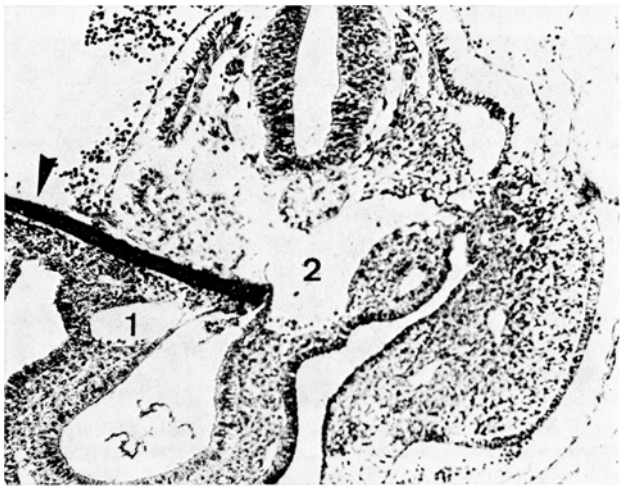

Fig. 3. Coupe transversale d'un embryon de poulet de $3^1/_2$ jours. La lamelle d'aluminium a été placée médialement par rapport à l'aorte (1).

En résumé, plusieurs agents tératogènes produisent des altérations vasculaires semblables – vasodilatation, œdème – avec la conséquente perturbation métabolique dans la région affectée. Si cette perturbation survient au stade critique de différentiation, les altérations sont irréversibles, et viennent se joindre aux malformations spécifiques.

Summary. Different teratogenic agents—hemorrhage, hypoxy, CO_2, etc.—give rise, among other non-specific changes, to anomalous vascularization. These vascular alterations have a similar evolution and produce diverse malformations that accompany the specific ones. Such malformations of a vascular genesis are specially frequent when the alteration takes place in a critical stage of differentiation.

L. M. Gonzalo-Sanz

Departamento de Anatomía, Facultad de Medicina, Universidad de Nevarra, Pamplona (España),
5 Avril 1971.

Induction of Neurosarcoma by Injections of N-Nitrosobutylurea in Suckling Syrian Golden Hamsters

The carcinogenic effect of N-nitrosobutylurea (NBU) was first reported by Druckrey et al.[1], who observed the development of subcutaneous sarcomas at the site of application in adult BD rats that received repeated subcutaneous injections of this chemical dissolved in oil. Odashima[2] has demonstrated that NBU induced erythroblastic leukaemia in adult, female Donryu rats when it was given in drinking water. However, in the Sprague-Dawley strain myeloid leukaemia was developed in treated rats (Takahashi and Sugano, personal communication). The chemical also induced mammary adenocarcinoma in Wistar/Furth rats and thymic lymphoma in C57BL/Ka mice[3]. These results show that NBU has different target organs among different species and strains of animals used, and that the route of the application and amount of the chemical may modify the target cells. This communication reports the induction of neurosarcoma of the various region of Syrian golden hamsters injected with NBU during the suckling period.

NBU (synthesized by Dr. Y. Sakurai, Cancer Institute, Tokyo), dissolved in 1% ethyl alcohol, was s.c. injected into the interscapular region of hamsters of 5 litters when they were 7 days of age, at a dose of 20 μg/g of body weight. 5 further injections of the same dosage were given at weekly intervals. Another 5 litters which were injected with 1% ethyl alcohol served as controls. The origin of the hamster colony was described in the previous paper[4]. The young of both groups were weaned and separated according to sex. They were given CMF diet (Oriental Yeast, Tokyo) and water ad libitum. The mortality due to the agent was very low and the majority of the animals survived more than 8 months. The survivors were killed at 16 months.

In 12 out of 21 treated hamsters large, elastic soft tumours were found in the subcutaneous tissue, and the parathymic, mesentelic, and retroperitoneal regions. The first subcutaneous tumour was palpable 11 weeks follow-

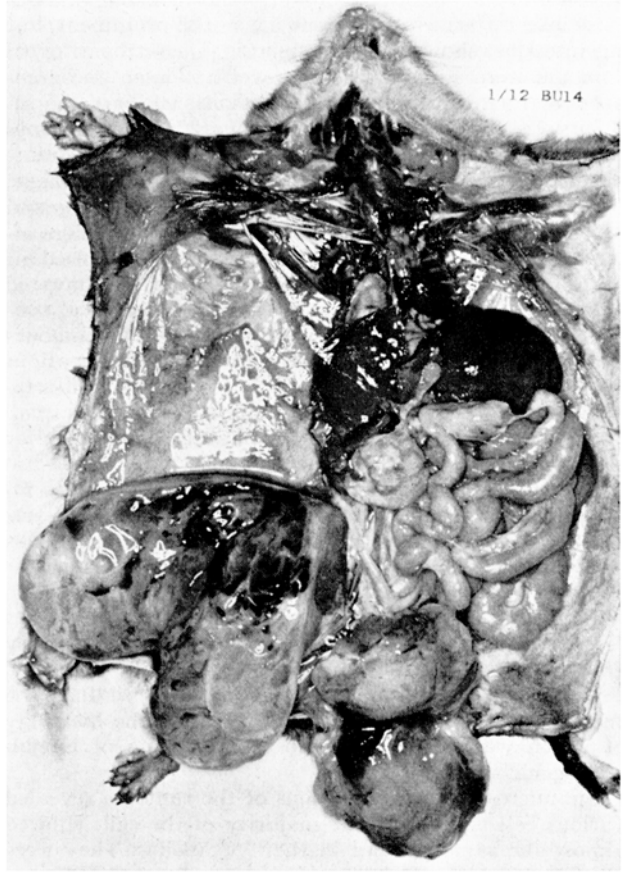

Fig. 1. Female hamster bearing 2 large tumours of neurosarcoma in the inguinal region, showing cut surface. The animal was given 6 weekly injections of NBU during the suckling period. ×0.5.

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[2] S. Odashima, Gann 61, 245 (1970).
[3] K. Yokoro, N. Imamura, S. Takizawa, H. Nishihara and E. Nishihara, Gann *61*, 287 (1970).
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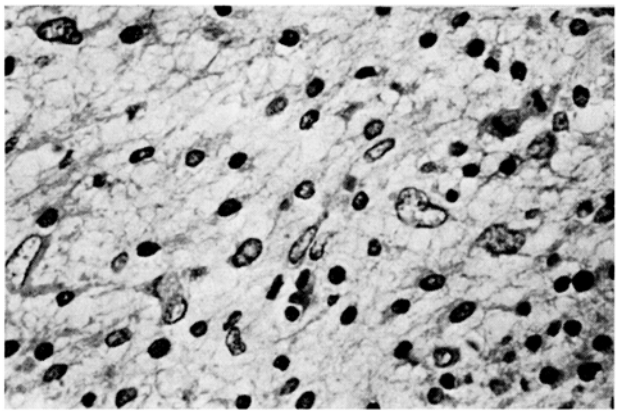

Fig. 2. Myxoid pattern of the tumour, containing large cells with attenuated cytoplasm and a mitotic cell. Stained with hematoxyl in and eosin. ×520.

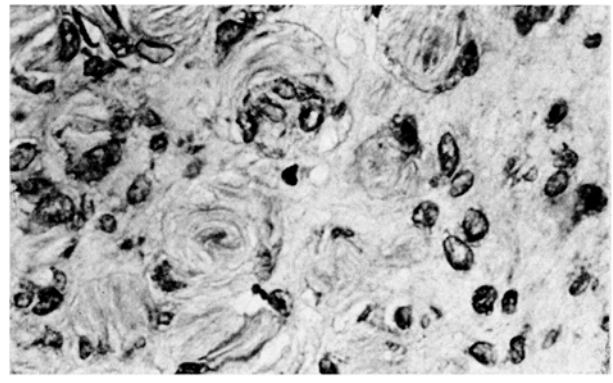

Fig. 3. Area with numerous Wagner-Meissner-like tactile corpuscles, showing a gradual transition to adjacent myxoid area (right). Stained with toluidine blue at a pH 7.0. ×520.

ing the last injection. The tumours were usually multiple (Figure 1), but they were never found at the site of application, the interscapular region. The subcutaneous tumours grew slowly and killed the hosts about 6 months following the onset. The tumours developed in the anterior mediastinum and occupied almost the whole chest cavities, showing bilateral thymoma-like appearance. The mesenteric tumours were round or oval in shape, and enclosed the intestines. Adhesions was not so prominent, but the intestines showed a slight stenosis. The retroperitoneal tumours were situated in the lower abdomen and compressed the intestines upward. The cut surface of the tumours was glistening and slightly elevated, and sometimes revealed a cystic change in the center. They were oedematous and white, yellow, or red in colour, due to haemorrhage. Necrosis was not prominent. Metastases in the lung and lymph nodes were found in 3 animals. In 18 hamsters injected with 1% alcohol no such tumour was observed.

Histologically, most parts of the tumours were myxoid (Figure 2), but some parts were rich in cellurality, containing moderate numbers of mitotic cells. The tumours were usually composed of small nodules, in which various types of cell were noticed; large cells with attenuated cytoplasm, medium-sized round and stellate-shaped cells, small vacuolated cells with picnotic rounded nuclei, and/or elongated fibroblasts. A few bipolar spindle cells were also interspersed. Cell border of all of these cell types was indistinct. Infiltration into other organs was not conspicuous. In the myxoid area of the tumours, the vacuolated cells showed intense Sudan black B staining of perinuclear cytoplasm.

Furthermore, Wagner-Meissner-like tactile corpuscles (Figure 3), arrangements of pseudo-rossettes, and solitary ganglion cells were found in the substance of 5 out of 20 tumours and in their transplants. From these findings the tumours were diagnosed as neurosarcoma, the histology of which was very similar to myxoid type of human neurogenic sarcoma[5,6].

Submicroscopic examinations of the tumours revealed various cell types, but the majority of the cells showed almost the same pattern in their organelles. They were characterized by the distorted nuclei with many indentations and the cytoplasm with severely attenuated processes, containing many lipid droplets and well developed and dilated rough endoplasmic reticulum which enclosed a large amount of amorphous substance. Some of the cells were partially surrounded by the basement membrane-like substance. Infrequently the cells which had flattened, laminated, and superimposed cytoplasm were identified. These submicroscopic features had a large similarity to those of human peripheral nerve tumours[7]. No virus-like particle was seen in the tumour cells.

DRUCKREY et al.[1] induced 8 fibrosarcomas, 3 spindle cell sarcomas, 6 polymorphic cell sarcomas, and 1 fibromyxosarcoma in the site of injection in 18 rats, by subcutaneous application of NBU. The same chemical gave rise to neurosarcomas in suckling hamsters in the present experiment. This discrepancy can be explained by differences either in the species or age of the animals. The hamster is known as an animal which can induce malignant tumours in the peripheral nerves by adenovirus type 12[8]. This may mean that Schwann cells of the hamster are more susceptible to carcinogenic agents than those of other species. Suckling animals have also more loose connective tissue than adult animals and NBU may reach more remote regions from the injection site. The subject of neurosarcoma is hopelessly confused from a century-old dispute over the essential nature of the cells involved in the tumour. There has, however, been few experimental method to induce peripheral nerve tumours by chemicals. Therefore, weekly injections of NBU into the suckling Syrian golden hamster will be a useful method in obtaining more knowledge regarding human neurosarcoma[9].

Zusammenfassung. Durch Injektion von N-Nitrosobutylharnstoff in junge Goldhamster wurden in über 50% der Versuchstiere Neurosarkome erzeugt.

M. MATSUYAMA and H. SUZUKI

Aichi Cancer Center Research Institute, Chikusa-ku, Nagoya (Japan), 26 May 1971.

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[9] This work was partly supported by a grant from the Japanese Ministry of Health and Welfare. We thank Dr. S. ODASHIMA for his kind supply of NBU, and Prof. T. NAGAYO, Dr. H. USIZIMA, Prof. H. KISHIMOTO, Dr. K. KOJIMA, Dr. S. HOSODA and Dr. M. HOSHINO for their helpful discussion.