Studies on the Outflow Tracts of the Liver *

II. On the Outflow Tracts of the Canine Liver with Particular Reference to its Regulation by the Hepatic Vein Sphincter Mechanisms

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THE METHOD of intrahepatic parenchymal injection of radiopaque medium developed for the hemodynamic demonstration of the outflow tracts of the liver and its use in the rat has been previously reported by this group.[11] In the process of extending its use to a larger laboratory animal—the dog—the unexpected opportunity to observe the canine hepatic vein sphincters in operation was offered to these investigators.

At the beginning of this study it was noted that dye from the intrahepatic parenchymal injection consistently failed to be removed by vascular structures. Contrary to the findings observed in rats where prompt delineation of the outflow tracts was readily obtained, in the dog dye remained near the site of injection within the confines of well-defined, sharply limited formation that closely resembled the radiological appearance of the gallbladder. This phenomenon consistently repeated itself in a considerable number of dogs and could be reproduced simultaneously in several lobes of the liver of the same animal.

In an attempt to explain the different response of the canine liver to the intraparenchymal injection of contrast medium, several hypotheses were considered. The possibility that the local use of the enzyme hyaluronidase might facilitate the removal of the contrast medium was explored with consistent failure. As a new starting point it was tentatively assumed that the hepatic vein sphincter mechanisms, known to be highly developed in the dog, might have been set in operation by the irritant properties of the radiopaque dye. Although this hypothesis left unexplained the nature of the bizarre, sharply delineated formations so consistently observed, it was decided to explore its possible merits.

In an effort to minimize the irritant effects of the dye and thus overcome the contraction of the sphincters thought to be preventing visualization of the outflow tracts, a solution of procaine hydrochloride was locally intraduced prior to the injection of the contrast medium. This attempt did not result in sufficient relaxation of the sphincter mechanisms to allow complete visualization of the outflow tracts. However, unexpected insight into the very nature of the entire phenomenon being observed was gained. It was realized that

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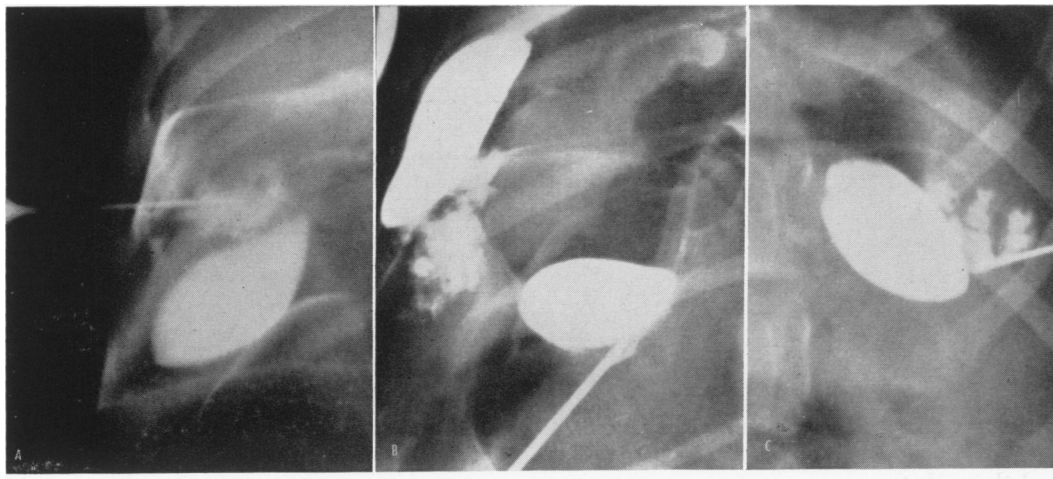

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FIG. 1. Results of intrahepatic parenchymal injection of radiopaque medium into the livers of three dogs. a) The contrast medium can be seen remaining near the site of injection within a well defined sharply limited formation resembling the radiological appearance of the gallbladder. The outflow tracts of the liver are not outlined by the dye. b) In this animal, two similar formations corresponding to two different injections can be observed. c) In the third animal, a comparable situation has followed the intraparenchymal injection into the left lobe of the liver.

at least some of the sharply delineated formations outlined by contrast medium may have been segments of hepatic veins enormously dilated in response to tightly contracted sphincters. Complete relaxation of the sphincter mechanism with corresponding visualization of the hepatic outflow tracts was subsequently obtained by the use of epinephrine.

With this newly gained knowledge, it became apparent that no study of the outflow tracts of the canine liver could be separated from the study of its regulatory mechanisms. Complete reviews of the extensive work on the regulatory mechanisms of hepatic blood flow, primarily by anatomists and physiologists, can be found in the literature.[1-6, 8] With the exception of the *in vivo* demonstration in small animals by quartz illumination technics, the majority of the methods used have offered indirect evidence of the operation of these sphincters.

It is the purpose of this paper to report on the use of the intrahepatic parenchymal injection of radiopaque medium for the direct functional demonstration of the outflow tracts of the canine liver; on the visual demonstration of the hepatic vein sphincters in operation in the anesthetized dog; and on the unusual ability of the hepatic veins to undergo extreme dilatation in response to contraction of these sphincters.

Materials and Methods

Fifty-one normal mongrel dogs, weighing 7.0 to 25 kilograms were used in this study.

Under intravenous thiopental sodium (Pentothal®), dogs were submitted to laparotomy on the x-ray table. Intrahepatic parenchymal injection of contrast medium was performed as follows: With the selected lobe of the liver held between the thumb and forefinger, a No. 20 needle was introduced into the parenchyma to a depth of 2.5 to 3.0 cm. Palpation and direct examination confirmed the correct position of the needle. With the needle attached to a length of plastic tubing, suction was applied by a syringe to ascertain that the tip of the needle was not in the lumen of a vessel or a biliary duct. Injection of 10

ml. of 50 per cent sodium diatriozoate (Hypaque®) was performed at the rate of 2.0 ml. per second. As a rule, an average of 10 x-ray exposures was obtained at one-second intervals starting from the time of initiating the injection. Exposure factors were 300 Ma, 1/15 second, 82–86 kv (depending on the size of the animal), at a target field distance of 100 cm.

When epinephrine was used, it was introduced either locally via the same needle used for the introduction of dye or systemically into a vein of the foreleg. In the cases where procaine was given, it was introduced through the same needle as the dye.

Results

Intrahepatic parenchymal injection of radiopaque medium was performed in 62 instances in 51 dogs. No immediate or delayed untoward reactions that could be ascribed to the procedure were detected.

In 39 animals subjected only to the intraparenchymal injection of contrast medium, the outflow tracts of the liver failed to be demonstrated. The dye remained within sharply delineated formations that closely resembled the radiological appearance of the gallbladder (Fig. 1).

In the two animals in which 10 ml. of procaine were locally administered prior to

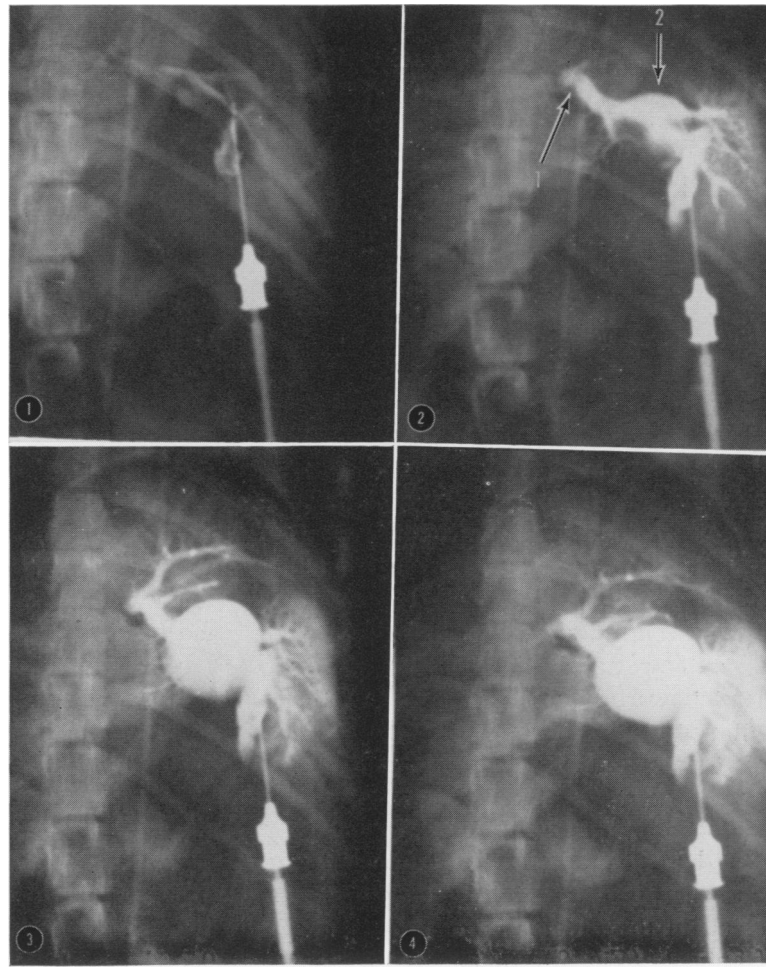

FIG. 2. Four films from a multiple exposure serial radiological study performed during the intrahepatic parenchymal injection of contrast medium (one second intervals). This examination confirmed the vascular nature of the phenomenon being observed. Ten ml. of procaine were injected though same needle two minutes prior to injection of radiopaque medium. In Frame 1, apparent partial relaxation of sphincter mechanisms has followed injection of procaine. Branches of hepatic vein are delineated by dye. In Frame 2, a perhaps more powerful sphincter has tightly contracted at entrance of hepatic vein to the vena cava (Arrow 1). Simultaneously, and possibly in response to contraction of sphincters, an intervening segment of the hepatic vein is beginning to dilate (Arrow 2). In Frames 3 and 4, sphincter remains contracted and intervening segment of hepatic vein has acquired unusual size and shape. As an additional result of obstruction to hepatic vein outlet, retrograde flow of dye into distal branches and even capillary vessels is seen.

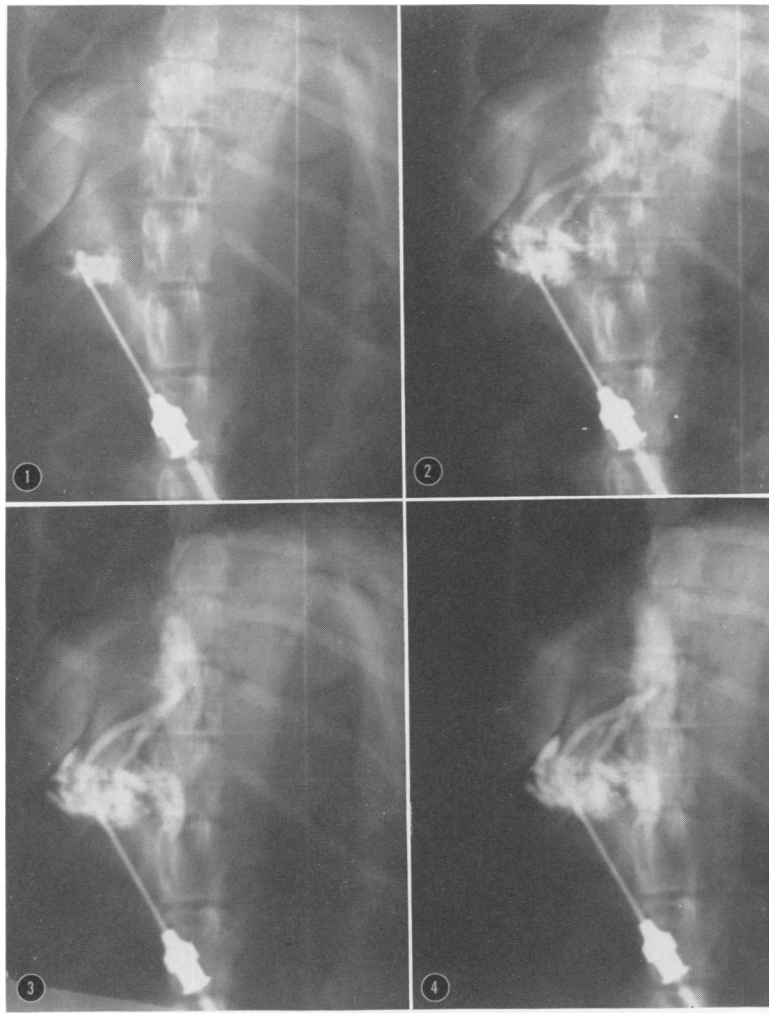

FIG. 3. Four films from a multiple exposure serial radiological study performed during the intrahepatic parenchymal injection of contrast medium. Films are separated by one second intervals. Representative example of complete visualization of the outflow tracts of the liver following the injection of epinephrine in a dog. Two minutes after the local injection of 0.5 ml. of epinephrine, the radiopaque medium was injected through the same needle. Under the effect of epinephrine, no contraction of the sphincter occurred and the dye can be seen outlining a hepatic vein which in turn empties into the inferior vena cava.

the injection of contrast medium, relaxation of the sphincter mechanisms in the small and intermediate branches of the hepatic veins appeared to occur permitting visualization of a considerable portion of the outflow tracts. However, a seemingly more powerful sphincter located at the entrance of the hepatic vein to the vena cava contracted tightly. As a result of this contraction an intermediate segment of the corresponding hepatic vein progressively dilated to finally acquire the unusual size and sharply limited characteristics observed in the previously mentioned group of animals (Fig. 2).

In four animals subjected to the local administration of 0.5 ml. of epinephrine prior to the injection of the contrast medium, complete relaxation of the sphincter mechanism appeared to have occurred. Dye from the site of injection delineated the outflow tracts draining the injected area, rapidly entering the vena cava and finally reaching the heart (Fig. 3). In two animals where the sphincter mechanisms had already been set in operation by a previous intraparenchymal injection of contrast medium, relaxation was not obtained by the subsequent local administration of 0.5 ml. of epinephrine. The sphincter mech-

anisms set in operation by the intraparenchymal injection of contrast medium also failed to be released by the subsequent systemic administration of 0.5 ml. of epinephrine.

Finally, in two animals that suffered unusual conditions of stress immediately prior to the intraparenchymal injection of contrast medium, self-release of the sphincter mechanisms appeared to occur and complete visualization of the outflow tracts draining the area of injection was observed (Fig. 4).

Discussion

The evidence collected during this investigation tends ot demonstrate that the outflow tracts of the canine liver are regulated to a great extent by the hepatic vein sphincter mechanisms. Although this concept is not new, and has received support from physiological experiments and radiological evidence,[13] it is believed that the type of visual demonstration provided by this study has not been reported before.

Under the conditions of these experiments it would appear that the intrahepatic parenchymal injection of contrast medium triggered, in some way, the mechanism responsible for contraction of the hepatic vein sphincters.[12] The nature of this reaction has not been completely clarified by these investigations. The original hypothesis, that local irritation of the intima of the

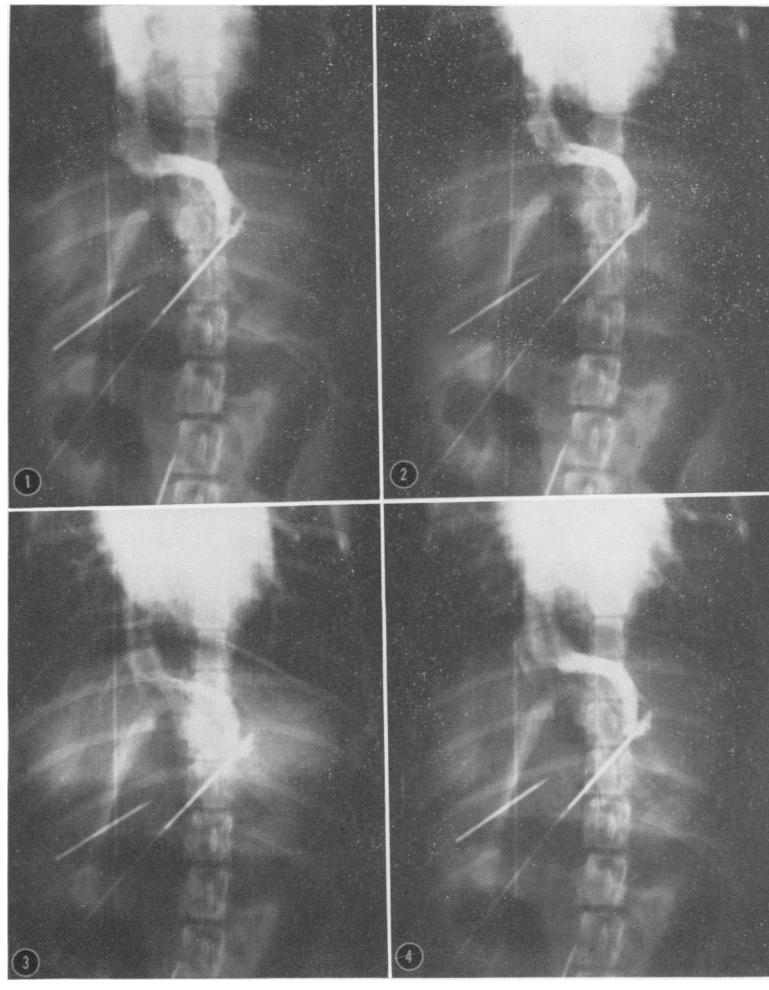

FIG. 4. Four films from a multiple exposure serial radiological study performed during the intrahepatic parenchymal injection of contrast medium. Films are separated by one second intervals. Intrahepatic parenchymal injection immediately after the animal was subjected to unusual conditions of stress. Self-release of the animal's own adrenalin may have occurred in this case. No contraction of the hepatic vein sphincters is seen. The contrast medium is removed from the site of injection by two vessels which converge to form a large hepatic vein. The thoracic segment of the inferior vena cava is well visualized. The fact that two vessels can be observed removing the dye from the site of the intraparenchymal injection shows that this was not a direct intravascular injection.

vessel by the iodinated compound was responsible for contraction of the sphincters, may have been invalidated by the fact that at least on one occasion, direct injection into a hepatic vein did not initiate this response. On the other hand, it is conceivable that the sphincter response may have been mediated through an altogether different mechanism such as a histamine-like reaction associated with the localized destruction of tissue caused by the intraparenchymal injection.

Whatever the nature of the reaction may be, some positive findings have been made evident by these studies. It was demonstrated that the local administration of epinephrine prior to the injection of the contrast medium completely prevented contraction of the hepatic vein sphincters and permitted opacification of the outflow tracts of the liver. Conversely, the same dose of epinephrine given after the sphincter mechanisms were set in operation by the intraparenchymal injection of dye failed to release the already contracted sphincters. It is possible that, once the sphincter mechanism has been set in operation, the resulting powerful contraction could only be released by considerably larger doses of exogenous epinephrine than the ones used in this investigation.

The possibility that self-release by the animal of its own epinephrine may have been responsible for the lack of contraction observed in the two animals that suffered unusual stress immediately before the intraparenchymal injection of dye may be considered. In both animals the response of the sphincter mechanism failed to occur.

One of the most outstanding findings in this investigation was the actual visual demonstration of the ability of the hepatic veins to undergo extreme dilatation in response to the contraction of the sphincters. Although this dilatation of the hepatic veins has been demonstrated to be responsible for the storage of blood in amounts equivalent to 59 per cent of the liver weight,[7] it was still difficult to accept that some of the huge formations being visualized were dilated segments of this venous system. It was necessary to see one segment of a hepatic vein actually "growing" behind a contracted sphincter before this facts was accepted (Fig. 3).

The extent to which the operation of these highly developed flow regulation mechanisms may have interfered with reported experiments investigating hepatic hemodynamic situations in dogs is difficult to evaluate.

The implications of the blood reservoir function of the liver are not well understood at this time. Specific release of the sphincter mechanisms by epinephrine, with the corresponding delivery of large amounts of blood into the circulation, may perhaps indicate that this type of response is intended to meet the increased circulatory demands associated with conditions of stress. That, to a lesser degree, this blood reservoir function of the liver may exist in man has been suggested by the work of other investigators.[9]

Summary and Conclusions

The intrahepatic parenchymal injection of contrast medium triggered in some way, the response of the hepatic vein sphincter mechanisms in the canine liver.

Contraction of the sphincters prevented visualization of the outflow tracts of the liver and induced extreme dilatation of the segments of hepatic veins located behind closed sphincters.

Contraction of the sphincters was prevented by administration of epinephrine prior to the intraparenchymal injection of contrast medium. The same dose of epinephrine failed to release the sphincter contraction once that it was evoked by the intraparenchymal injection of radiopaque dye.

In certain experiments in this series, self-release of the animal's own epinephrine may have occurred as a response to conditions of unusual stress. Corresponding failure of the intraparenchymal injection of contrast medium to induce contraction of the sphincters was observed in these animals.

The blood reservoir function of the canine liver, as suggested by other investigators, seemed to receive support from the unique ability of the hepatic veins to store blood as demonstrated by these studies. The fact that epinephrine was the specific agent controlling the hepatic vein sphincters may, perhaps, indicate that sudden release of large amounts of stored hepatic blood into the circulation is part of the response intended to meet increased circulatory demands associated with conditions of stress.

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