrs. D	45-64 yrs. P	45-64 yrs. D	65+ yrs. P	65+ yrs. D	Total P	Total D	% Survival
Infectious hepatitis	22	15	50	41	17	17	4	4	93	77	17.2
Serum hepatitis blood-produced	5	2	23	20	16	14	5	4	49	40	18.4
Needle			5	3	2	2	2	2	9	7	22.2
Drug abuse			27	18					27	18	33.3
Drugs			8	2	6	5			14	7	50.0
Halothane	2	2	16	14	29	29	6	6	53	51	3.8
Reye's syndrome	7	4							7	4	42.8
Pregnancy			3	2					3	2	33.3
Other	1	1	5	5	4	3	1	1	11	10	9.1
Unknown	1	1	8	8	7	7	2	2	18	18	none
Total	38	25	145	113	81	77	20	19	284	234	17.6
% Survival	34.2		22.1		4.9		5.0		17.6		

P = patients
D = deaths

Table II
284 patients in Stage IV hepatic coma: Age, treatment and survival

	0-14 yrs. P	0-14 yrs. D	15-44 yrs. P	15-44 yrs. D	45-64 yrs. P	45-64 yrs. D	65+ yrs. P	65+ yrs. D	Total P	Total D
Without procedure (Survival %)	5	5 (none)	49	40 (18.4%)	34	33 (2.9%)	13	13 (none)	101	91 (9.9%)
Exchange transfusion (Survival %)	33	20 (39.4%)	89	66 (25.8%)	39	36 (7.7%)	5	4 (20.0%)	166	126 (24.1%)
Other procedures (Survival %)		——	7	7 (none)	8	8 (none)	2	2 (none)	17	17 (none)
Total (Survival %)	38	25 (34.2%)	145	113 (22.1%)	81	77 (4.9%)	20	19 (5.0%)	284	234 (17.6%)

P = patients
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more effective than one. However, one inoculation gave enough protection to prevent some cases and modify others. The results of these studies are summarized in Table III.

(Questions following Dr. Krugman's special comments.)

QUESTION: I would be interested to know why Dr. Krugman did not do the experiment before.

DR. KRUGMAN: In 1967 we tested the effect of heat (boiling for one minute) on the infectivity of MS-1 (hepatitis Virus A) serum. The results indicated that this treatment inactivated the serum (*J Infect Dis* 122:432, 1970). However, the recipients of the inactivated preparation were infected by a subsequent exposure to unheated MS-1 serum. It was logical to repeat the procedure with MS-2 serum. When we observed that boiling for one minute eliminated infectivity without affecting antigenicity, we realized that we had unwittingly prepared an immunizing agent. The next step in this exploration was obvious.

QUESTION: If virus A hepatitis is such a benign disease, particularly in children, what is the rationale for preventing it in contacts with gamma globulin?

DR. KRUGMAN: The disease is usually benign in children. However, under extraordinary circumstances, possibly related to host or other factors, the course of the disease may become chronic and progressive. In very, very rare situations the disease may be fulminant with rapid onset of coma followed by death. Gamma globulin is a safe and highly effective preparation for the prevention or modification of viral hepatitis, type A. Consequently I believe it should be used for children as well as adults when it is indicated.

General discussion Session IV

QUESTION: A few years ago Dr. Giles and Dr. Krugman reported changes in serum immunoglobulins in MS-1 and MS-2 hepatitis. They showed that MS-1 hepatitis could be differentiated from MS-2 by a rise in IgM and a change in thymol turbidity. Is this observation being applied clinically?

DR. KRUGMAN: We have observed a correlation between the IgM and thymol turbidity levels in patients with viral hepatitis. During the acute state of viral hepatitis, type A (MS-1), both IgM and thymol turbidity values are consistently elevated. On the other hand, during the acute phase of viral hepatitis, type B (MS-2), IgM and thymol turbidity levels are usually normal in anicteric cases and occasionally slightly increased in icteric cases. Consequently, if a patient with viral hepatitis has normal IgM and thymol turbidity levels, the most likely cause is virus B; if these values are elevated it could be either virus A or virus B.

DR. DONIACH: We have done serial determinations of serum IgM in 45 patients with acute viral hepatitis and have found raised IgM levels in the first few weeks of illness in Australia-Ag positive and negative cases, as well as in hepatitis associated with infectious mononucleosis.

DR. TOBE: Should we allow the anicteric drug user to go back into the community or should we do something to try and reduce his infectivity?

DR. SCHAFFNER: Short of putting them in prison I don't know what you can do to them.

DR. TOBE: I have the impression that steroids do reduce the elevation in transaminases and the amount of pathology demonstrable by liver biopsy. Is this treating the disease?

DR. SCHAFFNER: Our experience has been that the steroids have very little effect on the Australia antigen.

QUESTION: When does Dr. Mackay use steroids and when does he decide to use other immuno-suppressive drugs?

DR. MACKAY: I do not use corticosteroids in either type of acute virus hepatitis, because there has been no good study showing that they are of benefit. I don't use corticosteroids in the long-drawn-out cases of presumed viral hepatitis which may go on for months. However, when the immunological markers are persistently present in serum and the patient has the other attributes of lupoid hepatitis, then I think this is the indication to use corticosteroids, combined or not with azathioprine. In regard to corticosteroids and Au antigen, I recall it being said that there is no increased tendency for persistence of Au antigen during corticosteroid therapy of hepatitis, but I cannot comment from my own experience.

DR. BARKER: Why does Dr. Trey divide serum hepatitis and hippie or drug hepatitis into two categories?

DR. TREY: The only reason I took the drug abusers out of the serum hepatitis group is that we have noticed that these people seem to do better than the average documented patient who develops serum hepatitis. I have shown you this on the one graph indicating survival between the ages of 15 and 44. I don't know why. The drug abuser gets out of hospital within a period of weeks whereas the usual patient who survives an episode of fulminant hepatic failure usually requires months of hospitalization. The complication rate of ulcers in this group is less. It is just that once they have recovered from fulminant hepatic failure their ultimate recovery is quicker than what I have experienced in patients of the same age group with a documented history of blood or serum transfusions.

Table III

Active immunization for viral hepatitis, Type B MS-2 Strain*.

Inoculum	Total no. inoculated	Evidence of hepatitis: Number positive for HAA	Evidence of hepatitis: Abnormal SGOT	Evidence of hepatitis: Clinical hepatitis
MS-2 serum	25	25	24	24
Boiled MS-2 serum, 1 inoculation	10	5 + 1**	5 + 1**	5
Unheated MS-2 serum 4 or 8 mos. later				
Boiled MS-2 serum 2 inoculations at 4 month intervals	4	1**	1**	0
Unheated MS-2 serum 4 months after 2nd inoculation				

*From Krugman, S., Giles, J. P., and Hammond, J. JAMA 217:41, 1971.

**HAA was detected and SGOT level was abnormal on only 1 day.

Envoi

It remains for me to thank and congratulate most warmly the sponsors of the Canadian Hepatic Foundation and the organizers of this symposium. Our sponsors are the first in the world to promote a foundation devoted to the study of the liver, which has been somewhat neglected despite its being the largest single organ in the body. Over these two days they have brought together, from far and wide, many scientists interested in various aspects of liver disease. It must be gratifying that this inaugural symposium has so well delineated the many and rapid advances being made in relation to acute and chronic hepatitis. Finally our hopes are that this Foundation will thrive and prosper, and promote enthusiastic research into all aspects of acute and chronic diseases of the liver. In doing so, it should set an example to other countries which should then in turn be encouraged to set up similar foundations, so creating new pathways for scientific communication and interchange of knowledge.

Dr. Ian R. Mackay

Concluding Remarks

The program which has been presented during the last two days has explored in depth all aspects of viral hepatitis — its history and pathology, epidemiology, virology, and the clinical picture — from the point of view of its prevention, diagnosis and management. An attempt has been made to relate the frontiers of research in progress to the every-day reality of the patient with viral hepatitis who presents himself to the clinician. We are in debt to the excellent faculty who have achieved this aim. At the advancing edge of knowledge there are still many problems unsolved, but we can leave this meeting with the conviction that solutions can and will be provided in the not too distant future. The importance of the conference transcends its purely scientific benefits. It has made a tangible contribution to the welfare of patients. Since most of you who have participated in the symposium are teachers, the benefits to future physicians which will derive indirectly from this conference are incalculable.

Dr. J. W. Steiner
University of Toronto
and
Director, The Canadian Hepatic Foundation