BACTERIOLOGY OF THE HUMAN LIVER

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Attention has recently been focused upon the potential role played by the intestinal flora in hepatic disease. The experiments of Gyorgy and his co-workers (1, 2) have pointed to a possible relationship existing between intestinal bacteria and the production of massive hepatic necrosis in rats. With the addition of aureomycin and other antibiotics to the diet of such animals, these investigators have shown that survival is possible under conditions which will otherwise produce a diffuse hemorrhagic necrosis of the liver. A similar phenomenon may explain, at least in part, the improvement noted in certain cases of chronic hepatic disease who have been treated with antibiotics (3, 4). Dramatic but temporary improvement has also been observed with the use of aureomycin administered intravenously in cases of hepatic coma (5). Whether the improvement noted in such cases can be related specifically to an antibiotic effect remains subject to final proof.

Current interest in the bacteriology of the liver has been aroused by Rienhoff (6) and others who propose ligation of the hepatic artery in man for the relief of portal hypertension and bleeding esophageal varices. In dogs such a procedure is known to be highly fatal (7). Markowitz (8) has recently demonstrated, however, that death from the interruption of arterial blood flow to the liver in dogs can be prevented in most cases with the use of penicillin administered immediately postoperatively. This is thought to be related to the prevention of spread of gas bacillus infection in the liver which otherwise ensues in such preparations when the antibiotic is omitted (7, 9).

It has been conclusively demonstrated that bacteria, especially of the genus *clostridia,* are regularly present in the livers of dogs (10–14). Experimental studies in these and other animals have suggested that intestinal bacteria present in the liver and other tissues may be of importance in the pathogenesis of shock and radiation injury (15, 16). Because of these animal experiments and the known function of the liver as the significant filtering organ for portal blood, it seemed of some importance to ascertain whether or not viable bacteria are present in the human liver. If bacteria were demonstrated to be consistently present, conclusions from animal experiments in these important areas of trauma would be more directly applicable to human situations.

Mason and Hart (17) have demonstrated anaerobic organisms in five human livers studied post mortem. This observation is not particularly surprising since it is believed that bacteria of all types may invade the blood stream and the tissues after death. The principal source of such organisms is probably the intestinal tract from which anaerobes reaching the liver could easily originate. Romieu and Brunschwig (18) have recently reported a series of twelve human patients from whom liver biopsies were taken and cultured at the time of laparotomy for neoplasms of the lower gastrointestinal tract. In one of these a positive culture of *Bacillus pyocyaneus* was found not only in the liver but also in the urine and in the operative wound. From this study the authors concluded that there is no "normal flora" of the human liver.

The present investigation was undertaken to determine the possible presence of living bacteria in the human liver in normal persons and in acute and chronic liver disease. It was believed that if the liver is capable of a bactericidal function in life, this bactericidal function was more likely to be impaired when other structural and functional impairment of the liver coexisted. Positive results in such a study would provide a firmer

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basis than now exists for the use of antibiotic therapy in such patients.

EXPERIMENTAL METHODS

All of the specimens used in this study were obtained by means of a biopsy of the liver with a Vim-Silverman needle. Eighty-six samples were obtained from 66 patients, some of the patients having been biopsied on more than one occasion (Table I). Twenty-five of the specimens were obtained with the Silverman needle at the time of laparotomy; eleven from the right lobe and fourteen from the left lobe. All the others were from the right lobe via the transpleural approach. Liver biopsies were also taken from twenty anesthetized dogs (Table II).

A sterile technic was employed in all instances. In the non-laparotomized humans and in the dogs, the biopsy site was thoroughly cleansed and painted twice with merthiolate. The area was then draped and a stab wound made after infiltration with one per cent novocaine (novocaine was not used in the anesthetized dogs). When the specimen of liver was obtained a small piece was immediately removed and planted in 20 cc. of broth prepared according to the formula of Kämmerer and Miller (19).[4] The liver specimens were macerated against the bottom of the tube with a sterile blunt glass rod, and the

[4] This media was used as a primary one in this study since it was experimentally shown that it would support the growth of certain intestinal anaerobic flora not supported by Brewer's thioglycollate media.

TABLE I

Bacteriological studies of human liver biopsies

	Diagnosis	Cultures		Remarks
		Aerobic	Anaerobic	
Case 1	Acute hepatitis	Negative	Negative	
Case 2	Acute hepatitis	Negative	Negative	
Case 3	Acute hepatitis	Negative	Negative	
Case 4	Acute hepatitis	Negative	Negative	
Case 4	Acute hepatitis	Negative	Negative	Biopsy 10 days later
Case 4	Acute hepatitis	Negative	Negative	Biopsy 6 months later
Case 5	Acute hepatitis	Negative	Negative	
Case 5	Acute hepatitis	Negative	Negative	Biopsy 30 days later
Case 6	Acute hepatitis	Negative	Negative	
Case 6	Acute hepatitis	Negative	Negative	Biopsy 30 days later
Case 7	Acute hepatitis	Negative	Negative	
Case 8	Acute hepatitis	Negative	Negative	
Case 9	Acute hepatitis	Negative	Negative	
Case 10	Acute hepatitis	Negative	Negative	
Case 11	Acute hepatitis	Negative	Negative	
Case 12	Acute hepatitis	Negative	Negative	
Case 13	Acute hepatitis	Negative	Negative	
Case 14	Acute hepatitis	Negative	Negative	
Case 15	Acute hepatitis	Negative	Negative	
Case 16	Acute hepatitis	Negative	Negative	
Case 17	Acute hepatitis	Negative	Negative	
Case 18	Acute hepatitis	Negative	Negative	
Case 19	Acute hepatitis	Negative	Negative	
Case 20	Chronic hepatitis	Negative	Negative	
Case 21	Chronic hepatitis	Negative	Negative	
Case 21	Chronic hepatitis	Negative	Negative	Biopsy 9 weeks later
Case 22	Chronic hepatitis	Negative	Negative	
Case 23	Chronic hepatitis	Negative	Negative	
Case 24	Chronic hepatitis	Negative	Negative	
Case 25	Chronic hepatitis	Negative	Negative	
Case 26	Chronic hepatitis	Negative	Negative	
Case 27	Chronic hepatitis	Negative	Negative	
Case 28	Chronic hepatitis	Negative	Negative	
Case 29	Hepatic cirrhosis	Negative	Negative	
Case 30	Hepatic cirrhosis	Negative	Negative	
Case 30	Hepatic cirrhosis	Negative	Negative	Biopsy 6 weeks later
Case 31	Hepatic cirrhosis	Negative	Negative	
Case 32	Hepatic cirrhosis	Negative	Negative	
Case 32	Hepatic cirrhosis	Negative	Negative	Biopsy 8 weeks later
Case 33	Hepatic cirrhosis	Negative	Negative	
Case 34	Hepatic cirrhosis	Negative	Negative	
Case 35	Hepatic cirrhosis	Negative	Negative	
Case 35	Hepatic cirrhosis	Gram neg. bacillus*	Gram neg. bacillus*	Left lobe at laparotomy
Case 36	Hepatic cirrhosis	Negative	Negative	

TABLE I—*Continued*

	Diagnosis	Cultures		Remarks
		Aerobic	Anaerobic	
Case 37	Hepatic cirrhosis	Fungus at 3 weeks†		Left lobe at laparotomy
Case 38	Hepatic cirrhosis	*Strep. pyogenes, E. coli, P. vulgaris & P. mirabilis*		Biopsy 30 minutes after death
Case 39	Hepatic cirrhosis	Negative	Negative	
Case 40	Hepatic cirrhosis	Negative	Negative	
Case 41	Hepatic cirrhosis	Negative	Negative	Right lobe at laparotomy
Case 41	Hepatic cirrhosis	Negative	Negative	Left lobe at laparotomy
Case 42	Hepatic cirrhosis	Negative	Negative	Right lobe at laparotomy
Case 42	Hepatic cirrhosis	Negative	Negative	Left lobe at laparotomy
Case 43	Hepatic cirrhosis	Negative	Negative	Right lobe at laparotomy
Case 43	Hepatic cirrhosis	Negative	Negative	Left lobe at laparotomy
Case 44	Hepatic cirrhosis	Negative	Negative	
Case 45	Fatty liver	Negative	Negative	
Case 46	Fatty liver	Negative	Negative	
Case 47	Fatty liver	Negative	Negative	
Case 48	Fatty liver	Negative	Negative	
Case 49	Fatty liver	Negative	Negative	
Case 50	Fatty liver	Negative	Negative	
Case 51	Hemolytic jaundice	Negative	Negative	
Case 52	Amebic hepatitis	Negative	Negative	
Case 53	No liver disease	Negative	Negative	
Case 54	No liver disease	Negative	Negative	
Case 55	No liver disease	Negative	Negative	
Case 56	No liver disease	Negative	Negative	
Case 57	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 57	No liver disease	Negative	Negative	Left lobe at laparotomy
Case 58	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 58	No liver disease	Negative	Negative	Left lobe at laparotomy
Case 59	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 59	No liver disease	Negative	Negative	Left lobe at laparotomy
Case 60	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 60	No liver disease	Negative	Negative	Left lobe at laparotomy
Case 61	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 61	No liver disease	Negative	Negative	Left lobe at laparotomy
Case 62	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 62	No liver disease	Negative	Negative	Left lobe at laparotomy
Case 63	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 63	No liver disease	Negative	Negative	Left lobe at laparotomy
Case 64	No liver disease	Negative	Negative	
Case 65	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 65	No liver disease	Negative	Negative	Left lobe at laparotomy
Case 66	No liver disease	Negative	Negative	Right lobe at laparotomy
Case 66	No liver disease	Negative	Negative	Left lobe at laparotomy

* A Klebsiella-like organism not further identified.
† Not believed to be a contaminant; grown directly from a piece of liver tissue.

tube was shaken manually to distribute the particulate material. Ten milliliters of the inoculated medium were then transferred by pipet to another tube and 1 ml. of this was placed in 10 ml. of Brewer's thioglycollate broth. The initial culture was incubated anaerobically under tensions of ten per cent hydrogen, ten per cent carbon dioxide, and eighty per cent nitrogen in Brewer's anaerobic jars. The 10 ml. transfer and the thioglycollate subculture were incubated aerobically at 37° C. Microscopic examination of stained preparations and subcultures to blood-agar plates were made at forty-eight and ninety-six hours from all three liquid media. The blood-agar plates were made in duplicate with one set incubated aerobically and the other anaerobically under the conditions described above. The blood-agar plates were examined for growth at twenty-four hours and forty-eight hours. Positive cultures were identified by the usual bacteriological procedures.

RESULTS

Eighty-five biopsies of human livers were taken from living patients and handled in the above manner. One biopsy was obtained thirty minutes after death from a patient with advanced liver disease. The results of these studies are summarized in Table I.

It can be seen in Table I that there were three cultures that yielded organisms both aerobically and anaerobically (case 35, case 37, and case 38) in the human material. One of these (case 38)

TABLE II

	Diagnosis	Aerobic	Anaerobic
1. Dog 1	Normal liver	Negative	Clostridia
2. Dog 2	Normal liver	Negative	Clostridia
3. Dog 3	Normal liver	Negative	Negative
4. Dog 4	Normal liver	Negative	Negative
5. Dog 5	Normal liver	Negative	Negative
6. Dog 6	Normal liver	Negative	Negative
7. Dog 7	Normal liver	Negative	Negative
8. Dog 8	Normal liver	Negative	Negative
9. Dog 9	Normal liver	Negative	Negative
10. Dog 10	Normal liver	Negative	Negative
11. Dog 11	Normal liver	Negative	Negative
12. Dog 12	Normal liver	Negative	Negative
13. Dog 13	Normal liver	Negative	Clostridia
14. Dog 14	Normal liver	Negative	Clostridia
15. Dog 15	Normal liver	Negative	Clostridia
16. Dog 16	Normal liver	Negative	Negative
17. Dog 17	Normal liver	Negative	Clostridia
18. Dog 3a	Normal liver	Negative	Negative
19. Dog 4a	Normal liver	Negative	Clostridia
20. Dog 5a	Normal liver	Negative	Negative

was in the patient from whom a biopsy was taken thirty minutes after death. There were found growing from this liver a *Streptococcus pyogenes, Escherichia coli, Proteus vulgaris,* and *Proteus mirabilis.* From a specimen of case 35 obtained from the left lobe of the liver at the time of laparotomy there was grown a gram-negative facultative aerobic organism, species unknown, which resembled closely a *Klebsiella.* Also from the left lobe of the liver at laparotomy a fungus was found to grow in case 37 which was of the *Aspergillus* species and believed to be non-pathogenic. This appeared to be growing out of a tiny fleck of liver tissue and was not believed to be a contaminant. None of these patients was receiving antibiotics at the time of biopsy. The cultures from all of the other cases were negative, both under aerobic and anaerobic conditions. The biopsies taken from the dogs, on the other hand, showed a growth in seven of the twenty specimens (Table II). This is considered to be a significant check against both the technic used for obtaining the biopsy specimen and for the bacteriological method of isolation.

DISCUSSION

There is abundant evidence in the literature that not only the liver but other organs of dogs, cats, guinea pigs, hogs and rabbits may harbor bacteria during life (10, 11, 20). The liver has been cited as the source of bacteria or bacterial products resulting in the death of dogs where liver fragments have been placed in the peritoneal cavity (12, 14, 21, 22) Although there has been some controversy as to the actual cause of death in these experiments, it appears likely that it results from the breakdown products of bacterial growth in the liver implanted in the peritoneal space rather than directly from the bacteria themselves (23–26). It has been shown that fresh sterile liver implanted in the peritoneal cavity will not cause death, but fresh sterile liver incubated with added bacteria will cause death when implanted in the peritoneum of a recipient animal (14). The importance of these experimental findings from a practical point of view seem to relate to hepatic trauma either through an external force or secondary to abdominal surgery where hepatic tissue may be left free in the peritoneal cavity (25, 27). Such a possibility also exists when a portion of the liver is rendered relatively anoxic by interruption of its arterial blood supply (17). An actual or potential bacterial flora of the liver may likewise be of some importance in shock where an insufficient oxygenation of the liver may lead to a rapid multiplication of anaerobic organisms.

The role of the liver as a screening organ for bacteria coming from the intestinal tract has received some attention in the past. Berg, Zau, and Jobling (13) pointed out a possible bacteriostatic function of the liver by demonstrating positive cultures from the livers of dogs with negative cultures from pure bile in the same animals. When the bile was diluted, however, these cultures then became positive, suggesting that the bacteriostatic property was altered with dilution. Whipple and Harris (28) have reported four cases of hepatic cirrhosis in whom there was found a *Bacillus coli* septicemia. The authors believed that this reflected an interference of the function of the liver as a bacterial filter due to the circulatory changes of cirrhosis and to a possible lowering of resistance to bacteria. Beeson, Brannon, and Warren (29) conclusively demonstrated in patients with subacute bacterial endocarditis that the liver served as a filtering organ for bacteria. They showed that the concentration of bacteria in the hepatic vein blood was strikingly less than that in the peripheral circulation.

It has not as yet been definitely established that there is seeding of the liver with bacteria coming from the intestine. This seems likely, however,

since it has been shown by Ellis and Dragstedt (14) that fetal dog livers will not produce the "liver autolysis" previously described. It has also been shown by Brim (30) that only six of one hundred livers from human stillborn infants showed positive growth upon culture. In these six cases, the organisms grown were characteristically those present in the intestinal tract. These experiments tend to show that when there are no bacteria in the intestine, as in the fetus, bacteria are not likely to be present in the liver.

That the portal blood contains bacteria has likewise not been established. Arnold demonstrated, on the other hand, by cannulating the thoracic duct in dogs that bacteria could be found in the thoracic lymph five to thirty minutes after they had been placed in the duodenum along with alkaline solutions of egg white (31). Thus, it is entirely possible that such bacteria as are present may have reached the liver and other tissues of animals via the thoracic duct and the general circulation.

The experimental data herein reported show that in hepatic diseases and in normal livers viable bacteria are present in the liver in life only in a very small proportion of cases. As soon as thirty minutes after death, however, multiple organisms may be demonstrated.

Some criticism may be directed at the technic employed in these cases. Since a Vim-Silverman needle was used in all cases, the biopsy undoubtedly came from the peripheral portion of the liver. Trusler and Martin (32) have shown that the stromal elements, that is, blood vessels, bile ducts and connective tissue are far more effective in the production of fatal hepatic peritonitis in dogs than are the parenchymal elements. These authors state that the periphery of the liver contains a relatively large proportion of parenchymal tissue and hence fewer bacteria. It was for this reason that the livers of the dogs used in this study were biopsied and cultured with a technic identical to that used in the human cases. With the same procedure, therefore, dog livers were found to harbor bacteria in a far greater percentage than did human livers.

Of some interest is the fact that growth was demonstrated in the left lobe of two of the cases (case 35 and case 37). The right lobe in case 35 had previously been biopsied and found to contain no bacteria. Trusler and Reeves (33) found that the bacterial content in the left lobe of the liver in dogs is more profuse than in the right lobe. This may be related to the stream lining of portal blood to the liver, causing a greater concentration of organisms or otherwise creating local conditions which are more favorable for bacterial survival and multiplication (34, 35). It should be remembered at the same time, however, that both of these biopsies were taken *at surgery,* and the manipulation of the gastrointestinal tract, the anesthesia administered, or the presence of anoxia may have influenced the finding of bacteria in the liver. The biopsies taken at surgery from the right and left lobes of other cases with hepatic cirrhosis (cases 34, 41, 42, and 43), on the other hand, and from patients with no hepatic disease (cases 57, 58, 59, 60, 61, 62, 65, and 66) showed no growth.

Although it would appear from this study that bacteria ordinarily are not found in the liver of humans, it does not seem possible to conclude that the presence of bacteria in the liver arising from the intestinal tract play no major role in disease. It has been shown that bacteria may invade the liver within a very short time after death. It is also possible that this may take place in certain abnormal physiologic states such as in connection with abdominal trauma, surgery, irradiation, shock, anoxia, or other circumstance leading to local changes in the intestinal wall. These data seem to show, however, that bacteria are much less commonly present in the human liver than in the liver of dogs. Due caution must therefore be exercised in the application to man of experimental data from dogs involving the flora of the liver.

SUMMARY AND CONCLUSIONS

Animal experiments point to a possible role played by the intestinal flora in hepatic disease. The presence of bacteria in the liver suggests an explanation for death due to "liver autolysis" and for death following hepatic artery ligation in dogs. The presence of bacteria in human liver was sought for by means of culture of liver biopsy material under aerobic and anaerobic conditions. Only two of eighty-five cultures from living patients were found to be positive. It may be of some significance that these cultures were taken from the left

lobe of the liver at the time of laparotomy. As a check of the technic, biopsies were taken from dogs and handled in an identical fashion. Thirty-five per cent of these were positive. It is conceded that although under special circumstances bacteria from the intestinal tract invade the human liver and may contribute to morbidity, caution should be exercised in the transfer to man of conclusions drawn from animal experiments.

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