total fatty acid values of the skin in Case 1 are greatly diminished when compared with those of the control subject (Case 2). In spite of the great difference in the amount of fat present in this tissue, we find that the qualitative characteristics of the fatty acids as regards average molecular weight and average iodine number are practically the same in both instances.

That there is a definite lack of fatty acids in these tissues becomes even more striking when we consider the calculated values for the neutral fatty acids. These calculations disclose that the approximate values for the neutral fat fatty acids in the hepatic tissue of our control subject (Case 2) are 5 times that of those for the child with the generalized lipodystrophy, while those in the skin are 50 times that of those in Case 1. Even more striking is the finding that the tissues in the perirenal region of Case 2 contained almost 400 times as much neutral fat as those in Case 1. From these data, it appears that there is a marked lack of fatty material in the body of the child with generalized lipodystrophy, which confirms the clinical and pathological (gross and microscopic) diagnosis. Further, we may conclude that this deficiency apparently is specifically due to a lack of neutral fat fatty acids from the various tissues studied. The name "lipohistiodiaresis" (lack of fat in the tissues) has been suggested to describe this phase of the condition.

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Increased Serum Phosphatase Activity Without Hyperbilirubinemia after Ligation of Hepatic Ducts in Dogs.

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In man with complete obstruction of the common bile duct, hyperbilirubinemia is associated with markedly increased phosphatase activity of the serum. When obstruction of the common duct is incomplete (as frequently in choledocholithiasis, cholangeitis) or in intrahepatic biliary tract obstruction (hepatic metastases, etc.), little or no jaundice may result but the serum phosphatase is usually

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distinctly elevated. In hepatitis ("catarrhal" jaundice), even marked hyperbilirubinemia is associated quite regularly with comparatively little rise in serum phosphatase activity.[1]

Corresponding changes in serum phosphatase have been produced experimentally in the dog: Ligation with complete obstruction of the common bile duct[2,3,4] results in extremely high serum phosphatase levels; hepatitis produced by hepatotoxic drugs[4,5,6] or by Leptospiral inoculation[4] causes increases in serum phosphatase generally considerably less than those observed after common duct ligation, though hyperbilirubinemia may be as marked or more marked.†

The dissociation of serum phosphatase and serum bilirubin levels observed clinically with incomplete obstruction of the biliary tract has been little studied experimentally but was reproduced by Freeman, Chen and Ivy[4] in 2 dogs following ligation of hepatic ducts draining approximately ⅓ of the liver. Though jaundice did not develop, the serum phosphatase rose to 25.8 and 37.9 Bodansky units per 100 cc, respectively; in the one instance followed, there was a spontaneous, gradual fall to almost normal levels after 2 months. Confirmatory data are recorded here together with such additional studies on the urine as bear upon the interpretation of the blood changes.

Methods. In 4 dogs following nembutal anesthesia, the hepatic ducts were identified by aspiration of bile and a variable number (draining 1/5, 1/4 or 1/2 of the liver) were tied off with silk. Periodic postoperative examinations were made of the serum for phosphatase (Bodansky method), total cholesterol (Bloor method) and bilirubin, and of the urine for "alkaline" phosphatase (King

[1] For references and additional data see Gutman, A. B., Olson, K. B., Gutman, E. B., and Flood, C. A., *J. Clin. Invest.*, 1940, **19**, 129.

[2] Bodansky, A., and Jaffe, H. L., PROC. SOC. EXP. BIOL. AND MED., 1934, **31**, 1179.

[3] Armstrong, A. R., King, E. J., and Harris, R. I., *Canad. M. A. J.*, 1934, **31**, 14.

[4] Freeman, S., Chen, Y. P., and Ivy, A. C., *J. Biol. Chem.*, 1938, **124**, 79.

[5] Armstrong, A. R., and King, E. J., *Canad. M. A. J.*, 1935, **32**, 379.

[6] Bodansky, A., *Enzymolog.*, 1937, **3**, 258.

† An interesting exception is *m*-toluylenediamine jaundice in dogs, which is associated with very high serum phosphatase and cholesterol values.[6] This type of jaundice, however, appears to be partly hemolytic, partly due to stasis of bile in the finer biliary radicles rather than to parenchymal injury.[7] A somewhat analogous condition, with high serum phosphatase, is seen clinically in certain drug-hypersensitive cases of post-arsphenamine jaundice, in which liver biopsies show obstruction of the intrahepatic biliary tract.[8]

[7] Naunyn, B., *Mitt. Grenzgeb. Med. u. Chir.*, 1919, **31**, 537.

[8] Hanger, F. M., and Gutman, A. B., *J. A. M. A.*, in press.

and Armstrong method) and bile. The animals were sacrificed after 4-9 weeks and the presence of intact ligatures with dilatation of the proximal hepatic ducts verified at postmortem.

Control preoperative serum and urine analyses were obtained. Nembutal anesthesia was found not to affect serum phosphatase values. Urine samples were obtained by catheter to avoid contamination with phosphatase- and bile-rich feces.

Results. The serum phosphatase activity increased within 24 hours after operation to reach 5-20-fold levels in 4 days and a peak usually between the first and second week; the maximum level varying with the number of hepatic ducts ligated. A spontaneous decline followed, with return to approximately normal levels after some 2 months. A roughly parallel rise in the total cholesterol content of the serum was noted though the return to normal was more rapid. No significant increase in serum bilirubin occurred except a transient rise to 0.5 mg % on the fourth day in Dogs 1 and 3. Bile pigments appeared in the urine within 24 hours after operation and persisted for many weeks, gradually decreasing in amount. Significant "alkaline" phosphatase activity was not present in any urine specimens with the exception of small amounts in the urine of Dog 3. At postmortem, the liver lobes tied off appeared to be normal grossly and showed only slight changes histologically.

Discussion. It is not clear whether the dissociation of serum phosphatase and bilirubin levels observed clinically with incomplete biliary obstruction and reproduced in these experiments should be regarded as incompatible with the "phosphatase retention" theory—that the increase in serum phosphatase levels in obstructive jaundice is due to retention of phosphatase normally excreted in the bile. One factor that might cause such dissociation in blood levels following

TABLE I.

Phosphatase Activity (P, in Bodansky units/100 cc) and Total Cholesterol (C, in mg/100 cc) of the Serum after Ligation of Hepatic Ducts in the Dog.

	Dog 1 ¼ liver ligated		Dog 2 ⅕ liver ligated		Dog 3 ½ liver ligated		Dog 4 ¼ liver ligated	
Time post-op.	P	C	P	C	P	C	P	C
Pre-op.	3.7	120	4.1	154	3.4	138	2.8	176
1 day	7.3	172						
4 "	26.2	171	19.6	182	61.7	250		
1 wk			21.7	247			29.4	235
1½ "	16.9	192	22.1		74.0	435		
2½ "	11.2	117	9.9	154	49.1	268	25.1	207
4 "	6.8		6.8	149	28.2		13.4	205
5 "	4.4				14.7	195	7.8	169
7 "					9.2	149	7.2	
9 "					4.5		3.7	138

bile retention would seem to be the differential excretion of bilirubin and phosphatase in the urine.

In *man* with incomplete obstruction of the biliary tract and therefore only moderate retention of bile, urinary excretion of bile pigments may increase sufficiently to maintain the patient virtually free of jaundice. The human kidney is impermeable to serum phosphatase, however, and this difference in available excretory channels appears to be partly responsible for the observed dissociation of serum phosphatase and bilirubin levels. In the *dog*, the blood and urine studies recorded here suggest that the same factors are responsible for the analogous dissociation in serum levels. By varying the number of hepatic ducts tied off, a positive correlation between the serum phosphatase level and the degree of obstruction could be demonstrated. The serum phosphatase values in our dogs are relatively high as compared with man but this corresponds with the extraordinarily high values in dogs with complete biliary obstruction; the serum bilirubin levels are relatively low, due to the greater clearance of the dog kidney. In the *cat*, on the other hand, "alkaline" phosphatase as well as bilirubin appears in the urine[9] and complete obstruction of the common bile duct results in comparatively little rise in either serum phosphatase or bilirubin.[10]

Factors other than differential renal excretion may contribute to the dissociation of serum phosphatase and bilirubin levels following bile retention since their level in the serum represents a quite complex dynamic equilibrium between the rate of secretion into the blood stream and the rate of excretion (by one or more channels), metabolism or deposition in the tissues. Though not open to direct measurement, the important influence of these latter factors on the serum phosphatase level is indicated by the wide range in serum phosphatase values in man with complete common duct obstruction.[1‡]

We conclude that the occurrence of increased serum phosphatase activity with little or no jaundice following incomplete biliary tract

[9] Flood, C. A., Gutman, E. B., and Gutman, A. B., *Am. J. Physiol.*, 1937, **120**, 696.

[10] Cantarow, A., Stewart, H. L., and McCool, S. G., PROC. SOC. EXP. BIOL. AND MED., 1936, **35**, 87.

‡ We are concerned here only with incomplete biliary obstruction, not with liver parenchymal injury as a cause of dissociated blood values. Bodansky has shown[6,11] that in the latter case there is selective impairment of different liver functions by various hepatotoxic drugs.

[11] Bodansky, A., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 800.

obstruction is not inconsistent with the "phosphatase retention" theory. As to whether the increased serum phosphatase is of hepatic or osseous origin, our results do not exclude the one or the other possibility since occlusion of the excretory biliary channels would tend to cause retention of bile constituents of both hepatic and extra-hepatic origin.

Summary. Ligation of hepatic ducts in 4 dogs resulted in increased phosphatase but not bilirubin in the serum, increased bilirubin but not phosphatase in the urine. The dissociation in the blood is thought to be due largely to differential renal excretion and to be consistent with the "phosphatase retention" theory.

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Breast Cancer Produced in Male Mice of the C57 (Black) Strain of Little.

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Bittner[1] has shown that hybrids from a cross between a mouse from a strain having a high incidence of mammary cancer and one from a low tumor strain have a high or low incidence of breast cancer depending on what type of mother they nurse. If the nursing mother comes from the strain having the high incidence of spontaneous tumors, a large percentage of the female hybrids will develop mammary cancer. If they are nursed, on the other hand, by a female from the low tumor strain very few will develop breast cancer. Female mice from a high cancer strain nursed by their own mothers have a high incidence of mammary cancer while if they are foster-nursed by a mouse from a low tumor strain the chance that they will develop breast cancer will be materially reduced.

An attempt was made to confirm this observation on a different strain of animals. Mice of the RIII (Paris) strain of Dobrovolskaia Zavadskaia were given to a female of the C57 (black) strain of Little to nurse while the young of the latter were given to the RIII mother. The RIII females have an incidence of spontaneous mammary cancer of 70% in virgin females. The incidence in C57 black females is less than 1%. The incidence of breast

[1] Bittner, J. J., *Am. J. Ca.*, 1939, **35**, 90.