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Effect of Codeine Phosphate by Mouth on Oxygen Consumption in Normal Humans.

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(Introduced by Chauncey D. Leake.)

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In studying the effects of drugs on basal metabolism, Boothby and Rowntree[1] reported two experiments with codeine in which they found 3% and 8% depression respectively of the basal metabolic rate one hour following the administration of a therapeutic dose of codeine (0.03 gm.). Investigating the effect of pre-anesthetic medicants on functional activity in normal humans, we found that morphine in oral doses ranging from 0.1 to 0.5 mgm. per kilo generally depresses within an hour the basal metabolic rate and tactile discrimination,[2] while pulse rate, interestingly, is increased but respiration is unaffected. In a similar study of the barbituric acid hypnotics we noted[3] a definite depression of oxygen consumption and tactile discrimination with the oral use of therapeutic doses of sodium di-ethyl barbiturate and of some of its common derivatives. Iso-amyl ethyl barbiturate and phenyl ethyl barbituric acid in ordinary doses, however, both increase the basal metabolic rate, but decrease the tactile discrimination. Codeine was next studied from the same aspect and the results of 10 experiments on 8 normal human subjects are reported here.

The determinations of oxygen consumption were made by the closed method with the Sanborn "graphic" apparatus and the Sanborn averages were used for estimating the basal metabolic rate. The subjects were trained healthy adults and the usual precautions were observed in making determinations. Codeine phosphate, in doses ranging from 0.2 to 1.0 mgm. per kilo, was dissolved in water and administered by mouth. The "normal" basal metabolic rate was estimated before administration of the drug and subsequent tests were carried out at 20, 40, and 75 minutes after the drug was given. Pulse rate and blood pressure determinations and tactile discrimination tests were made before and after the drug was given, while the respiratory rate was obtained from the "graphic" record.

[1] Boothby, W. M., and Rowntree, L. G., *J. Pharmacol. Exp. Therap.*, 1923, xxii, 99.

[2] Anderson, H. H., PROC. SOC. EXP. BIOL. AND MED., 1929, xxvii, 102.

[3] Anderson, H. H., and Leake, C. D., in press.

TABLE I.
Maximum Functional Changes During One Hour's Observation Following Oral Administration of Codiene Phosphate in Normal Humans.

Subject	Sex	Age	Wt. kg.	Ht. cm.	Dose mgm./kg.	Resp. per min.	Pulse per min.	O_2 consump. cc. per min.	Tactile Discrim.
H.P.	F	28	62	165	0.2	+3	0	—13	—
M.C.	F	25	36.5	154	0.3	+1	—6	—13	—
E.C.	M	22	83	182	0.4	+3	0	—25	No change
M.P.	M	20	97	185	0.4	+2	—4	—15	Increase
E.C.	M	22	83	182	0.6	+2	—4	—20	No change
H.S.	M	23	66	172	0.6	+1	—8	—10	Decrease
M.F.	M	22	63	160	0.8	+2	0	—29	Increase
E.J.	M	22	66	175	0.8	+1	0	—10	Decrease
H.P.	F	28	62	165	1.0	+2	—4	—13	"
H.A.	M	26	70	170	1.0	+3	0	—30	"

Table I shows the results of this study. Although the effect on the basal metabolic rate was not marked there was uniformly a depression of 4% to 13% following the drug. The extent of depression seemed independent of the dosage in the range we used. In most cases the basal rate returned to "normal" within 75 minutes after the drug was given. There was, surprisingly, an increase of respiratory rate in every case. The pulse rate was decreased when affected. Changes in blood pressure and tactile discrimination were inconstant. A tendency to sleep was noted only in the highest doses used.

Codeine, even in twice the dosage of morphine, is not nearly as powerful a depressant agent in the normal human. It is often said, on the authority of Issekutz,[4] who worked on animals, that the effects of morphine derivatives, including codeine, are essentially the same on respiration as those of morphine. Again, Macht[5] stated that morphine and, to a lesser degree, codeine are sedative or depressant to the respiratory center. During the first hour after administration in normal humans, however, codeine definitely and consistently seems to stimulate the respiratory rate in normal humans, while we failed to note any such effect following morphine. Another interesting difference between the effects of morphine and codeine is on pulse rate after administration of therapeutic doses to normal humans. Morphine tends within an hour to increase the heart rate while codeine tends to slow it.

[4] Issekutz, B., *Arch. f. d. ges. Physiol.*, 1911, cxlii, 255.

[5] Macht, D., *J. Pharmacol. Exp. Therap.*, 1915, vii, 339.