Fulminant Hepatitis

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Introduction

Fulminant hepatitis (FH) as a consequence of hepatitis B virus infection is a rapidly fatal disease occurring within 4–6 weeks of onset of jaundice leading to acute liver insufficiency, complicated by hepatic encephalopathy (HE) [9, 100]. If the HE occurs in less than 2 weeks after the onset of jaundice, the disease is termed acute FH, whereas subacute FH is defined as acute liver failure complicated by HE 2 weeks to 3 months after the onset of jaundice [9]. The incidence of FH is thought to be 0.1%–1.0% of all cases of acute hepatitis [7, 82, 83] and the mortality varies with the severity of HE, from 60% in stage II to over 90% in stage IV encephalopathy [4, 38, 60, 102]. Death can be attributed to a number of complications of FH [17, 99], but in 20% of cases, the cause of death is unknown. At autopsy, the liver shows massive hepatic necrosis with collapse and minimal evidence of hepatic regeneration [15, 61]. At the time of presentation viral antigens (HBV surface and core antigens; HBsAg, HBcAg) and the viral genome (HBV-DNA) usually are not found in liver tissue [15, 16]. No satisfactory medical treatment exists for FH. Management to date consists of supportive measures including repletion of plasma coagulation factors, glucose infusion, treatment of sepsis and correction of fluid and electrolyte imbalances [6]. No significant benefit of corticosteroids was shown in this setting [33, 39, 85] and in a recent randomized controlled trial, charcoal hemoperfusion was also shown to be of no benefit [3, 78]. Liver transplantation has been proposed for patients with FH; however, the survival in the most ill patients (stages III and IV hepatic encephalopathy) remains only 30%–40%, suggesting that if transplantation is to be offered, it should be considered earlier [18, 81, 91].

The pathogenesis of the disease is unknown but appears to involve viral factors as well as host factors including age, sex and the immune status of the host [15,
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Fig. 1. Postulated mechanisms for hepatocyte injury in hepatitis B virus (HBV)-induced fulminant hepatitis. PGE Prostaglandin E; IL-1 interleukin-1; TNF tumour necrosis factor.

16, 30]. There is considerable evidence to suggest that the hepatitis B virus (HBV) is not directly cytopathic for hepatocytes, but rather, hepatic injury may be a result of both humoral and cellular immune-mediated processes [51, 94–96]. Evidence exists in experimental models of FH and in man which suggests that following viral infection, the immune coagulation system is activated [53, 54]. This results in intravascular thrombosis and localized microcirculatory disturbances within the liver [68–70]. Agents which interfere with activation of the classical or immune coagulation systems have been shown to be beneficial in the setting of FH [68].

Based upon these observations, we have developed the following hypothesis for the pathogenesis of FH (Fig. 1). Viral infection results in cellular and/or humoral immune responses which are either directly injurious to the liver, or result in activation of the immune coagulation system with formation of sinusoidal microthrombi, platelet activation and hepatic necrosis. The failure of regulation of these pathways results in the clinical syndrome of FH. The remainder of this chapter will discuss the evidence which forms the basis for this hypothesis.

Pathogenesis

Humoral Immune Response to HBV

Vigorous immune responses to HBsAg have been reported in FH B infection [17, 36]. HBsAg was cleared from the serum significantly faster in patients with FH than in serum from patients with non-FH. Furthermore, in a significant proportion of the patients with FH, an antibody response to HBsAg (anti-HBsAg) was detectable at presentation [7, 98, 103]. Since little or no antibody to HBsAg is detected during acute viral hepatitis B infection it has been postulated that the presence of both antigen and antibody (immune complexes) in these patients (FH) may be
responsible for the severe liver disease that ensues [8, 76, 98, 103]. More recently it has been demonstrated that antibodies to the translation products of the PreS1 and PreS2 regions of the envelope gene of HBV occur early during the course of FH B and may participate in the severe hepatic injury and early clearance of virus, characteristic of this disease [44]. These results suggest that the enhanced humoral immune response with production of antibody may lead to an Arthus-like reaction in the sinusoids of the liver with ensuing ischemic necrosis [98].

**Cellular Immune Response**

It has been suggested that cellular immune mechanisms are responsible for hepatocellular injury in viral hepatitis [15, 16, 21, 22, 30, 41, 42, 45, 62, 63, 66, 80]. Elimination of virally infected hepatocytes is dependent upon the recognition of viral determinants in association with major histocompatibility complex (MHC) proteins (class I) on infected hepatocytes by cytotoxic T cells [21, 45, 51, 104]. More recent studies have suggested that natural killer (NK) cells play a role during the acute phase of the disease [31]. Autologous cytotoxicity studies suggest that the target antigens known to be expressed on the surface of infected hepatocytes are HBCAg and/or HBsAg [15, 16]. Using dual-color fluorescence analysis, an elevation in Leu-2a+15− (cytotoxic) cells as well as a reduction of Leu-2a+15+ (suppressor) cells were found in the peripheral blood in patients with FH [41]. Serial studies showed an imbalance of these two Leu-2a subsets of cells in the acute phase of infection, but not in the recovery phase (Table 1).

In an attempt to identify intrahepatic lymphocyte subpopulations in patients with FH, it was demonstrated that there was an increase in cytotoxic T cells in liver tissue and that these cells were in broad contact with the surface of hepatocytes. In contrast, T helper cells were scarce in liver tissue. These results suggest that there is a loss of suppressor T cells and an increased number of cytotoxic T cells in the livers of patients with acute FH [21, 22, 80].

**Activation of the Immune Coagulation System in FH**

About 50% of cases of FH are associated with a moderate to severe consumption coagulopathy, or disseminated intravascular coagulation (DIC) [17, 52, 67–69]. Histopathological studies in man have revealed severe and extensive hepatic cell necrosis as the most conspicuous and common abnormality seen in the liver. This morphologically resembles hepatic necrosis produced experimentally in the rabbit by a Schwartzman reaction using *Escherichia coli* endotoxin [67]. This has led

| T lymphocytes | Peripheral blood | Liver tissue |
|---------------|------------------|-------------|
| Suppressor    | Decreased        | Decreased   |
| Cytotoxic     | Increased        | Increased   |
| Helper        | ----             | Decreased   |

---: Data not available
to the hypothesis that the acute, severe and extensive hepatic cell necrosis which is seen in these cases is probably the result of an anoxic state caused in most instances by intrahepatic circulatory disturbances [67-69]. Thrombi formation has been noted in and around the necrotic areas in a significant number of cases of FH in man [69]. Further experimental evidence to support a role for activation of the immune coagulation system was seen in a murine model of viral hepatitis (MHV-3) in which production of a macrophage serine protease [procoagulant activity (PCA)] precedes and is genetically linked to the evolution of FH [26]. Abrogation of production of PCA either by heparin and/or prostaglandins prevented FH, although it did not prolong survival [1, 68]. Macrophages stimulated with endotoxin can be induced to express monokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF). These have been shown to be capable of initiating induction of procoagulants by endothelial cells [10, 13, 14, 23]. Activated endothelial cells also produce an adhesion molecule (endothelial-leukocyte adhesion molecule 1, ELAM-1) which promotes adhesion of lymphocytes to endothelial cells and produces vascular stasis [11, 12, 23]. The normal function of endothelium is to inhibit thrombosis [37], therefore nonstimulated endothelial cells have very little surface procoagulant activity and normally augment the anticoagulant function of activated protein C [32, 71-74]. However, following stimulation of endothelial cells, the balance is tipped in favor of thrombosis [23, 37]. The promotion of coagulation as a result of interaction of monocytes and endothelial cells may be beneficial in limiting the spread of the infectious agent and act as a natural defence mechanism. On the other hand, the same tendency to coagulation may lead to disseminated intravascular coagulation as has been seen in certain infections and malignancies and this may be detrimental to the host [52].

**Interferon (IFN) and Fulminant Viral Hepatitis**

IFN is not normally found in measurable quantities in serum but is detected in the acute phase of a number of viral infections [25, 50, 92]. The detection of IFN has not been noted consistently in acute hepatitis B, but indirect evidence such as increased expression of MHC class I antigens on hepatocyte membranes [25, 70, 87] and increased 2,5-oligoadenylate synthetase (2,5-AS) activity in peripheral blood mononuclear cells suggest that IFNs play an important role in the clearance of the virus [25, 49]. Adult HBV carriers have a decreased capacity for production of IFNs by mononuclear cells in response to appropriate in vitro stimulation [43]. The hepatocytes of these patients do, however, show augmented 2,5-AS activity in response to exogenous IFN-α [43]. It is not clear whether this apparent IFN deficiency is a primary phenomenon which predisposes the patients to chronic HBV infection or a secondary phenomenon related to chronic infection [88]. In a small series of patients with FH, IFN activity could not be detected in the serum [64]. In addition, infusion of IFN appeared to have no beneficial effect, with no increased survival [46]. In an experimental animal model of FH (MHV-3), although the exogenous infusion of IFN prolonged survival, there were no long-term survivors and all animals died of fulminant hepatic failure. Thus, although there may be an intrinsic defect in the IFN system in patients with FH, exogenous
IFN administration appears to confer no beneficial effects. Thus, the role of IFN in FH remains to be defined.

**Prostaglandins in FH**

Prostaglandins (PG) belong to a family of bioactive lipids derived from arachidonic acid via the cyclooxygenase pathway [47] (Fig. 2). Almost all of the cells of the body are able to produce PG, the most frequent type being PGE2, a mediator of pain and edema in inflammation [47]. PGE1 is much less abundant than PGE2, but has similar biological effects. Both compounds are equally potent in causing fever, promoting pain and suppressing the synthesis of leukotriene B4 by granulocytes [40]. PGE1 induces the chemotactic response of neutrophils [40], and suppresses the effect of histamine and of other mediators of increased vascular permeability [34]. As with PGE2, most of the PGE1 effects may be explained by a stimulation of adenylate cyclase and the resulting elevated cyclic adenosine monophosphate (cAMP) levels [19, 20, 40]. In addition, PG have been demonstrated to inhibit IL-2 production [84], MHC class I and class II antigen expression [35, 59, 90, 93, 101], the induction of macrophage PCA by MHV [1] and cytotoxic T cell activity against autologous hepatocytes [77].

PG have been shown to have a beneficial effect in a variety of animal models of hepatic failure due to toxins (CCl4, acetaminophen, galactosamine, alcohol, hypoxia, ischemia and immune mediation [4, 5, 24, 58, 65, 75, 77, 86]) (Table 2). Our group has shown hepatic cytoprotection by dimethyl PGE2 (dmPGE2) in fulminant murine viral hepatitis infection (MHV-3) [1]. Furthermore, preliminary evidence suggests that PG prevents the evolution and progression of brain edema
Table 2. Summary of hepatoprotective effects of prostaglandins (PG)

| Type of injury | Damaging agent | Species | PG       | Model            |
|---------------|----------------|---------|----------|-----------------|
| Fatty liver   | Ethanol        | Rat     | PGE₁     | In vivo         |
|               | Ethanol        | Rat     | dmPG     | In vivo         |
|               | CCl₄           | Rat     | dmPG     | In vivo         |
| Hypoxia       | ↓PO₂ Preservation at 4 °C without perfusion | Cat | PGI₂ | Perfused liver |
|               |                | Dog     | PGI₂     | Transplantation |
| Necrosis      | Acetaminophen  | Rat     | dmPG     | In vivo         |
|               | Galactosamine  | Rat     | dmPG     | In vivo         |
|               | Galactosamine  | Rabbit  | PGE₁     | In vivo         |
|               | Aflatoxin      | Rat     | dmPG     | In vivo         |
|               | CCl₄           | Rat     | dmPG     | In vivo         |
|               | Endotoxin      | Mouse   | PGE₁     | In vivo         |
|               | Virus (MHV-3)  | Mouse   | dmPG     | In vitro/In vivo|

*PGE₁* prostaglandin E₁; *dmPG* dimethyl PG; *PGI₂* prostacyclin; *MHV-3* murine hepatitis virus

in comatose FH rats [27–29]. Since brain edema is an important complication and cause of death in the setting of FH, prevention of brain edema by PGE₂ may explain the increased survival in animal models of FH [27–29].

**Treatment**

**Medical**

To date there is no known effective medical treatment for FH [6]. IFN therapy has proven to be of little value in this setting [46, 88]. The enthusiasm for charcoal hemoperfusion has declined since the recent report of a randomized controlled trial in which survival was not prolonged in patients with FH [79]. We have recently reported that infusions of PGE₁ results in increased patient survival in patients with FH [2, 89] (Table 3). Furthermore, in three patients with recurrent HBV infection following liver transplantation, infusion of PGE₁ resulted in clearance of HBsAg and HBeAg from the liver and amelioration of FH (manuscript in preparation). All three patients required oral PG to maintain this remission. Although the mechanism for the ameliorative effect is not known, PG may exert its beneficial effects by decreasing expression of class I and II antigens, inhibition of induction of monocyte/macrophage PCA and by preventing reinfection of hepatocytes (manuscript in preparation).

**Liver Transplantation**

Orthotopic liver transplantation has become the therapy of choice for chronic end-stage liver disease [18, 78, 81, 91]. More recently liver transplantation has been performed in patients with FH [18, 78, 81, 91]. Initial results suggest that this is an effective form of therapy in selected patients [18, 78, 81, 91]. However,
Table 3. Effect of PG in FH in man

| Patient number | Etiological agent | Pre-PGE | Post-PGE |
|---------------|------------------|---------|----------|
|               |                  | AST     | BIL | PT | AST | BIL | PT |
| 1             | HBV              | 456     | 370 | 28 | 29  | 64  | 11 |
| 2             | HBV              | 1420    | 214 | 38 | 34  | 80  | 12 |
| 3             | HBV              | 2295    | 345 | 36 | 25  | 24  | 10 |
| 4             | HBV*             | 750     | 161 | 28 | 66  | 22  | 12 |
| 5             | HBV*             | 1100    | 451 | 17 | 45  | 238 | 11 |
| 6             | HBV*             | 550     | 18  | 16 | 110 | 17  | 11 |

* Recurrent hepatitis B virus (HBV) infection following liver transplantation. Patients 4, 5 and 6 remain on oral PGE₂.

AST aspartate transaminase (normal < 20 U/l)
BILI bilirubin (normal < 20 μmol/l)
PT prothrombin time (normal 11 s)

the most severely ill patients (stage III and IV hepatic encephalopathy) have only a 30%-40% survival following liver transplantation [18, 78, 81, 91]. Thus, transplantation for patients with FH, if to be considered, should be considered earlier rather than after the patients lapse into stage IV hepatic coma. Until controlled trials demonstrate the efficacy of PG or other agents, transplantation remains the treatment of choice for FH.

**Discussion**

The pathogenesis of FH B is not well understood. However, there is a body of evidence to suggest that HBV is not directly cytopathic to hepatocytes. Rather, the disease may be mediated by the humoral and cellular immune response to viral infected hepatocytes. At the time of the most severe injury there is usually an absence of both serological and virological markers of HBV infection, although a significant number of patients with FH have been shown to have anti-HBsAg, and aggregates of HBsAg and anti-HBsAg have been demonstrated in the sinusoids of the liver parenchyma. Surviving hepatocytes are devoid of hepatitis viral antigens and HBV-DNA [15, 16]. The predominance of cytotoxic T cells in the liver at the time of most severe injury would argue in favor of a cell-mediated immune response in the clearance of the virus.

The lesion of fulminant hepatic failure which is occasionally accompanied by fibrin thrombi deposition resembles the lesion of a disseminated Schwartzman reaction [67-69]. This observation suggests a participatory role for activation of the immune coagulation system in this disease process. It is known that both monocyte/macrophages and endothelial cells in response to endotoxin, viral antigens and immune complexes can produce proteases capable of initiating fibrin formation [23, 57]. This could result in microcirculatory thrombosis and hepatocyte hypoxia with progressive necrosis [67-69]. This sequence of events has been clearly elucidated in MHV infection [55, 56]. In vivo microscopic studies
of transilluminated livers in MHV-infected mice showed localized rounded areas
with absent blood flow corresponding to the lesions seen in cast studies [55, 56].
Decreased velocity of red blood cells in adjacent sinusoids and complete stasis
of blood flow was observed in some areas. Transmission electron microscopic
studies of livers of infected mice have confirmed the obstruction of sinusoidal
lumens by protruding lining cells, platelets and fibrin. These studies demonstrate
that microvascular blockage may be an initial step leading to necrosis in a model
of FH [55, 56].

It is known that eicosinoids and leukotrienes represent extremely potent
mediators of inflammation and anaphylactic reactions [97]. While PG appear to
be primarily vasodilatory, peptido-leukotrienes (LTC₄, LTD₄) are mainly
vasoconstrictive [48, 97]. Treatment of animals with leukotrienes has been shown
to result in FH, thus suggesting a possible role for these compounds in liver injury
[97]. We, as well as others, have observed a beneficial effect of exogenous PG
(PGE₁ and PGE₂) in the treatment of FH in an experimental animal model of FH
and in man [1, 2]. PG of the E series are known to inhibit induction of
monocyte/macrophage PCA [1] and activation of cytotoxic T cells [77]. Thus,
the imbalance in production of prostanoids and leukotrienes during FH may
account at least in part for the evolution of FH.

Conclusion

In conclusion, evidence exists that cellular and humoral immune-mediated pro-
cesses result in hepatic necrosis in FH. Activation of the immune coagulation
system appears to be an integral part of the inflammatory process resulting in fibrin
thrombi which have been demonstrated in the liver, kidneys and lungs of patients
with FH. A beneficial role of PG in the treatment of FH has been demonstrated,
but controlled trials are required to firmly establish the efficacy of these agents.
At present liver transplantation remains the treatment of choice in selected patients
with FH. Further studies of the role of the immune system in the pathogenesis
of this disease are required to devise more effective therapeutic strategies.

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References

1. Abecassis M, Falk JA, Makowka L, Dindzans VJ, Falk RE, Levy GA (1987) 16, 16-Dimethyl
prostaglandin E₂ prevents the development of fulminant hepatitis and blocks the induction of
monocyte/macrophage procoagulant activity after murine hepatitis virus strain 3 infection. J
Clin Invest 80: 881
2. Abecassis M, Falk R, Blendis L, Falk J, Langer B, Greig P, Superina R, Strasberg S, Taylor
B, Glynn M, Levy G (1987) Treatment of fulminant hepatic failure with a continuous infusion
of Prostin VR (PGE₁) (Abstract). Hepatology 7: 1104
3. Alp MH, Hickman R (1986) Plasmaphoresis, charcoal and resin perfusion in experimental por-
cine hepatic failure. Dig Dis Sci 31: 181
4. Alp MH, Hickman R (1987) The effect of prostaglandins, branched-chain amino acids and other drugs on the outcome of experimental acute porcine hepatic failure. J Hepatol 4: 99
5. Araki H, Lefer AM (1980) Cytoprotective actions of prostacyclin during hypoxia in the isolated perfused cat liver. Am J Physiol 238: H176
6. Auslander MO, Gitnick GL (1977) Vigorous medical management of acute fulminant hepatitis. Arch Intern Med 137: 599
7. Bal V, Amin SN, Rath S, Kamat SA, Zuckerman AJ, Marathe SN, Kamat RS (1987) Virological markers and antibody responses in fulminant viral hepatitis. J Med Virol 23: 75
8. Bernuau J, Goudeau A, Poynard T, Dubois F, Lesage G, Yvonnet B, Degott C, Bezeaud A, Rueff B, Benhamou JP (1986) Multivariate analysis of prognostic factors in fulminant hepatitis B. Hepatology 6: 648
9. Bernuau J, Rueff B, Benhamou JP (1986) Fulminant and subfulminant liver failure: definitions and causes. Semin Liver Dis 6: 97
10. Bevilacqua MP, Pober JS, Majeau GR, Cotran RS, Gimbrone MA Jr (1984) Interleukin 1 induces biosynthesis and cell surface expression of procoagulant activity in human vascular endothelial cells. J Exp Med 160: 618
11. Bevilacqua MP, Pober JS, Wheeler ME, Cotran RS, Gimbrone MA (1985) Interleukin 1 acts on cultured human vascular endothelium to increase the adhesion of polymorphonuclear leukocytes, monocytes and related leukocyte cell lines. J Clin Invest 76: 2003
12. Bevilacqua MP, Pober JS, Wheeler ME, Cotran RS, Gimbrone MA (1985) Interleukin 1 activation of vascular endothelium: effects on procoagulant activity and leukocyte adhesion. Am J Pathol 121: 394
13. Bevilacqua MP, Pober JS, Majeau GR, Fiers W, Cotran RS, Gimbrone MA (1986) Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. Proc Natl Acad Sci USA 83: 4533
14. Bevilacqua MP, Schleef RR, Gimbrone MA, Loskutoff DJ (1986) Regulation of the fibrinolytic system of cultured human vascular endothelium by interleukin 1. J Clin Invest 78: 587
15. Bianchi L (1986) Necroinflammatory liver diseases. Semin Liver Dis 6: 157
16. Bianchi L, Gudat F (1979) Immunopathology of hepatitis B. In: Popper H, Schaffner F (eds) Progress in liver diseases. Grune & Stratton, New York, pp 371-392
17. Bihari DJ, Gimson AES, Williams R (1986) Cardiovascular, pulmonary and renal complications of fulminant hepatic failure. Semin Liver Dis 6: 119
18. Bismuth H, Samuel D, Gugenheim J, Castaing D, Bernuau J, Rueff B, Benhamou JP (1987) Emergency liver transplantation for fulminant hepatitis. Ann Intern Med 107: 337
19. Bourne HR, Lichtenstein LM, Melmon KL, Henney CS, Weinstein Y, Shearer GM (1974) Modulation of inflammation and immunity by cyclic AMP. Science 184: 19
20. Brass EP, Alford CE, Garrity MJ (1987) Inhibition of glucagon-stimulated cAMP accumulation and fatty acid oxidation by E-series prostaglandins in isolated rat hepatocytes. Biochim Biophys Acta 930: 122
21. Chisari FV, Bieber MS, Josepho CA, Xavier C, Anderson DS (1981) Functional properties of lymphocyte subpopulations in hepatitis B virus infection II. Cytotoxic effector cell killing of targets that naturally express hepatitis B surface antigen and liver-specific lipoprotein. J Immunol 126: 45
22. Chisari FV, Castle KL, Xavier C, Anderson DS (1981) Functional properties of lymphocyte subpopulations in hepatitis B virus infection I. Suppressor cell control of T lymphocyte responsiveness. J Immunol 126: 3844
23. Cole EH, Levy GA (1989) Interaction of monocytes with vascular endothelium. In: Asherson G (ed) The human monocyte. Academic Press, London, pp 353-360
24. Davis DC, Potter WZ, Jollow DJ, Mitchell JR (1974) Species differences in hepatic glutathione depletion, covalent binding and hepatic necrosis after acetaminophen. Life Sci 14: 2099
25. Davis GL, Hoofnagle JH (1986) Interferon in viral hepatitis: role in pathogenesis and treatment. Hepatology 6: 1038
26. Dindzans VJ, Skamene E, Levy GA (1986) Susceptibility/resistance to mouse hepatitis virus strain 3 and macrophage procoagulant activity are genetically linked and controlled by two non-H-2-linked genes. J Immunol 137: 2355
27. Dixit V, Chang TMS (1982) Effects of prostaglandin E₂ on the survival time of fulminant hepatic failure rats. Int J Artif Organs 5:388
28. Dixit V, Chang TMS (1985) Preliminary report on effects of prostaglandin E₂ on brain edema in fulminant hepatic failure rats. Int J Artif Organs 8:55
29. Dixit V, Chang TMS (1987) Effects of prostaglandin E₂ on brain edema and liver histopathology in a galactosamine-induced fulminant hepatic failure rat model. Biomater Artif Cells Artif Organs 15:559
30. Dudley FJ, Fox RA, Sherlock S (1972) Cellular immunity and hepatitis-associated, Australia antigen liver disease. Lancet I:723
31. Eggink HF, Houthoff HJ, Huitema S, Walters G, Poppema S, Gips CH (1984) Cellular and humoral immune reactions in chronic active liver disease II: Lymphocyte subsets and viral antigens in liver biopsies of patients with acute and chronic hepatitis B. Clin Exp Immunol 56:121
32. Esmon CT (1987) The regulation of natural anticoagulant pathways. Science 235:1348
33. European Association for the Study of Liver (1979) Randomized trial of steroid therapy in acute liver failure. Gut 20:620
34. Fantone JC, Kunkel SL, Ward PA, Zurier RB (1980) Suppression by prostaglandin E₁ of vascular permeability induced by vasoactive inflammatory mediators. J Immunol 125:2591
35. Franco A, Barnaba V, Natali P, Galsano C, Musca A, Balsano F (1988) Expression of class I and class II major histocompatibility complex antigens on human hepatocytes. Hepatology 8:449
36. Galbraith RM, Eddleston AL, Williams R (1975) Fulminant hepatic failure in leukemia and choriocarcinoma related to withdrawal of cytotoxic drug therapy. Lancet II:528
37. Gimbrone MA (1981) Vascular Endothelium and Atherosclerosis. In: Moore S (ed) Vascular Injury and Atherosclerosis. Dekker, New York, chapter 2 pp 25-45
38. Gimson AES, White YS, Eddleston ALWF, Williams R (1983) Clinical and prognostic differences in fulminant hepatitis type A, B and non-A, non-B. Gut 24:1194
39. Gregory PB, Knauer CM, Kempton RL, Miller R (1976) Steroid therapy in severe viral hepatitis. A double-blind, randomized trial of methyl-prednisolone versus placebo. N Engl J Med 294:681
40. Ham EA, Soderman DD, Zanetti ME, Dougherty HW, McCauley E, Kuehl FA (1983) Inhibition by prostaglandins of leukotriene B₄ release from activated neutrophils. Proc Natl Acad Sci USA 80:4349
41. Hasegawa K, Yamauchi K, Furukawa T, Obata H (1988) Dual color fluorescence analysis of peripheral T cell subsets in hepatitis B virus-induced liver disease. Hepatology 8:1134
42. Hopf U, Meyer Zum Buschenfelde, Freudenberg J (1974) Liver specific antigens of different species II. Localization of a membrane antigen at cell surface of isolated hepatocytes. Clin Exp Immunol. 16:117
43. Ikeda T, Lever AML, Thomas HC (1986) Evidence for a deficiency of interferon production in patients with chronic hepatitis B virus infection acquired in adult life. Hepatology 6:962
44. Ise I, Tsuda F, Aihara S, Machida A, Takai E, Miyamoto H, Akahane Y, Miyakawa Y, Mayumi M (1988) Antibodies to translation products of the pre-S₁ and pre-S₂ regions of the envelope gene of hepatitis B virus in fulminant hepatitis B. Hepatology 8:1089
45. Kakumu S, Hara T, Goji H, Sakamoto N (1978) Lymphocyte cytotoxicity against Chang liver cells in chronic active hepatitis. Cell Immunol 36:117
46. Kato Y, Noda Y, Unoura M, Tanaka N, Kobayashi K, Hattori N, Hatano K, Kobayashi S (1986) Effect of exogenous mouse interferon on murine fulminant hepatitis induced by mouse interferon virus type 2. Dig Dis Sci 31:177
47. Lands WEM (1979) The biosynthesis and metabolism of prostaglandins. Annu Rev Physiol 41:633
48. Lefer AM (1986) Leukotrienes as mediators of ischemia and shock. Biochem Pharmacol 35:123
49. Lengyel P (1982) Biochemistry of interferons and their actions. Annu Rev Biochem 51:251
50. Levin S, Hahn T (1982) Interferon system in acute viral hepatitis. Lancet I:592
51. Levy GA, Chisari FV (1981) The immunopathogenesis of chronic HBV induced liver disease. Springer Semin Immunopathol 3:439
52. Levy GA, Cole EH (1989) The monocyte and disseminated intravascular coagulation. In: Asherson G (ed) The human monocyte. Academic Press, London, pp 429-438
53. Levy GA, MacPhee PJ, Fung LS, Fisher MM, Rappaport AM (1983) The effect of mouse hepatitis virus infection on the microcirculation of the liver. Hepatology 3: 964
54. Levy GA, MacPhee PJ, Fung LS, Fisher MM, Rappaport AM (1984) The effects of mouse hepatitis virus type 3 on the microcirculation of the liver in inbred strains of mice. Adv Exp Med Biol 173: 397
55. MacPhee PJ, Dindzans VJ, Fung LS, Levy GA (1985) Acute and chronic changes in the microcirculation of the liver in inbred strains of mice following infection with mouse hepatitis virus type 3. Hepatology 5: 649
56. MacPhee PJ, Schmidt EE, Keown PA, Groom AC (1988) Microcirculatory changes in livers of mice infected with murine hepatitis virus. Evidence from microcorrosion casts and measurements of red cell velocity. Microvasc Res 36: 140
57. Maier RV, Hahnle GB (1984) Microthrombosis during endotoxemia: potential role of hepatic versus alveolar macrophages. J Surg Res 36: 362
58. Marinovich M, Flaminio LM, Papagni M, Galli CL (1987) Evaluation of the cytoprotective effect of natural and synthetic prostaglandins in CCl4-induced liver cell damage. In: Samuelsson B, Paolletti R, Ramwell PW (eds) Advances in prostaglandin, thromboxane and leukotriene research. Raven Press, New York, pp 1094
59. Massa PT, Dorries R, ter Meulen V (1986) Viral particles induce la antigen expression on astrocytes. Nature 320: 543
60. Mathiesen LR, Skinoj P, Nielsen JO, Purcell RH, Wong D, Ranek L (1979) Hepatitis type A, B and non-A non-B in fulminant hepatitis. Gut 21: 72
61. McCaul TF, Fagan EA, Tovey G, Portmann B, Williams R, Zuckerman AJ (1986) Fulminant hepatitis an ultrastructural study. J Hepatol 368: 276
62. Meyer Zum Buschenfelde KH, Hopf V (1974) Studies on the pathogenesis of experimental chronic active hepatitis in rabbits I. Induction of the disease and protective effect of allogeneic liver specific proteins. Br J Exp Pathol 55: 498
63. Meyer Zum Buschenfelde KH, Hutteroth TH, Arnold W, Hopf U (1979) Immunologic liver injury: the role of hepatitis B viral antigens and liver membrane antigens as targets. In: Popper H, Schaffner F (eds) Progress in liver diseases. Grune & Stratton, New York, pp 407-000
64. Milazzo F, Galli M, Fassio PG, Cargnel A, Pugliese A, Tovo PA, Vigevani GM, Esposito R, Lazzarin A, Caredda F, Almaviva M, Gavazzeni G, Perna MC, Crocchiolo P, Moroni M (1985) Attempted treatment of fulminant viral hepatitis with human fibroblast interferon. Infect Med 13: 130
65. Mizoguchi Y, Tsutsui H, Miyajima K, Sakagami Y, Seki S, Kobayashi K, Yamamoto S, Morisawa S (1987) The protective effects of prostaglandin E1 in an experimental massive hepatic necrosis model. Hepatology 7: 1184
66. Mondelli M, Eddleston ALWF (1984) Mechanisms of liver cell injury in acute and chronic hepatitis B. Semin Liver Dis 4: 47
67. Mori W, Naoto A, Shiga J (1981) Acute hepatic cell necrosis experimentally produced by viral agents in rabbits. Am J Pathol 103: 31
68. Mori W, Machinami R, Shiga J, Taguchi T, Tanaka K, Fukusato T, Hasegawa A, Aoki N, Narita T, Kikuchi F, Kodama T, Irie H, Oka T, Yoshimura A, Aoyama H (1984) A pathological study of fulminant hepatic disease. Acta Pathol Jpn 34: 727
69. Mori W, Shiga J, Irie H (1986) Schwartzman reaction as a pathogenetic mechanism in fulminant hepatitis. Semin Liver Dis 6: 267
70. Morris A, Cooley M, Blackmon M (1986) The interaction of interferon with the immune response. J Hepatol 3: 5161
71. Nawroth PP, Stern DM (1986) Modulation of endothelial cell hemostatic properties by tumor necrosis factor. J Exp Med 163: 740
72. Nawroth PP, Stern DM (1985) A pathway of coagulation on endothelial cells. J Cell Biochem 28: 253
73. Nawroth PP, Handley DA, Esmen CT, Stern DM (1986) Interleukin-1 induces endothelial cell procoagulant while suppressing cell surface anticoagulant activity. Proc Natl Acad Sci USA 83: 3460
74. Nawroth PP, Handley D, Stern DM (1986) The multiple levels of endothelial cell-coagulation factor interactions. Clin Haematol 15: 293
75. Noda Y, Hughes RD, Williams R (1986) Effect of prostacyclin (PGI2) and a prostaglandin analogue BW 245C on galactosamine-induced hepatic necrosis. J Hepatol 2: 53
76. Nowoslawski A (1979) Hepatitis B virus-induced immune complex disease. In: Popper H, Schaffner F (eds) Progress in Liver Diseases. Grune & Stratton, New York, pp 393–406
77. Ogawa M, Mori T, Mori Y, Ueda S, Yoshida H, Kata K, Isatos K, Wakashin Y, Wakashin M, Okuda K (1988) Inhibitory effects of prostaglandin E on T cell mediated cytotoxicity against isolated mouse liver cells. Gastroenterology 94: 1024
78. O'Grady JJ, Williams R, Calne RY (1986) Transplantation in fulminant hepatic failure. Lancet II: 1227
79. O'Grady JJ, Gimson AES, O'Brien CJ, Pucknell A, Hughes RD, Williams R (1988) Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. Gastroenterology 94: 1186
80. Onji M, Kumon I, Kanaoka M, Horiike N, Ohta Y (1987) Identification of intrahepatic lymphocyte subpopulations in patients with fulminant hepatitis by the immunoenzymatic technique, using monoclonal antibodies. Hepatogastroenterology 34: 141
81. Peleman RR, Gavaler JS, Van Thiel DH, Esquivel C, Gordon R, Iwatsuki S, Starzl TE (1987) Orthotopic liver transplantation for acute and subacute hepatic failure in adults. Hepatology 7: 484
82. Rakela J (1983) Fulminant hepatitis: treatment or management? Mayo Clin Proc 58: 690
83. Rakela J, Lange SM, Ludwig J, Baldus WP (1985) Fulminant hepatitis: Mayo Clinic experience with 34 cases. Mayo Clin Proc 60: 289
84. Rappaport RS, Dodge GR (1982) Prostaglandin E inhibits the production of human interleukin 2. J Exp Med 155: 943
85. Redeker AG, Schweitzer IL, Yamahiro HS (1976) Randomization of corticosteroid therapy in fulminant hepatitis. N Engl J Med 254: 728
86. Robert A, Ruwart MJ (1982) Effects of prostaglandins on the digestive system. In: Lee JB (ed) Prostaglandins. North Holland, New York, pp 113–176
87. Schultz RM, Kleinschmidt WJ (1983) Functional identity between murine gamma interferon and macrophage activating factor. Nature 305: 239
88. Sherker AH, Levy GA (1990) New therapeutic strategies for chronic hepatitis. Curr Top Gastroenterol (in press)
89. Sinclair SB, Greig PD, Blendis LM, Abecassis M, Roberts EA, Phillips MJ, Cameron R, Levy GA (1989) Biochemical and clinical response to fulminant viral hepatitis to administration of Prostaglandin E: a preliminary report. J Clin Invest 84: 1063
90. Snyder DS, Beller DI, Unanue ER (1982) Prostaglandins modulate macrophage Ia expression. Nature 299: 163
91. Steiber AC, Ambrosino G, Van Thiel D, Iwatsuki S, Starzl TE (1988) Orthotopic liver transplantation for fulminant and subacute hepatic failure. Gastroenterol Clin N Am 17: 157
92. Stewart WE II (ed) (1979) The interferon system. Springer, Berlin Heidelberg New York, pp 1–42
93. Suzumura A, Lavi E, Weiss SR, Silberg DH (1986) Coronavirus infection induces H-2 antigen expression on oligodendrocytes and astrocytes. Sciences 232: 991
94. Thomas HC, Lok ASF (1984) The immunopathology of autoimmune and hepatitis B virus-induced chronic hepatitis. Semin Liver Dis 4: 36
95. Thomas HC, Shipton U, Montano L (1979) The HLA system: its relevance to the pathogenesis of liver disease. In: Popper H, Schaffner F (eds) Progress in liver diseases. Grune & Stratton, New York, pp 517–527
96. Thomas HC, Pignatelli M, Scully LJ (1985) Viruses and immune reactions in the liver. Scand J Gastroenterol 114: 105
97. Tiegs G, Wendel A (1988) Leukotriene-mediated liver injury. Biochem Pharmacol 37: 2569
98. Trepo CG, Motin RJ, Trepo D, Sepetjian M, Prince AM (1976) Hepatitis B antigen (HBsAg) and/or antibodies (anti-HBs and anti-HBc) in fulminant hepatitis: pathogenic and prognostic significance. Gut 17: 10
99. Trey C (1972) The fulminant hepatic failure surveillance study brief review of the effects of presumed etiology and age of survival. Can Med Assoc 106: 525
100. Trey C, Davidson CS (1970) The management of fulminant hepatic failure. In: Popper H, Schaffner F (eds) Progress in liver diseases. Grune & Stratton, New York, pp 282–298
101. Tripp CS, Wyche A, Unanue ER, Needleman P (1986) The functional significance of the regulation of macrophage Ia expression by endogenous arachidonate metabolites in vitro. J Immunol 137: 3915
102. Tygstrup N, Ranek L (1986) Assessment of prognosis in fulminant hepatic failure. Semin Liver Dis 6: 129
103. Woolf IL, El Sheikh N, Cullens H, Lee WM, Eddleston ALWF, Williams R, Zuckerman AJ (1976) Enhanced HBsAb production in pathogenesis of fulminant viral hepatitis type B. Br Med J 2: 669
104. Zinkernagel RM, Doherty PC (1974) Restriction of in vitro T cell-mediated cytotoxicity in lymphocyte choriomeningitis within a syngeneic or semiallogeneic system. Nature 248: 702