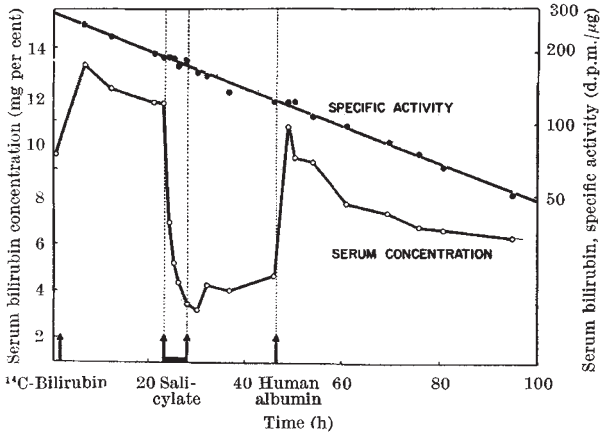

Fig. 3. Effect of salicylate and of human albumin on serum bilirubin concentration in hyperbilirubinaemic Gunn rat. The specific C^{14}-activity of serum bilirubin declined at a single exponential rate; the biologic half-life was 37 h and the total miscible pigment pool 4·77 mg

larly organic anions, may compete for shared binding sites on the protein. Displacement of bilirubin from albumin has been demonstrated *in vitro* with salicylate and other weak organic acids[7]. *In vivo*, those compounds were found to increase significantly the incidence and severity of bilirubin encephalopathy in young Gunn rats[8], and sulphisoxazole[9] and fatty acids[10] were suspected of having a similar effect in neonatal infants.

Qualitative differences in the binding properties of albumin from different species have been reported with various dyes[11–13]. The present observations indicate that human albumin has a much higher affinity for bilirubin than does albumin from rats or guinea-pigs. This difference undoubtedly accounts for the finding that in unconjugated hyperbilirubinaemia, the extravascular bilirubin space of the rat is larger than in man, and pigment turnover reaches a 'steady-state' at lower plasma bilirubin-levels[6].

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R. Schmid
I. Diamond*
L. Hammaker
C. B. Gundersen*

Department of Medicine,
University of Chicago.

* Postdoctoral Research Fellow, National Institutes of Health, U.S. Public Health Service.

[1] Ostrow, J. D., and Schmid, R., *J. Clin. Invest.*, **42**, 1286 (1963).
[2] Malloy, H. T., and Evelyn, K. A., *J. Biol. Chem.*, **119**, 481 (1937).
[3] Mehl, J. W., *J. Biol. Chem.*, **157**, 173 (1945).
[4] Lester, R., Hammaker, L., and Schmid, R., *Lancet*, ii, 1257 (1962).
[5] Scherr, G. H., *Trans. N.Y. Acad. Sci.*, **23**, 519 (1961).
[6] Schmid, R., and Hammaker, L., *J. Clin. Invest.*, **42**, 1720 (1963).
[7] Odell, G. B., in *Kernicterus*, edit. by Sass-Kortsak, A., 199 (Univ. Toronto Press, 1961).
[8] Johnson, L. M., in *Kernicterus*, edit. by Sass-Kortsak, A., 208 (Univ. Toronto Press, 1961).
[9] Silverman, W. A., Andersen, D. H., Blanc, W. A., and Crozier, D. N., *Pediatrics*, **18**, 614 (1956).
[10] Melichar, V., Polaček, K., and Novak, M., *Biol. Neonat.*, **4**, 94 (1962).
[11] Baxter, J. H., *Proc. Soc. Exp. Biol. and Med.*, **113**, 197 (1963).
[12] Andrews, W. H. H., and Del Rio Lozano, I., *Quart. J. Exp. Physiol.*, **46**, 238 (1961).
[13] Snyder, A. L., and Schmid, R., *J. Lab. Clin. Med.*, **65**, 817 (1965).

End-product Repression and Tissue Phenotype

Recent work from a number of laboratories suggests that the acquisition of tissue-specific enzyme patterns during embryonic development, and maintenance of these patterns in the adult, probably involves control of the expression of polycistronic operons by specific regulator compounds. These compounds can be recognized hormones[1], specific macromolecules[2,3], or, quite possibly, metabolic end-products of controlled cistrons. The number of regulator compounds required depends on the complexity of the organism and on the number and size of its operons; it is conceivable that an individual operon may carry instructions for more than one biosynthetic sequence. In this report the role of end-products in establishing tissue phenotypes will be examined.

One of the systems in higher animals known to be subject to regulation by a specific end-product is the control by endogenous or exogenous creatine of the steady-state tissue level of arginine : glycine amidinotransferase[4]. In vertebrates, the normal amidinotransferase-level differs markedly from tissue to tissue in a species-specific pattern[5]. However, in all vertebrates tested, amidinotransferase activity is extremely low in muscle and brain, tissues which have the highest concentrations of endogenous creatine. Since the normal endogenous levels of creatine in muscle and brain are well above the amidinotransferase cut-off concentration observed in embryonic chick liver[4], the role of end-product repression in establishing and maintaining amidinotransferase levels cannot be evaluated in these tissues, unless a means can be found of drastically lowering the endogenous creatine concentration. Tissues with lower endogenous creatine levels are, however, suitable experimental systems. The results of Table 1 show that for normally low-creatine, high-enzyme tissues in the rat, changes in amidinotransferase-levels depend on the relative, not absolute, changes in creatine concentration. This behaviour may reflect differences between the tissues in compartmentation of creatine, conversion of creatine to phosphorylcreatine, normal rates of protein synthesis and degradation, or tertiary configuration of regulator macromolecules[6] with which creatine interacts, as modified by different intracellular environments. Decidual tissue, which is analogous to a benign tumour, is relatively insensitive to feedback control.

Table 1. Relation between Creatine Concentration and Amidinotransferase-levels in Different Tissues of the Pregnant Rat

	Kidney		Pancreas		Decidua	
	Control	Cr-fed	Control	Cr-fed	Control	Cr-fed
Creatine conc.	0·22	0·78	0·31	1·09	0·34	0·84
Amidinotransferase	6·7	1·86	14·1	4·2	26·5	16·7
Relative creatine increase		3·5		3·4		2·5
Relative repression (%)		72		70		37

Rats were fed control chow diet or chow containing 5 per cent creatine from the 6th to 16th day of pregnancy; tissues were assayed on the 16th day. Creatine conc.[4] : mg creatine (as creatinine)/g tissue (wet wt.). Amidinotransferase[4]: μmoles hydroxyguanidine/h/g tissue.

Although no case is known of a normally high-creatine tissue with high amidinotransferase activity, a low level of endogenous creatine does not guarantee a high level of amidinotransferase. For example, rat liver, which has no detectable amidinotransferase activity, was found to have a somewhat lower creatine concentration (0·06 mg/g) than other rat tissues (Table 1) and human liver (0·17 mg/g), which have relatively high amidinotransferase activity. It would appear that, while end-product repression may influence tissue phenotype, other factors are also involved.

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James B. Walker*

Department of Biochemistry,
Baylor University College of Medicine,
Houston, Texas.

* Present address: Department of Biology, William Marsh Rice University, Houston, Texas.

[1] Clever, U., and Karlson, P., *Exp. Cell Res.*, **20**, 623 (1960).
[2] Levi-Montalcini, R., and Cohen, S., *Proc. U.S. Nat. Acad. Sci.*, **42**, 695 (1956).
[3] Lash, J. W., Hommes, F. A., and Zilliken, F., *Biochim. Biophys. Acta*, **56**, 313 (1962).
[4] Walker, J. B., and Wang, S.-H., *Biochim. Biophys. Acta*, **81**, 435 (1964).
[5] Walker, J. B., *Advances in Enzyme Regulation*, **1**, 151 (1963).
[6] Monod, J., Changeux, J.-P., and Jacob, F., *J. Mol. Biol.*, **6**, 306 (1963).