be taken into consideration in the analysis of the possible mechanisms of the pyrogenic effect of ricin. During ricin intoxication there is an endogenous corticosteroid mobilization. The elevated blood-corticosteroid level[14] can influence the ricin-induced fever in many ways: 1. Under certain circumstances it can inhibit or retard the release of endogenous pyrogen; moreover it can produce an antipyretic effect by acting directly on the hypothalamus[15]. 2. Among the corticosteroids released by the adrenals are substances with a 5-β-hydrogen of 3-α-hydroxyl group. Steroid compounds with such a structure have a pyrogenic effect on humans[5,16]. This is a possibility which has not been investigated in this work.

BALINT[17] has shown that, under the influence of ricin, the Mg^{2+} content of blood significantly decreases, while the Ca^{2+} content increases. The physiological Ca^{2+}:Mg^{2+} ratio of the blood is thus characteristically changed.

MYERS et al.[5,18], FELDBERG et al.[19] showed almost conclusively that in warm-blooded animals the Na^+: Ca^{2+} balance of the hypothalamus is responsible for the constant body temperature. According to this statement, the shifted Ca^{2+}: Mg^{2+} ratio, as well as the the elevated Ca^{2+} level, could have an inhibitory effect on the ricin fever. This hypothesis is strengthened by BALINT's data (1965, unpublished) that ricin has no pyrogenic effect on cold-blooded animals, for example, on toads.

LIN et al.[20–22] showed convincing results to the effect that ricin antagonized the process of protein-synthesis in cells. Since it is also true that during the early production of endogenous pyrogen, protein synthesis also takes place[9], it seems very likely that the direct inhibitory effect of ricin also prevails in this situation.

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The Effect of Combined Chronic Hypoxia and N-Ethyl-N-Nitrosourea on the Carotid Bodies of Rats

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Summary. We measured the carotid body volume of rats treated with chronic hypoxia alone and chronic hypoxia together with a single neonatal injection of N-ethyl-N-nitrosourea (10 mg/kg). All the animals so treated showed enlargement of their carotid bodies, but no carotid body chemodectomas occurred.

The carotid body enlarges in man[2] and animals[3] exposed to chronic alveolar hypoxia. In the rat this is often due to a hyperplasia of the type 1 (chief) cells[4]. Neoplasms (chemodectomas) of the carotid body are rare in people living at sea-level, but their incidence is greatly increased in individuals born and permanently residing at high altitude in the Peruvian Andes[5]. Such chemodectomas may represent an extreme degree of hyperplastic response of chemoreceptor tissue to prolonged hypoxia. We investigated this problem by studying the effects of chronic hypoxia combined with the neurotropic carcinogen N-ethyl-N-nitrosourea (ENU) on the carotid body of the rat. The carotid body is of neural crest embryonic derivation[6]. We wondered if the administration of ENU would convert the hypoxic hyperplasia of the carotid body type 1 cells into neoplasia. Accordingly, we divided 110 newborn Wistar albino rats of either sex into 4 groups (Table). Group I rats were control animals and were not exposed to chronic hypoxia or given ENU. Animals in groups II and IV were given a single s.c. injection of ENU dissolved in acidified ethanol at a dose of 10 mg/kg within 24 h of birth. After weaning at approximately 21 days of age, rats in group IV were transferred to a hypobaric chamber at a pressure of 460 mm Hg (equivalent to an altitude of 4300 m above sea-level) for the remainder of their lives. Rats in Group III were not given ENU, but after weaning were transferred to a hypobaric chamber under the same conditions as rats in Group IV. When a rat died the carotid bodies were examined histologically and their volume measured by a point-counting method[7].

No significant difference was found between the mean combined carotid body volumes of the 2 groups of rats (I and II) which were not exposed to chronic hypoxia, so that it is unlikely that treatment with ENU alone can induce carotid body enlargement. Exposure to chronic hypoxia produced significant enlargement of the carotid bodies. Histologically, these enlarged carotid bodies showed the capillary dilatation and increase in volume of type 1 cells that have been described before. None of the carotid bodies had the histological appearance of chemodectoma. ENU treatment did not increase the degree of carotid body enlargement produced by chronic hypoxia. In his study of high altitude hypoxia and chemodectomas, SALDAÑA[5] described 24 carotid body neoplasms. The smallest of these was increased 10-fold as compared with the mean carotid body weight of people born and living at high altitude. None of our chronically hypoxic rats showed such a degree of enlargement of their carotid bodies. We conclude that we were unable to stimulate chemodectoma formation in any of our rats. Both the

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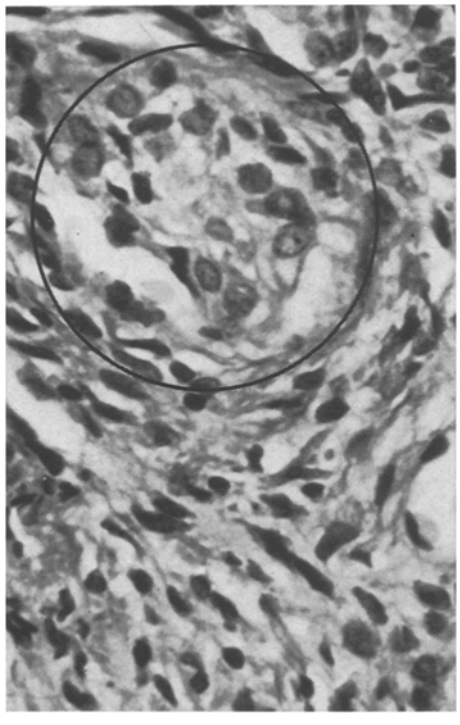
Number of neoplasms and carotid body volume in control rats and experimental rats treated with N-ethyl-N-nitrosourea (ENU) and chronic hypoxia, separately and in combination

Group	Treatment	No. of rats in group	Survival (days)	No. of rats with neoplasms	Number of neoplasms					Mean combined carotid body volume ($\mu m^3 \times 10^6$)
					Brain	Cranial nerves	Spinal cord	PNS	Others	
I	—	31	63–648	2	1	1	—	—	—	98 (28)
II	ENU	22	113–692	18	13	3	2	2	3	181 (34)
III	Chronic hypoxia	29	50–414	—	—	—	—	—	—	277 (29)
IV	Chronic hypoxia and ENU	28	57–383	10	12	1	1	—	—	242 (29)

Numbers appearing in brackets alongside mean values indicate one standard error of the mean. PNS, Peripheral nervous system.

carotid bodies of one of our normoxic rats which had received ENU (Group II) were diffusely infiltrated by a malignant spindle cell neoplasm (Figure) and we were unable to measure the carotid body volume. Fusiform malignant cells infiltrated between the type 1 cells which showed no neoplastic features. This neoplasm appeared to be derived from an extracranial extension of a malignant neurinoma of the trigeminal nerve also found in this rat. There was no histological resemblance to chemodectoma.

The brains of all our rats were divided into 6 serial coronal slices and examined for the presence of tumours. The numbers of neoplasms are shown in the Table. The 34 neural neoplasms found in rats treated with ENU comprized 11 astrocytomas, 10 oligodendro-astrocytomas, 5 ependymomas, 1 oligodendrocytoma, 5 malignant neurinomas, 1 fibroblastic meningioma and 1 neuroblastoma. The 3 other neoplasms found were a pituitary tumour and 2 carcinomas of the uterus. Only 4 of our 22 rats treated with ENU alone failed to develop neural tumours, so that we conclude that our rats treated with ENU received an effective dose of neurotropic carcinogen. The low incidence of tumours in chronically hypoxic rats treated with ENU (Group IV) is attributed to the short period of survival of many of the rats in this group. Two of the 60 rats not receiving ENU developed spontaneous cerebral tumors when they were 17 and 19 months of age, respectively. A survey[8] of spontaneous neoplasms in 6 sources of Sprague-Dawley rats revealed that approximately 1% develop spontaneous neural neoplasms. One source of rats had an incidence of 4 neural neoplasms in a total of 217 rats.



Carotid body from a normoxic rat given a single neonatal injection of N-ethyl-N-nitrosourea. A cluster of type 1 cells (encircled) is surrounded by small fusiform cells apparently derived from a malignant neurinoma of the trigeminal nerve. Haematoxylin and Van Gieson stain. ×600.

Only one spontaneous chemodectoma has been described in the rat, and this occurred in the aortic body[9]. Carotid body chemodectomas in rats have not been described. Chemodectomas are unusual neoplasms of dogs[10] and are rarely found in cats[11] and cows[12]. In all these animals, chemodectoma of the aortic body is more common than the carotid body neoplasm, while the reverse is true in man[13]. These species differences may explain our inability to stimulate the formation of chemodectomas of the carotid body in rats. SALDAÑA[5] considered that chemodectomas at high altitude represent the extreme degree of hyperplastic response to chronic hypoxia. This concept was supported by the slow rate of growth and benign clinical course of the chemodectomas in the 22 high altitude natives he described. Our inability to produce carotid body chemodectomas in rats exposed to the combined stimuli of chronic hypoxia and a neurotropic carcinogen supports the view that such tumours arizing in high altitude natives are hyperplastic lesions rather than true neoplasms.

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