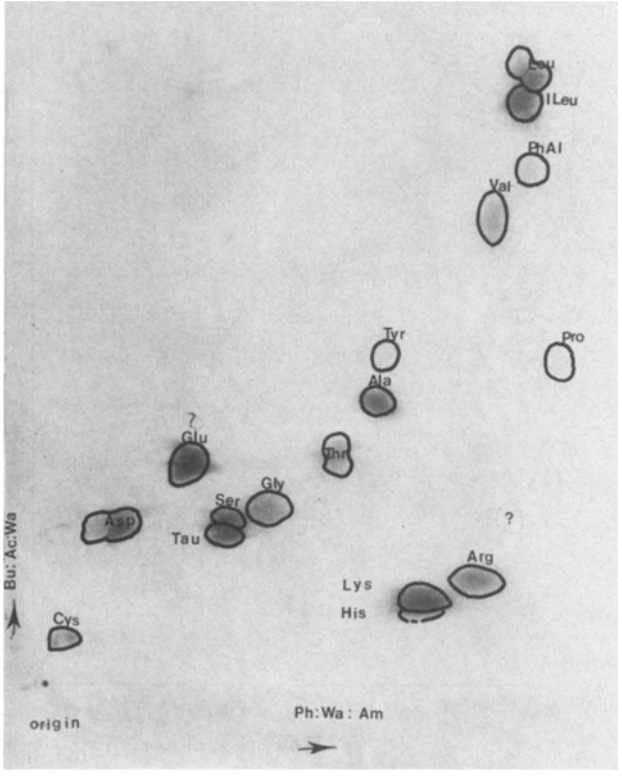
nilic acid had 2 spots with Rf values corresponding to dopa (0.2) and N-acetyl dopamine (0.67). This suggests that the tyrosine was hydrolyzed into dopa which in turn was converted into N-acetyl dopamine, as in insects[7]. The results on phenolase activity obtained from incubation experiments, using different phenolic substrates, revealed that the enzyme exists as prophenolase. This was inferred from the absence of color development in those specimens which were not treated with the activators. The enzyme was activated by sodium oleate and by injury. The activated enzyme reacted with the monophenol tyramine, the diphenolic substrates dopamine, catechol and epinephrine (adrenaline), the paraphenol hydroquinone, and the polyphenol pyrogallol. The enzyme showed no activity towards tyrosine, dopa, protocatechuic acid, and resorcinol. The enzyme activated by sodium oleate and injury was inhibited by phenylthiourea and diethyldithiocarbamate. The phenolase exists as the proenzyme in the vitellaria of *D. remorae* and is not substrate specific, oxidising mono, di and polyphenols. In contrast, phenolase of *Pricea multae* is substrate specific, reacting with only di and polyphenols without carboxyl- and amino-groups[8]. It would be interesting to extend the investigation to other monogeneans and determine whether the corresponding enzymes were substrate-specific or not. Although the amino acid cystine, considered to be involved in S-S linkages and stabilization of the egg-shell of *Fasciola hepatica, Pricea multae* and *Pseudomicrocotyle* sp.,[4,9] is also present in the acid hydrolysate of the eggs of *D. remorae*, further studies on the purified egg-shell would be necessary to confirm whether this amino acid is involved in the stabilization. In conclusion, evidence is presented for quinone tanning in the egg-shell of *D. remorae*.



2-dimensional chromatogram of acid hydrolysate of eggs showing ninhydrin-positive spots.

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Drug metabolism in spontaneously diabetic guinea pigs[1]

D. E. Cook[2], J. D. Jackson[2], M. R. Past[2,3], C. M. Lang[4] and L. P. Bullock[4,5]

Department of Biochemistry, College of Medicine University of Nebraska Medical Center, Omaha (NE 68105, USA), and Department of Comparative Medicine, College of Medicine, Milton S. Hershey Medical Center, Hershey (PA 17033, USA), 6 September 1983

Summary. Both sexes of spontaneously diabetic guinea pigs exhibit hyperinsulinemia (> 4-fold normal). This diabetic state is associated with the inhibition of hepatic drug metabolism in males but not females.

Although the guinea pig has been a useful experimental animal in the investigation of many pathologies, this has not been the case for diabetes. This is because the guinea pig is generally resistant to the production of sustained hyperglycemia after treatment with either alloxan[6] or streptozotocin[7-10]. Since hyperglycemia is the criterion most often used to indicate that experimentally induced diabetes has been established, attempts to use the guinea pig as a diabetic model in the traditional manner have been met with frustration. Consequently, the scant literature on biochemical studies in this model is limited to reports of acute studies[11]. Recently, however, spontaneous diabetes caused by an unknown infectious agent and characterized by non-ketotic glucosuria has been documented in a colony of guinea pigs[12,13]. This communication describes the effects of spontaneous diabetes in the guinea pig on hepatic drug metabolism, a process affected by diabetes in other laboratory animals[14].

Methods. Male and female spontaneously diabetic and normal

control guinea pigs were housed and maintained as previously described[12,13]. The diabetic guinea pigs had severe glucosuria (442–1512 mg%), elevated glucose tolerance test values and abnormal pancreatic pathology when sacrificed at 87–281 days of age. The normal control animals bracketed the age range of the diabetics at sacrifice (55–341 days) but exhibited none of the diabetic characteristics or pathologies. All animals were sacrificed over a 2-month period. Drug metabolism assays were conducted as previously described in detail[15]. Plasma insulin concentrations were determined by a radioimmunoassay[16] using purified guinea pig insulin supplied by the National Pituitary Agency and rabbit anti-guinea pig insulin serum supplied by Cecil Yip, Banting & Best Institute.

Table 1. Hepatic microsomal drug metabolism of a type I compound in normal and spontaneously diabetic guinea pigs[a]

	Aminopyrine metabolism (formaldehyde produced)			
	Male nmoles/min/mg protein	% change	Female nmoles/min/mg protein	% change
Normal	2.77 ± 0.51 (6)		1.92 ± 0.40 (3)	
Diabetic	1.76 ± 0.26 (8)	− 37	1.96 ± 0.17 (6)	+ 2

[a] Numbers given are mean ± SEM (number of animals).

Table 2. Hepatic microsomal drug metabolism of a type II compound in normal and spontaneously diabetic guinea pigs[a]

	Aniline metabolism (p-aminophenol produced)			
	Male nmoles/min/mg protein	% change	Female nmoles/min/mg protein	% change
Normal	0.66 ± 0.04 (6)		0.47 ± 0.03 (3)[b]	
Diabetic	0.42 ± 0.02 (8)[c]	− 36	0.44 ± 0.01 (6)	− 6

[a] Numbers given are mean ± SEM (number of animals);
[b] $p < 0.05$ vs normal male;
[c] $p < 0.001$ vs normal male.

Table 3. Effect of spontaneous diabetes in the guinea pig on plasma insulin concentration[a]

	Insulin, ng/ml	
	Male	Female
Normal	5.17 ± 1.30 (6)	6.33 ± 1.20 (3)
Diabetic	34.33 ± 5.20 (6)[b]	25.40 ± 2.35 (5)[b]

[a] Numbers given are mean ± SEM (number of animals);
[b] $p < 0.001$ vs normal.

Results and discussion. Table 1 shows the effects of spontaneous diabetes on the hepatic metabolism of a type I compound, aminopyrine[17]. Although diabetes had no effect in the female on aminopyrine metabolism, its metabolism was decreased by spontaneous diabetes in the male. The effects of spontaneous diabetes on the metabolism of a type II compound, aniline[17] were similar. That is, spontaneous diabetes had no effect on aniline metabolism in the female, but significantly decreased aniline metabolism in the male (table 2). Therefore, spontaneous diabetes in the guinea pig inhibited in vitro hepatic drug metabolism in males but not females. It should also be noted that the metabolism of both type I and type II compounds was greater in normal male than normal female guinea pigs and that the effect of spontaneous diabetes was to reduce the rates of drug metabolism in males to be similar to that observed in females. Although a sex difference in hepatic drug metabolism in rats is well documented[18], this is the first observation of a clear sex difference in drug metabolism in guinea pigs.

Spontaneously occurring or chemically induced diabetes in male rats decreases the metabolism of type I compounds but increases the metabolism of type II compounds such as aniline[19,20]. Therefore, the present results raise the question, as to whether rats and guinea pigs respond differently to diabetes or whether diabetes is different between rats and the guinea pigs. A partial answer to this question was provided by determination of the plasma insulin concentrations in the spontaneously diabetic guinea pigs and their normal colony mates. The spontaneously diabetic guinea pigs had greatly elevated (> 4-fold) plasma insulin concentrations (table 3) compared to decreased plasma insulin concentrations that occur in alloxan, streptozotocin and spontaneously diabetic rats[21–23]. Therefore, the present results indicate that drug metabolism is influenced by an excess of insulin as well as the lack of sufficient insulin[14,20]. The inhibitory effect of hyperinsulinemic diabetes on drug metabolism reported in this communication supports the concept derived from comparative studies in streptozotocin diabetic (hypoinsulinemic) and genetically hyperglycemic (hyperinsulinemic) mice[24] that insulin has a 'repressor' effect on drug metabolism. The mechanisms by which insulin and other hormones[18,25] influence drug metabolism remain to be determined. However, the present report indicates that the spontaneously diabetic guinea pig will be a useful model in which to study these phenomena.

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2 Department of Biochemistry, University of Nebraska College of Medicine, Omaha, NE 68105.
3 Present address: Department of Biochemistry, Armed Forces Radiobiology Research Institute, Bethesda, MD 20814.
4 Department of Comparative Medicine, College of Medicine, Milton S. Hershey Medical Center, Hershey, PA 17033.
5 Present address: Department of Medicine, School of Veterinary Medicine, Tufts University, Jamaica Plain, MA 02130.
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