sent in myxedema following total ablation of the thyroid. In both groups the retention of ingested creatin was normal. In spontaneous myxedema small doses of thyroid substance caused a pronounced creatinuria and a diminished tolerance to ingested creatin. This was observed before any elevation in the basal metabolism. In one case, at the height of the creatinuria, administration of glycine resulted in an excretion of extra creatin. This is comparable to our findings in Graves' disease.[8] With continued thyroid administration, with the basal metabolism at normal levels, the creatin excretion gradually fell, and approached normal values. Apparently there is an eventual adjustment to thyroid administration. Whether a similar adjustment takes place in hypothyroid children cannot be answered from the data in the literature. This sensitivity of the creatin metabolism of adult myxedema to small doses of thyroid substance at low levels of basal metabolism offers an additional criterion for diagnosis.

8087 P

Effect of 4-6 Dinitro-o-Cresol on Yeast Respiration.*

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Field, Martin and Field[1-4] have shown that stimulation or inhibition of yeast respiration by 2-4, 2-5 or 2-6 dinitrophenol or by p- or m-nitrophenol is determined by the concentration of the undissociated form. It is well known that other nitrated phenols are direct stimulants of cellular metabolism, one of the most active of these being 4-6 dinitro-o-cresol (hereinafter DOC) which has been

[8] Shorr, E., Richardson, H. B., and Wolff, H. G., *J. Clin. Invest.*, 1933, **12**, 966.

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[1] Field, J., 2nd, Martin, A. W., and Field, S. M., PROC. SOC. EXP. BIOL. AND MED., 1933, **31**, 56.

[2] Field, J., 2nd, Martin, A. W., and Field, S. M., *J. Cell. and Comp. Physiol.*, 1934, **4**, 405.

[3] Field, J., 2nd, Martin, A. W., and Field, S. M., *J. Pharmacol. and Exp. Therap.*, 1935, **53**, 314.

[4] Field, J., 2nd, Martin, A. W., and Field, S. M., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1043.

studied by Dodds and his co-workers.[5-9] The experiments reported below show that DOC, like the other nitrated phenols mentioned, affects yeast respiration only in the undissociated form. The pure culture of *Saccharomyces cerevisiae* and the experimental procedure were the same as in our previous work.[1, 2, 3]

It is shown in Table I that in doses of DOC evoking optimal stimulation of yeast respiration the concentration of the undissociated form is quite constant over a wide pH range, while the total concentration causing optimal stimulation varies about 80-fold between pH 5.4 and pH 7.8. The table represents the summarized data from 36 experiments.

TABLE I.

Constancy of the Concentration of Undissociated DOC Evoking Optimal Stimulation of Yeast Respiration at Various pH Levels. The Dissociation Constant of DOC Was Found to Be 1×10^{-5}.

pH	Total conc'n DOC mg. %	Total conc'n DOC molar	Molar conc'n undissociated DOC	O_2 consumption of control in mm^3 per 10^8 cells per hr.	O_2 consumption with optimal dose of DOC in mm^3 per 10^8 cells per hr.	Rate of O_2 consumption at opt. dosage control = 100
5.8	0.6	3.06×10^{-5}	8.71×10^{-6}	33.3	54.5	164
6.0	2.0	1.02×10^{-4}	9.26×10^{-6}	30.7	46.7	152
6.8	10.0	5.1×10^{-4}	7.96×10^{-6}	33.0	52.6	159
7.8	40.0	2.04×10^{-3}	3.22×10^{-6}	15.9	21.9	138

It was also found that change in pH during a run modifies or reverses the effect of DOC on yeast respiration in a manner most directly explicable by changes in concentration of the undissociated form, and that the action of the drug develops rapidly, being comparable in this respect to the action of 2-4 and 2-6 dinitrophenol (Field, Martin and Field[2, 3]). Study of the increased respiration evoked by a dose (total) of 0.1 mg. % DOC at pH 5.2 showed that in 3 hours the extra oxygen consumption evoked by the drug was 14 times the amount required for complete oxidation of the DOC present, which is clear evidence that DOC serves to increase the rate of oxidative metabolism of yeast in catalytic fashion rather than merely as another fuel.

Conclusions. 4-6 dinitro-o-cresol affects the respiration of yeast only in the undissociated form. Inhibition is reversible by increase

[5] Dodds, E. C., and Pope, W. J., *Lancet*, 1933, **2**, 352.

[6] Dodds, E. C., and Robertson, J. D., *Lancet*, 1933, **2**, 1137.

[7] Dodds, E. C., and Robertson, J. D., *Lancet*, 1933, **2**, 1197.

[8] Dodds, E. C., and Greville, G. D., *Nature*, 1933, **132**, 966.

[9] Dodds, E. C., and Greville, G. D., *Lancet*, 1934, **1**, 398.

in pH within wide limits of concentration and exposure time. The drug acts on enzyme systems located in the periphery of the yeast cell and the action is catalytic rather than stoichiometric.

8088 C

Physiological Activity of Some Catechol Derivatives.

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Muhlmann,[1] and later Dakin[2] determined that catechol and certain of its derivatives that resemble epinephrine in their skeletal structure were capable of raising the blood pressure of the anesthetized rabbit. Barger and Dale[3] found that catechol raised the blood pressure of the decapitated cat, showing that this drug acts peripherally to the vasomotor center. They claimed also that catechol did not dilate the pupil of the intact animal, but did cause contraction of the isolated virgin cat uterus, and drew the conclusion that catechol raises the blood pressure by direct muscle stimulation, rather than by sympathetic imitation.

We have confirmed their results, on blood pressure and pupil, but have determined further that catechol depresses the uterus and intestine of many animals. On the basis of these findings, it occurred to us to test anew the suggestion of Dakin that epinephrine owes much of its typical sympathomimicity to the catechol group.

Our results show that catechol, ethylcatechol, acetocatechol, and chloracetocatechol possess sympathomimetic powers (Table I). In this, inhibitory effects predominate, so that when an organ contains but one type of sympathetic innervation, as in the dilator pupili, the nictitating membrane, or the intestine, that action is brought out by these drugs. On the other hand, when both motor and inhibitor fibers of the sympathetic are present in the same organ, as in the blood vessels and uterus, the inhibitory action predominates, although the action of catechol is not reversed after ergotoxine. In epinephrine, the motor effects are much more in evidence than the inhibitor, but other non-catechol containing amines

[1] Muhlmann, *Deutsch. Med. Wchnsch.*, 1896, **22**, 409.

[2] Dakin, *Roy. Soc. Proc. B.*, 1905, **76**, 498.

[3] Barger and Dale, *J. Physiol.*, 1910, **41**, 19.