TABLE I. Doses, Number of Female Rats Irradiated and Resulting Offspring.

Doses in r/rat	No.	Day after insemination 2	4	5	6	7	8	9	10	11	12	13	14	15	16	18
400	R.t.*	1	1		2	3	2	2	2	2	2	1	2			
	N†	0	0		0	0	0	0	0	0	0	0	0			
300	R.t.						1	1	2	1	1	3	1	1	1	1
	N						0	0	0	0	0	0	0	2(0)	0	10(0)
250	R.t.						1	1	1							
	N						0	0	0							
200	R.t.				1	1	1	2	2	2	2	1	1			
	N				5(3)	0	1(0)	0	1(0)	0	0	0	0			
125	R.t.	1	1	1	1	1	2	1	1	1	1	1	1			
	N	0	0	0	11(9)	0	2(0)	0	1(0)	0	0	2(0)	0			
75	R.t.						2	1	2	2	2	1	3		1	
	N						8(3)	8(2)	6(5)	3(1)	2(1)	14(12)	7(4)		8(6)	
Total No. newborn		0	0	0	16(12)	0	11(3)	8(2)	8(5)	3(1)	2(1)	16(12)	7(4)	2(0)	8(6)	10(0)

* R.t. = Rats treated. † N = Newborn; stillborn not included.
Figures within parentheses give No. of newborn living 10 days or more.

section is described. In 46 young rats that survived 10 days no cardiac abnormalities were found. Examination of young rats that died before 10 days was not carried out.

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Oxygen Tension of Subcutaneous Gas Pockets in Cobalt-Treated Mice and Adrenalectomized Mice.* (22871)

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Cobalt (II) chloride† and adrenalectomy (2) have both been shown by Gerschman *et al.* to give protection against the toxicity of oxygen at high pressures in mice. The experiments described below were undertaken to see if these two treatments furnish their protection by causing a generalized decrease of tissue pO_2, such as might result from a circulatory or respiratory response to the treatment.

Campbell(3) was the main proponent of utilization of subcutaneous or intraperitoneal gas pocket containing nitrogen as index of tissue tension, and the method has been applied in studies of oxygen at high pressures by Campbell(4,5,6,7), Sibree(8), Taylor(9,10), Lambertsen *et al.*(11) and Bahnson and Matthews(12).

Methods. Subcutaneous gas pockets were formed in 20 g female mice of Carworth Farms Webster strain, by injecting 4 to 8 cc of air or a gas mixture (7% CO_2, 7% O_2 in N_2) under the skin of the back. No anesthetic was used. It was assumed that after a day, the oxygen tension in the pocket had come to a steady state level which was within 2 mm of the mean tension in the surrounding tissues. To sample, approximately 2 cc of

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† Unpublished observations of Gerschman, R., and Gilbert, D. L.

the pocket gas were withdrawn into a syringe, the dead space of which had been filled with dilute acid solution. After sampling, the mouse's pocket was refilled by injection of air or gas mixture. Analysis for percentage CO_2 and O_2 were made on a Scholander Micro Gas analyzer. Percentages were converted to partial pressures on the assumption that the total pressure in the pocket was one atmosphere. The work included 3 series: (a) effect of previous injections of $CoCl_2$ on mice submitted to one atmosphere of O_2 and on mice breathing room air, (b) time course of cobalt effect, and (c) effect of adrenalectomy. (A) In the first series, 9 mice were given 10 daily intraperitoneal injections of .0012 mM $CoCl_2$ in a volume of 0.2 ml, and 9 mice were given 10 daily IP injections of 0.2 ml of 0.9% NaCl. On the day of tenth injection, all mice were given subcutaneous gas pockets. The next day, the pockets were sampled and then 5 mice of each group were placed in a chamber containing 100% O_2 at 1 atmosphere. The rest of the mice were left in room air. The pocket gas compositions were analyzed each day in all 4 subgroups until the mice in the O_2 chamber had died. (B)

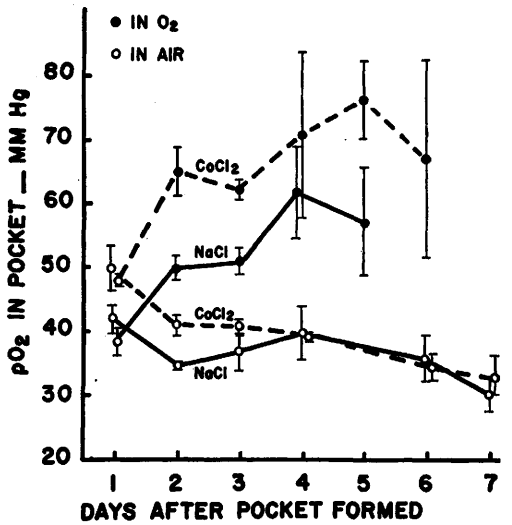

FIG. 1. Oxygen tension of subcut. tissue in mice as measured by the gas pocket method. Points are mean values and vertical lines represent stand. errors. ○, animals breathing air; ●, animal breathing O_2 at 1 atmosphere. For 10 days prior to day zero, 2 subgroups were inj. with $CoCl_2$ (– – – –) and 2 subgroups were inj. with saline (———). Pockets were formed on day zero.

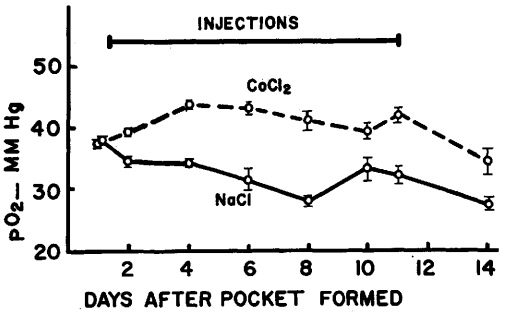

FIG. 2. Oxygen tension of subcut. tissue in air-breathing mice as measured by gas pockets during 10 daily inj. of $CoCl_2$ (– – – –) and of saline (———). Points are mean values and vertical lines represent stand. errors. Pockets were formed on day zero.

In the second series, 2 groups of 5 mice were given subcutaneous pockets. The next day, the pockets were sampled and then one group was started on a regimen of 10 daily IP injections of .0012 mM $CoCl_2$ and the other group started on 10 daily IP injections of 0.2 ml of 0.9% NaCl. Pocket O_2 tensions were analyzed throughout the injection period. (C) Gas pockets were formed in a group of 5 intact control mice and in 5 animals which had been adrenalectomized 5 days previously. Samples for gas analysis were taken 1 day after pocket formation and again a week later.

Results. Fig. 1 shows the results of the first series of $CoCl_2$ injections. The points on the graph are mean values and the vertical lines indicate standard errors. It is seen that the cobalt-injected mice had higher pocket O_2 tensions both in O_2-breathing and air-breathing animals during the first 3 days.

The second series of cobalt injections is shown in Fig. 2. There was a definite increase in pO_2 in the cobalt-treated mice after the first injection. After the second injection, the difference was about 10 mm, and this difference was maintained for the rest of the experiment.

The adrenalectomized mice had a mean pO_2 of 31.6 $\pm$ 0.6 (standard error) in a day-old pocket and 32.3 $\pm$ 5.8 in a week-old pocket; the intact control animals had a mean pO_2 of 33.6 $\pm$ 1.7 in one day and 30.8 $\pm$ 1.2 in one week. Therefore, adrenalectomy did not seem to have any significant effect on the pocket pO_2.

Discussion. It was found that when the mice were disturbed or handled in sampling, the pCO_2 of their gas pockets fell rapidly although the pO_2 remained nearly constant for as long as 10 minutes. Therefore, CO_2 analyses are not reported, since it was felt that only the O_2 values were accurate estimates of tissue tension of the undisturbed mice.

The data shown in Fig. 1 are consistent with the work of other investigators who analyzed gas pockets in animals subjected to a high percentage of O_2 at one atmosphere (4,5,6,8,9,12). The increase of pocket pO_2 on going from air to O_2 is small (about 20 mm) compared to the change of inspired pO_2 (590 mm). The pocket tensions in an O_2-breathing animal are fairly uniform until the last hours of the animal's life, when the pocket pO_2 falls and the pCO_2 rises. Samples were obtained from 3 of the O_2-breathing mice just before death:

Min. before death	pCO_2	pO_2
31	80	50 mm Hg
2	71	6
1	108	10

The CO_2 tensions are higher than 70 mm, the maximum found during the first 3 days in O_2 before terminal changes could be expected. Also, it is seen by the low pO_2 that the animal's death is accompanied by tissue anoxia, probably due to respiratory or circulatory collapse, or both.

Fig. 1 and 2 show that at least in the tissue surrounding the subcutaneous pocket, cobalt injections are associated with a pO_2 which is higher than normal, and the analyses in adrenalectomized mice indicate no change of pocket pO_2. These data are evidence against the hypothesis that the protective effect in O_2 poisoning is due to a general respiratory and/or circulatory depression which would deliver less O_2 to the tissues. However, there is still the possibility that blood may be shunted away from sensitive organs.

Several factors can be mentioned as possible explanations of the cobalt results: (a) Cobalt is a well-known hematopoietic agent so that the increased tissue pO_2 might be due to an increased carrying capacity of the blood for O_2. However, 5 cobalt-injected mice had a mean hematocrit ratio of 54 ± 2 (standard error) compared with 5 saline-injected animals who had a mean ratio of 51 ± 1 after 10 days of treatment; Gessert and Phillips(13) showed no significant cobalt-induced polycythemia in rats until after 10 days. Fig. 2 shows that there is a definite effect on the pocket pO_2 after only one injection so that polycythemia can probably be excluded as a factor. (b) It was noticed during these experiments that cobalt-injected mice were easily excited and more irritable than the normals, so the increased pO_2 could be caused by hyperventilation and increased cardiac output due to the chronic excitement of the animal. Why cobalt should cause an increased irritability remains to be explained. Such an irritability is not mentioned in reports of cobalt administration to human subjects where it would probably be easily noticed(14). (c) There is evidence that cobalt can cause a disturbance in regulation of blood sugar(15,16), but how this could be connected with tissue pO_2 is not clear. (d) Finally, cobalt is known to act as an enzyme inhibitor in some oxidative processes(17) so it is possible that decreased utilization of O_2 might explain in part the elevated pO_2.

It has often been suggested that cobalt leads to a histotoxic anoxia which stimulates erythropoiesis(18). If the increased pO_2 found in subcutaneous pockets of cobalt-treated mice can be generalized to the whole body, it is seen that there is an abundant supply of oxygen to the tissues, and any disturbance of oxidation must indeed be found at the cellular or enzyme level.

Summary. The gas pocket method of estimating O_2 tension of subcutaneous tissue was utilized to see if the protection afforded by $CoCl_2$ and adrenalectomy in high oxygen pressure could be due to a generalized depression of tissue pO_2. (a) Mice previously treated with cobalt and control animals previously treated with saline were studied in O_2 at one atmosphere and in room air. (b) Pockets were observed in an experimental group during a period of cobalt injections and

in control animals which received saline injections. (c) Gas pockets in a group of adrenalectomized mice were compared with those in intact, untreated controls. The cobalt injections produced an increase in pO_2 of the gas pocket which appeared the first day after beginning treatment. The adrenalectomized mice showed no difference from their controls in gas pocket pO_2. Since decreased pO_2 was not observed, it was concluded that the protection of the two treatments against oxygen toxicity must be due to other factors.

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Abolition by Hypophysectomy of the Anticortisol Action of Desoxycorticosterone. (22872)

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Numerous experiments have shown that there is an antagonism between glucocorticoids and mineralocorticoids, as regards their effects upon inflammation, in that the inhibitory action of the former can be blocked by the latter, under suitable experimental conditions. However, these opposing effects appear to be exerted through different mechanisms. The anti-inflammatory action is presumably direct, since it occurs even topically, at the site where glucocorticoid (*e.g.* cortisol) is applied, while the contrary effect of mineralocorticoids (*e.g.* desoxycorticosterone) is probably indirect because it can be obtained only by systemic treatment. An essential difference in modes of action of these two types of corticoids is also suggested by the observation that hypophysectomy does not interfere with most of the classic glucocorticoid effects, but does prevent many of the morbid lesions characteristic of mineralocorticoid overdosage, such as nephrosclerosis, periarteritis nodosa and hypertension(1,2,3,4,5,6).

In view of these facts it appeared of interest to determine whether, even in the absence of the hypophysis, systemic treatment with a mineralocorticoid would exert pro-inflammatory actions in itself, or block the anti-inflammatory effect of a glucocorticoid. It had been demonstrated that the "granuloma-pouch" technic lends itself well for quantitative assessment of inflammation in hypophysectomized rats(7) and, therefore, we used this test object for our studies.

Materials and technics. Eighty female Sprague-Dawley rats, with mean initial body-weight of 160 g (range: 150-168 g), were subdivided into 7 groups, as indicated in Table I. On the first day, a granuloma-pouch was produced as follows: (1) injection