PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE **147**, 289–292 (1974)

Anaphylactoid Edema Induced in Rats by Nickel and Cobalt Salts (38328)

GAETAN JASMIN

Department of Pathology, University of Montreal, Montreal 101, Canada

Investigations on the carcinogenicity of metal compounds have led us to observe that the injection of nickel sulfide into the renal parenchyma causes an anaphylactoid edema in rats. The acute cutaneous changes consist in an erythema and exoserosis involving mainly the ears, paws, and snout. Such phenomenon has been ascribed to histamine release and is more manifest in tissues rich in mast cells (1, 2). We have now extended these studies by administering intravenously or intraperitoneally a variety of divalent metallic compounds either related by their physicochemical properties or their ability of binding histamine (3, 4). Special attention has been given to mast cells in nickel- and cobalt-treated animals, in view of the fact that these metals allegedly act as mast-cell dischargers (5, 6). Since the topical administration of nickel sulfide into the kidney also causes a polycythemia (7), bilateral nephrectomy has been carried out in some animals to determine whether some renal factor plays a role in the production of the edema reaction. Pertinent to this reasoning is the finding that the plasma kininogen which serves as a substrate or a precursor for the production of erythropoietin is significantly elevated after subcutaneous injection of cobalt(ous) chloride in rats (8).

Materials and Methods. Female Sprague–Dawley rats averaging 100 g body wt were used. The animals were housed in cages at room temperature having free access to Purina Laboratory Chow and tap water. The kidneys were removed through a small dorsocostal incision under ether anesthesia, 24 hr prior to injection of nickel and cobalt sulfates. All metal preparations were reagent grades supplied by Fisher Scientific, Montreal and Platz & Bauer, N. Y. These were dissolved or suspended in physiologic saline and injected intraperitoneally or intravenously through the jugular vein, under ether anesthesia, at a regular dose of 5 mg in a volume of 0.5 ml.

The erythema and exoserosis which are more prominent in the snout and in the paws were appraised visually after an arbitrary scale of 0–3+. The readings were made during the first 30 min and thereafter at the hour during 5 consecutive hr. For a more accurate estimation of the exoserosis, some animals were given beside the metal preparations 0.2 ml of a 0.5% Evans blue solution intravenously.

Animals were killed with chloroform on the 6th hr and fresh or formalin-fixed cryostat-frozen section of the ear and the tongue were stained with a 1% methyl green aqueous solution for demonstration of mast-cell granules. Other sections were stained with ammonium sulfide or dimethylglyoxime in order to visualize the metals (9) or incubated in the appropriate substrate for demonstration of acid phosphatase using pararosaniline as indicator (10).

Results and Discussion. Nickel and cobalt were the only metals eliciting both erythema and exoserosis (Fig. 1, A, B); relevant data dealing with the effect of different salt preparations are given in Table I. Several other metals caused some degree of erythema but without evident exoserosis or a positive blueing reaction. These were: magnesium, calcium, strontium, chromium, and ferric chlorides; similarly lead citrate, zinc sulfate, and cadmium sulfide caused a reddening of the skin. No reaction whatsoever was demonstrable after administration of ferrous, zinc, lead, and cupric chlorides. With the exception of copper, all metals were well tolerated and the autopsy failed to demonstrate any evident macroscopic changes in the lungs, kidney, liver, and spleen.

Mast cells were found degranulated in the deeper regions of the ear derma. Within their cytoplasm there were no demonstrable metallic inclusions even after administering minute amounts of cobalt or nickel chloride in the lower part of the ear lobe. In order to be visualized,

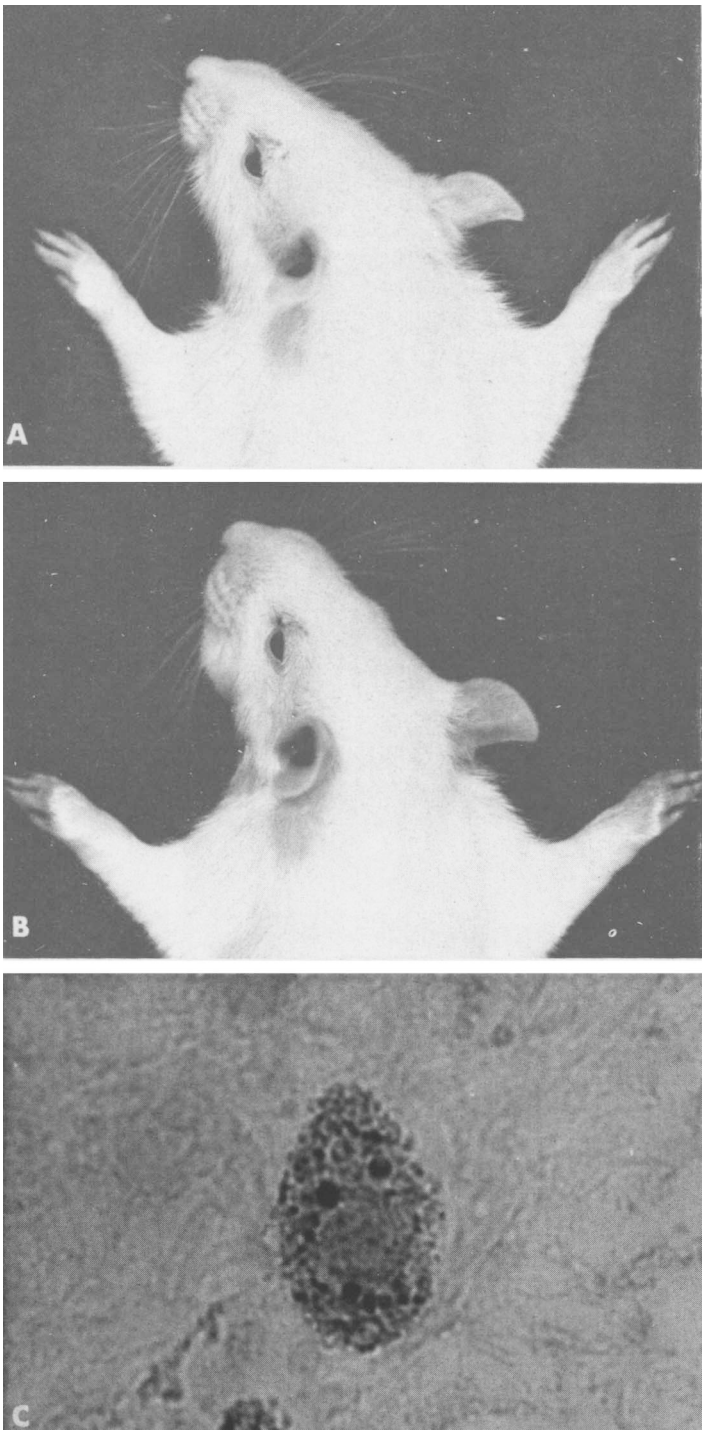

FIG. 1. Edema and blueing reaction of the snout, ears and paws in a nickel-treated rat. A. Control rat injected with Evans blue (1 mg iv). B. Nickel chloride-treated rat (5 mg ip) together with Evans blue iv. Note by comparison the edema and dark complexion of the extremities. C. Partly degranulated mast cell in the deep layer of the edematous ear. There are prominent granules strongly reacting to methyl green staining (X1800).

TABLE I. Edema Reaction in Rats Injected ip with Nickel and Cobalt Preparations.

Metals	Route of administration (5 mg)	Number of reactors (10 rats)	Readings of erythema and exoserosis (0 to +++)	Time of eruption (min)	Duration (hr)
Nickel metal powder	ip	10	±[a]	40	2
Nickel chloride	ip	9	+++	10	4
Nickel sulfate	ip	9	++	10	4
Nickel sulfide	iv	10	+	1	2
Cobalt metal powder	ip	10	±	60	1
Cobalt chloride	ip	9	++	10	4
Cobalt sulfate	ip	8	+	30	2
Cobalt sulfide	iv	0	0	0	0

[a] ± indicates that animals developed only erythema.

metals most probably should be injected in particulate form (11, 12). Interestingly, however, the muscle fibers located in the subcutaneous tissue of the ear showed affinity for nickel ions as evidenced by a positive staining reaction to dimethylglyoxime. It should be recalled that nickel sulfide has previously been shown to produce rhabdomyosarcoma when injected into the skeletal muscle (13, 14). When closely examining the mast cells, we were struck by the great differences in the size of their granules especially in the ear sections of animals topically treated with nickel chloride. Larger granules were found more prominent in partly degranulated cells; they strongly reacted to methyl green staining (Fig. 1C). Attempts to demonstrate acid phosphatase activity in these granules were unsuccessful and thus their exact nature or significance remains to be seen. There were no appreciable differences in the susceptibility of nephrectomized rats to nickel and cobalt salts as compared to intact animals. It may be concluded, therefore, that the anaphylactoid edema induced by the metallic agents quite as much as that induced by dextran (15, 16) is not mediated by a renal factor.

In recent years much attention has been paid to environmental pathology, namely, to manifestations resulting from exposure to metallic agents (17, 18). Besides their carcinogenic properties which have been recognized in man and experimental animals, nickel and cobalt are well known for eliciting acute toxic reactions. Nickel dermatitis has been noted for a long time to be a rather common occurrence (19). Excessive cobalt intake in man or in animals on the other hand leads to a myocardosis possibly through interference with cardiac energy metabolism due to its combination with α-lipoic acid (20, 21). Their ability in producing anaphylactoid edema in rats may prove interesting to further study the pathomechanisms underlying histaminergic reactions.

Summary. Nickel and cobalt, especially in form of hydrosoluble compounds, injected either intraperitoneally or intravenously in doses of 5 mg caused regularly anaphylactoid edema in rats. The mast cells in the subcutaneous tissue of edematous ear lobes were often degranulated but were unreactive to selective metal stains. Unusual large granules with no demonstrable acid phosphatase activity were found. The edema reaction developed after bilateral nephrectomy indicating that it cannot be ascribed to the release of a renal erythropoietic factor after the parenteral administration of the cobalt or nickel salts. The present observations may provide an interesting model for further investigating histaminergic reactions in rats.

1. Feldberg, W., and Talesnik, J., J. Physiol. **120,** 550 (1953).

2. Jasmin, G., J. Micros. (Paris) **17,** 68a (1973).

3. Parrot, J. L., *in* "Endocrine Aspects of Disease Processes" (G. Jasmin, ed.), p.138. Green, St. Louis (1967).

4. Jones, R. J., "Handbook of Experimental Pharmacology," Vol. 18, p. 9. Springer-Verlag, New York (1966).

5. Fiedler, H., and Hahn Von Dorsche, H., Acta Histochem. **34,** 193 (1969).

6. Hahn Von Dorsche, H., and Fiedler, H., Acta Biol. Med. Germ. **24,** 529 (1970).

7. Jasmin, G., Clin. Res. **21,** 1068 (1973).

8. Smith, R. J., and Contrera, J. F., Proc. Soc. Exp. Biol. Med. **141,** 895 (1972).

9. Ganter, P., and Jolles, G., "Histochimie normale et pathologique," pp. 1667 and 1682. Gauthier-Villars, Paris (1970).

10. Barka, T., Nature (London) **187,** 248 (1960).

11. Padawer, J., Lab. Invest. **25,** 320 (1971).

12. Padawer, J., Proc. Soc. Exp. Biol. Med. **129,** 905 (1968).

13. Gilman, J. P. W., and Ruckerbauer, G. M., Cancer Res. **22,** 152 (1962).

14. Jasmin, G., Brit. J. Cancer **17,** 681 (1964).

15. Jasmin, G., and Bois, P., Experientia **14,** 101, (1958).

16. Selye, H., Z. Immunitaetsforsch. Exp. Ther. **112,** 363 (1955).

17. Hueper, W. C., Arch. Pathol. **71,** 237 and 355 (1961).

18. Sunderman, F. W., Res. Chest **54,** 41 (1968).

19. Watt, T. L., and Bauman, R. R., Arch. Dermatol. (Chicago) **98,** 155 (1968).

20. Grice, H. C., Goodman, T., Munro, I. C., Wiberg, G. S., and Morrison, A. B., Ann. N. Y. Acad. Sci. **156,** 189 (1969).

21. Bonenfant, J. L., Auger, C., Miller, G., Chenard, J., and Roy, P. E., Ann. N. Y. Acad. Sci. **156,** 577 (1969).

Received May 15, 1974. P.S.E.B.M., 1974, Vol. 147.