mechanism of the action of dibutyl cyclic GMP in the cells is unknown, the Ca ions may be supplied to the contractile elements. Experiments to clarify the physiological and pharmacological roles of naturally occurring cyclic GMP and of exogenously applied dibutyl cyclic GMP in the intestinal smooth muscle are in progress.

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RELATIONSHIP OF HQ-275 TO BILIARY EXCRETION AND PORTAL BLOOD FLOW IN DOGS

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In a previous report we have demonstrated that 1-morpholinoacetyl-2-methyl-3-phenyl-4-oxo-1, 2, 3, 4-tetrahydro quinazoline hydrochloride (HQ-275) has a potent choleretic activity which is hydrocholeretic and preventive and/or therapeutic effects against CCl4-induced hepatic damages in rats (1). In this paper, the relationship of HQ-275 to biliary excretion and portal blood flow was examined minutely in dogs. In addition, the influence of HQ-275 on pancreatic-juice secretion was also tested.

Eight adult mongrel dogs of both sexes, weighing 13-18 kg were used. These were fasted for 18 hr before experiments, but water was given ad libitum. Animals were anesthetized with sodium pentobarbital (15 mg/kg, i.p.) and urethane (1.2 g/kg, s.c.) and a tracheal cannula was inserted. The surgical procedure consisted of a midline abdominal incision. All animals were ventilated artificially with air. When the common bile duct and main pancreatic duct had been carefully isolated, polyethylene tubes (I.D.: 1.0 mm, O.D.: 1.4 mm) were centrally inserted into the common bile duct and through the papilla into the main pancreatic duct, respectively. The gall-bladder was resected and the accessory pancreatic duct was also ligated and cut. After a tight ligation of the tubes, the
tube which had been inserted into the main pancreatic duct was connected to a drop counter and another tube was led to a graduated pipette. When the biliary and pancreatic-juice outflow had reached a steady state, the drugs were administered and the volume of the each sample of bile collected at 30-min periods for 5-min were measured. After measurement of biliary volume collected in a graduated pipette, 0.2 ml of each collection was dried for 10 hr in a constant oven at 105-110°C after which each dry residue was weighed and the concentration of biliary solid contents was determined.

For the experiment of portal vein circulation, portal blood flow was measured by multi-channel square wave electromagnetic flowmeter arranged flow probe (Nihon Kohden Co., Ltd.).

Blood pressure of the femoral artery was recorded with a routine mercury manometer method and for the heart rate a tachograph was used. The drugs, having been dissolved in physiological saline were injected into the femoral vein.

Recently, it has been demonstrated that one of the alterations in biliary excretion is temperature dependent (2). The animals were therefore maintained in a relative humidity of 60% at a room temp. of 24±1°C and body temp. during the experiment was monitored continuously (rectal thermistor probe) and maintained at 37±1°C by a heating pad placed under the body.

A statistical comparison of the data was performed employing the Student's t test. Values of P<0.05 were representative of significant differences between means (3).

As shown in Fig. 1, it is evident that biliary outflow was maximum during the first

![Graph](image-url)  
**Fig. 1.** Upper curves (solid lines): choleric activity as % increase of the biliary flows. Lower curves (dotted lines): solid content concentration. Bile, collected every 30-min for 5-min after administration of the drugs, was measured. Those values were in respect to those of basal. Administration of HQ-275 3 mg/kg, i.v. (△), 10 mg/kg, i.v. (○) was carried out at '0' time, respectively. Each vertical line indicates the S.E. of six or eight animals, *, indicates the values to be significantly different from controls. (P<0.05)
30 min. HQ-275 was observed in the biliary excretion in dogs where gall-bladder had been resected as well as rats which had undergone a cholecystostomy. It is therefore suggested that the biliary excretion of HQ-275 is not particularly affected by cholekinetic action.

The portion of the solid contents per biliary volume, excreted after HQ-275 administration, was lower in concentration than cholaneretic agents which accelerate the concentration of solid contents per biliary volume. Thus the effect of HQ-275 appears to be dependent on the hydrocholeretic action which mainly increases the portion of water in biliary excretion.

Influence of HQ-275 on pancreatic-juice excretion was not observed at all.

As for changes in portal vein circulation, administration of HQ-275 markedly increased, dose-dependently, portal blood flow. As shown in Fig. 2, i.v. doses of more than 1 mg/kg of HQ-275 caused a slight increase in the portal blood flow, the degree de-
pending on dosage. With a dose of 30 mg/kg of HQ-275, the flow increased markedly by 86% immediately after the injection, and then lasted approx. 20-25 min, the increase of portal blood flow being closely related to the volume of biliary excretion.

Changes in the femoral artery blood pressure were not recognized so clearly in a dose of 1 mg/kg, i.v., but with a dose of 10 mg/kg the pressure, which had been 125-145 mmHg originally, fell transiently by 10 mmHg immediately after the injection, and then returned to the control levels 5-20 min after the short-lasting elevation. On the other hand, HQ-275 slightly increased the heart-rate.

From these results, it has been clearly demonstrated in the dog that HQ-275, a hydrocholeretic drug, has an effect on the action of portal blood flow and biliary excretion.

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STUDIES ON PHOSPHOLIPIDS COMPOSITION OF HEPATIC MICROSONES FROM PROLONGED ETHANOL-TREATED RATS

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In a previous paper the authors reported that prolonged ethanol ingestion enhanced the activity of aniline p-hydroxylase and increased cytochrome P-450 content. By contrast, when ethanol was withdrawn and substituted for tap water 24 hr prior to sacrifice the activity of aniline p-hydroxylase and cytochrome P-450 content was identical with that of control rats (1-2).

The interaction of drugs with microsomes produces an enzyme-substrate complex and modifies the physical properties, amounts, composition and turnover of constitutive membrane components (3). It is thought that one of the functions of the phospholipids of the endoplasmic reticulum is participation in regulation of enzyme activity. The physical and biochemical properties of tightly-bound microsomal enzymes such as cytochrome P-450 appear to depend to a considerable degree on the phospholipid environment with which it is associated in the membrane.

Thus it is reasonable to expect that the treatment which affects the structure and composition of microsomal phospholipids alters the activity of microsomal mixed-function oxidase.