TABLE I. Incidence of Vomiting Following Veratrum Extracts Administered Intravenously.

Drug	No. of patients: Toxemias of pregnancy	Hypertensive encephalopathy	Nephritis	Avg effective dose, mg	No. patients showing vomiting on 1st inj.	%	No. patients vomiting on repeated inj.	%
Cryptenamine	15	4	2	.3	4	21	9	43
Vergitryl	8	4	3	.3	15	100	14	93
Veriloid	6	6	3	.4	15	100	13	87

TABLE II. Incidence of Vomiting Following Veratrum Extracts Administered Intramuscularly.

Drug	No. patients	Avg dose, mg	No. of patients vomiting	%
Cryptenamine	97	.5	8	7
Vergitryl	233	.5	27	11
Veriloid	56	.5	3	7.5

tion. When a veratrum preparation was given intravenously, however, though a smaller total dose was required to lower blood pressure than when it was given intramuscularly, the incidence of vomiting was greatly increased. It was observed further that vomiting occurred most frequently following the initial intravenous injection.

When given intramuscularly, Cryptenamine resembled the other veratrum alkaloids both in hypotensive effect and incidence of vomiting. When given intravenously, however, it differed from the other alkaloids since moderately rapid administration caused significantly less vomiting particularly following the initial injection. Our data showed that none of the veratrum alkaloids were particularly emetic when their absorption was slowed, but that the receptors initiating emesis were especially sensitive to the sudden higher concentration presented to it when the drugs were given intravenously. It was only in this respect that Cryptenamine differed from the other alkaloids studied. It is concluded, therefore, that the divergence between the hypotensive and emetic dose of Cryptenamine reported in animals also exists in man, and is most apparent after intravenous administration wherein vomiting is common with the other veratrum alkaloids.

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Effect of Immobilization on Oxygen Uptake of Skeletal Muscle.*† (20652)

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It has been shown(1) that following denervation of the gastrocnemius muscle the cytochrome oxidase activity of this muscle decreased progressively with time. Since these findings did not agree with the results reported by other laboratories(2-4), it seemed desirable to determine the effect of immobilization under conditions which would rule out any contributory effect of fibrillation on the oxygen uptake of the muscle studied.

It also appeared desirable to approach the problem from the opposite angle, *i.e.*, to determine the oxygen uptake of a denervated muscle subjected to constant passive move-

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TABLE I. Effect of Immobilization on Cytochrome Oxidase Activity of Gastrocnemius and Oxygen Uptake of Diaphragm.

Days after operation	No. of rats	μl O_2 taken up/mg wet wt of tissue/hr — Normal gastrocnemius Min	Max	Mean	Tenotomized gastrocnemius Min	Max	Mean	Mean difference*	P
0	5	9.13	13.47	11.33	9.73	12.87	11.60	+ .2 ± .5	<.80
3	8	11.00	14.13	12.53	8.47	11.33	9.87	—2.7 ± .3	<.001
5	7	8.00	12.27	10.80	6.33	9.33	7.93	—2.9 ± .3	"
10	7	7.27	11.80	9.73	3.60	9.80	5.80	—3.9 ± .2	"
15	7	7.07	12.80	9.80	4.47	7.27	5.60	—4.1 ± .8	<.01
20	9	9.13	14.60	11.47	4.20	9.93	7.40	—4.1 ± .5	<.001
		Q_{O_2} normal diaphragm (0.1% glucose)			Q_{O_2} denervated diaphragm				
0	21	5.60	8.94	7.31	5.17	8.51	7.38	— .07± .15	<.70
5	12	7.08	8.94	7.62	6.29	9.00	7.30	— .30± .18	<.20
10	11	6.27	8.84	7.53	5.90	8.02	6.46	—1.07± .29	<.01
15	11	4.65	11.03	7.03	4.49	8.01	5.69	—1.34± .39	"
20	11	6.38	9.56	7.56	4.40	7.11	5.59	—1.97± .31	<.001
		Normal diaphragm with 0.2% glucose			Normal diaphragm without glucose				
0	26	5.45	11.70	8.09	5.08	11.36	7.91	+ .25± .14	<.10

* Mean of differences between normal and tenotomized gastrocnemius, normal and denervated diaphragm, and normal diaphragm with and without glucose for each animal ± stand. dev. $/\sqrt{n}$.

ment and compare the changes in oxygen utilization under these conditions with the changes observed following tenotomy with more or less complete immobility.

Experimental. Tenotomies were performed on male mature albino rats as previously described(5). Cytochrome oxidase determinations were carried out by the method described earlier(1). Unilateral denervation of the diaphragm was performed on young rats (60-140 g) by making a ventral incision in the neck, parallel to and approximately over the external jugular vein. The carotid artery and the vagus nerve were exposed and traced caudally to the brachial plexus. The phrenic nerve, arising from the fifth cervical root, runs along the ventral surface of the brachial plexus in close proximity or sometimes even buried in the muscles close to the vertebral column. It may usually be seen with little difficulty as a very thin line coursing caudally across the brachial plexus. The respiration of the animals was examined to make sure that it was symmetrical, the phrenic nerve was grasped with fine forceps and evulsed. The respiration of the rat can immediately be observed to change and it is possible to press one's fingers under the ribs on the 2 sides simultaneously and feel the firm contraction of the diaphragm on the one side and the lack of contraction on the other. At stated time intervals the rats were sacrificed by decapitation and the diaphragm removed as quickly as possible, taking care to avoid traumatization, and immediately placed in an ice-cold buffer solution(6), containing 0.1% glucose. Without removal from the buffer the diaphragm was divided along the midline and trimmed to remove the central tendon and connective tissue. Each hemodiaphragm was then immediately transferred to a chilled Warburg vessel containing the same buffer. The air in the reaction flask was displaced with oxygen. After temperature equilibration of the vessels for 15 minutes, the oxygen uptake was measured at 10-minute intervals for one hour at 37°C. Each hemidiaphragm was then carefully blotted with filter paper and quickly weighed. For dry weight determination each hemidiaphragm was heated in an oven at 100°C to constant weight.

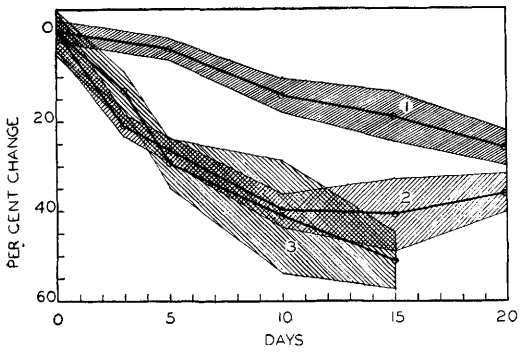

FIG. 1. Effect of immobilization on oxygen utilization on rat muscle. Curve 1: Rate of oxygen uptake of hemidiaphragms following denervation. Present study. Curve 2: Cytochrome oxidase activity of homogenates prepared from gastrocnemius muscle following tenotomy. Present study. Curve 3: Cytochrome oxidase activity of homogenates prepared from gastrocnemius muscle following neurotomy. See reference 1. Shaded areas represent the magnitude of the stand. error of the points of each curve.

Results. In interpreting the results of the present study it should be pointed out that in each case the immobilized muscle was compared with the contralateral normal muscle of the same animal. In the normal animal the activity of the cytochrome oxidase system is relatively constant for comparable muscles as shown in Table I. Immobilization of the gastrocnemius muscle, either by neurotomy or by tenotomy, produces a significant and progressive depression of the cytochrome oxidase system (Fig. 1). The present study, therefore, confirms previous work(6) and shows that changes in the muscle following immobilization follow a similar course irrespective of the manner by which it is produced. These findings, therefore, indicate that fibrillation which accompanies neurotomy is not the major cause of the atrophy which follows sectioning of the motor nerve supply as has been suggested(2). Following the 10th day postoperatively the activity of the cytochrome oxidase system seems to increase gradually in the case of the tenotomized muscle (Fig. 1, curve 2), whereas, the activity of the denervated muscle (curve 3) continues to decrease. This difference may be due to the fact that the severed tendon becomes reattached much sooner than the cut nerve regenerates. Similar observations have been made previously in this laboratory and elsewhere.

Table I also shows that the Qo_2 of the denervated diaphragm decreases progressively and significantly with time after denervation although it is subjected to constant passive movement during the process of breathing. Several investigators(7) have attempted with varying success to influence the rate of atrophy following neurotomy by passive exercise or electrical stimulation, but in the diaphragm of the rat at least, as the present study shows, constant passive exercise does not prevent the eventual decline in oxygen uptake and therefore, presumably will not prevent the ultimate atrophy of the muscle. In Fig. 1, the 2 curves representing the cytochrome oxidase activity of the immobilized gastrocnemius muscle of the rat show the most rapid decline in enzyme activity during the first 5 days following immobilization. The oxygen uptake of the denervated diaphragm (curve 1) on the other hand shows no significant decrease until after the fifth day. Studies are planned to determine if this difference in behavior is due to a possible beneficial result of passive movement or due to the different methods of evaluating oxidative metabolism.

While these studies were in progress Gruber *et al.*(8) reported that the oxygen uptake of the hemidiaphragm, denervated 10-14 days, was about 22% higher than that of the normal control in the absence of glucose, but they found no difference when 0.2% glucose was added to the medium. Table I shows that our results do not support these findings but are in accord with those reported by Gilmore *et al.*(9) and by Paasch and Reinwein(10).

Summary. 1. Following tenotomy of the gastrocnemius muscle of the rat the cytochrome oxidase activity of the muscle decreases progressively. 2. The oxygen uptake of the denervated hemidiaphragm of the rat decreases with time of denervation. This suggests that in this tissue at least passive exercise does not prevent the decline in oxygen uptake, although it may retard it somewhat. 3. The Qo_2 of hemidiaphragms measured in a medium containing 0.2% glucose

does not differ significantly from the Q_{O_2} of hemidiaphragms measured in a glucose free medium.

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Pharmacologic Differentiation Between Epinephrine- and HGF-Hyperglycemias: Application in Analysis of Cobalt-Hyperglycemia.*† (20653)

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Considerable interest has centered upon the hyperglycemic-glycogenolytic factor (HGF) and its putative role as a hormone. Since HGF is found in association with the alpha-cells of the Islets of Langerhans, definitive tests for a true hormonal role of HGF should be greatly simplified by the recent observations(1,2) that cobaltous chloride selectively damages the alpha-cells. Contrariwise, the similarity in action of HGF and epinephrine (and sympathetic nerve activity) is so pronounced that methods must be at hand to distinguish between these hyperglycemic agents. The hyperglycemia produced by each of these agents is related to an activation of hepatic phosphorylase activity(3). Conditions which interfere with the action of HGF affect equally the action of epinephrine(3,4). Our observation that the adrenergic-blocking drug dihydroergotamine (DHE) prevents the effect of epinephrine on liver slices, but does not interfere with the effect of HGF, has led to a practical differentiation of these two hyperglycemic agents *in vivo*.

This paper presents evidence for the selective blockade of the action of epinephrine on glucose liberation by liver slices and on blood sugar of the intact rabbit, under conditions which allow HGF to produce its usual effects. The information obtained on the intact rabbit has been applied to determine the mechanism of the hyperglycemia which follows the administration of cobaltous chloride, an agent which selectively damages the cells in which HGF is found. The maintenance of normal blood sugar level in rabbits was not influenced by the conjoint effects of damaging the alpha-cells with cobaltous chloride, fasting, and subsequent treatment with DHE.

Methods. Rabbit liver slices were tested as described by Sutherland and Cori(5). The tissues were usually incubated with DHE for 30 minutes before addition of the glycogenolytic agents. In a few cases DHE itself produced a small but significant glycogenolytic effect. For *in vivo* studies rabbits were fasted 20-24 hours before tests. Blood samples were obtained from the marginal ear veins. Glucose determinations were made *ad modum*

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