Oncogenic Response of Rat Skin, Lungs, and Bones to Vinyl Chloride[1]

P. L. Viola, A. Bigotti, and A. Caputo

Regina Elena Institute for Cancer Research, Rome, Italy

SUMMARY

Rats (Ar/IRE Wistar strain) exposed for 12 months to vapors of vinyl chloride developed tumors of the skin, lungs, and bones. The cutaneous tumors, which always appeared in the area in which submaxillary and parotid glands are located, have been histologically recognized as epidermoid carcinomas, papillomas, and mucoepidermoid carcinomas. The morphological characteristics of lung tumors, which occurred in a lower percentage, were mainly of the adenocarcinoma type, with the exception of a single epidermoid tumor originating from the epithelial covering cells. In a minor number of rats, a large proliferation of cartilaginous tissue diagnosed as osteochondroma developed in the metacarpal and metatarsal regions of the four limbs.

INTRODUCTION

The oncogenic properties of some chemical organic compounds used for the preparation of "plastics" have been widely investigated, and their limits and effectiveness have been well established. Detailed information on this subject may be found in the literature (5, 6, 8); however, all information and references are exclusively related to highly polymerized compounds of roughly the same size as used in various industries.

Oncogenic polymers produce sarcomatous tumors, with the exception of polyurethans which, as reported by Hueper (6), also induce adenocarcinomas. Recently, it has been demonstrated that sarcomatous tumors (1–4, 7) are transplantable and it has been suggested that they may originate from the tissues of the capsule that gradually covers the plastic film. Thus, Brand *et al.* (2–4) have observed premalignant areas made of poorly differentiated fibroblasts which were firmly attached to the plastic film up to the moment of malignant transformation.

This investigation demonstrates that even the monomer vinyl chloride possesses oncogenic properties when used with an appropriate model different from the models previously reported by several authors (9–12). The carcinogenic response to vinyl chloride follows a singular pattern for the different tissues and organs of the rat.

MATERIALS AND METHODS

The experiments were performed with vinyl chloride (CH_2=CHCl, the monohalogenate derivative of ethylene) of a commercial grade (99% purity) assumed to contain insignificant amounts of various noncarcinogenic contaminants.

Three-month-old Wistar (Ar/IRE) male albino rats (about 150 g body weight) were exposed to vinyl chloride vapors for 4 hr a day, 5 days a week, for 12 months. The animals were kept in metal or plastic, air-tight cages in which a constant flow of air, containing 3% v/v (equal to 30,000 ppm) of vinyl chloride, was introduced. Twenty-five rats of the same strain were the control group. At the end of the treatment, the surviving animals were killed at 20-day intervals, and the most important tissues and organs were examined histologically by standard methods. During the period of exposure, the animals were slightly soporific; however, the first few months of treatment were well tolerated and no changes in growth or behavior were noticed. After 10 months of treatment, some animals began to show a hard mass in the parauricular region which became progressively larger until it reached the size of a walnut or slightly larger. In most cases, the swelling was unilateral; it was bilateral in only a few animals. After 1 or 2 months, the growing masses became ulcerated and discharged necrotic debris, while a certain amount of tumorous tissue began to form on their surfaces. In addition, we observed that the masses were an integral part of the parauricular region and could not be distinguished from the local tissues. Caseous necrotic zones were found. Pleura and pericardium often showed diffuse inflammation of a fibrous nature and, in many cases, the lungs were covered with a number of white formations as large as grains of rice or even larger and harder than the lungs themselves. In 2 cases, the lungs were hemorrhagic with milky, thick fluid in the pleural cavities. The liver was sometimes increased in size and very fragile. The animals were subjected to X-ray analyses at different intervals from the beginning of treatment in order to control the state of the skeletal bones.

All the animals that inhaled vinyl chloride showed a series of parenchymal lesions. Among these, most prominent were the disappearance of granular and Purkinje cells, degeneration

[1] A preliminary report of the results reported here was given at the Tenth International Cancer Congress, Houston, Texas, May 22–24, 1970.

Received July 31, 1970; accepted January 12, 1971.

of the cerebellum, severe chronic hepatic interstitial pneumonia, and moderate swelling of the kidney parenchyma, often assuming the pattern of tubulonephrosis.

RESULTS

The rates of survival and the main findings are summarized in Table 1. Almost all the animals developed tumors of the skin and lungs. Very few animals developed bone tumors; in these cases, the tumors were localized in the metacarpal and metatarsal bones of all 4 extremities. Skin tumors were by far the most frequent, amounting to 65 or 70%.

Skin Tumors. The tumor that developed most frequently in the paraauricular region was the epidermoid carcinoma, but we also observed papillomas and rarely mucoepidermoid carcinomas. In all cases, the neoplasms were of epithelial nature. The 3 patterns noticed cannot be compared to various histotypes but rather to a transition of one type into the other or, and which is more likely, to different stages of the same proliferative type.

Warty subauricular growths occurred in some rats. The histological picture showed papillar epithelial proliferation, with progressive increase in the thickness of the epidermis (Fig. 1).

The papillary warts of exophytic type had a fibrous vascular stroma and various degrees of inflammatory lymphocytic infiltration, marked hyperkeratosis, parakeratosis, acanthosis, and areas of individual dyskeratosis or pearly horny formations.

The epithelial cells of the penetrating columns (Fig. 2) were irregularly arranged and were frequently accompanied by an inflammatory infiltration of the dermis. The typical features of the Malpighian layer and of the stratum corneum of the prickle cells and of germinal layers were easily recognized (Fig. 3). The horny layer was composed largely of cell nests, which appeared at certain points within the epithelial masses and assumed the well-known appearance of "horny pearls" (Fig. 3, *arrows*); they were made of flattened and compressed prickle cells without nuclei and were located around a central core of keratin.

Table 1

Oncogenic effects of inhaled vinyl chloride as a function of time

The animals were exposed to vinyl chloride vapors for 4 hr a day, 5 days a week, for a total of 12 months, in a constant flow of air containing 3% v/v vinyl chloride.

Rat	Survival rate	Tumors		
		Skin	Lungs	Bones
1	300	Muco-epidermoid carcinoma	Adenoacanthoma	Osteochondroma
2, 3	280–300	Epidermoid carcinoma, keratinizing type	No tumor	No tumor
4	310	Epidermoid carcinoma, keratinizing type	Adenocarcinoma	No tumor
5	333	Papilloma, keratotic type	No tumor	Osteochondroma
6	337	Epidermoid carcinoma	No tumor	Osteochondroma
7	347	Epidermoid carcinoma	No tumor	No tumor
8	347	Mucoepidermoid carcinoma	No tumor	Osteochondroma
14	354	Epidermoid carcinoma	No tumor	No tumor
16, 17	359	Epidermoid carcinoma	Adenocarcinoma	No tumor
21	360	Epidermoid carcinoma	No tumor	No tumor
22	380	Epidermoid carcinoma	Adenocarcinoma	Osteochondroma
23	380	Epidermoid carcinoma	No tumor	No tumor
24	380	Epidermoid carcinoma	Mucus-producing adenocarcinoma (alveolar cell carcinoma?)	No tumor
25	380	Epidermoid carcinoma	No tumor	No tumor
26	380	Epidermoid carcinoma	Squamous cell carcinoma	No tumor

Keratinization was irregular and often parakeratosis was observed in the areas of the tumor in which the cells were loosely aggregated and undergoing an individual rather than a collective type of keratinization (Fig. 4). In dyskeratotic areas, a few epithelial cells tended to form pearls. The tumor seldom showed an undifferentiated growth with cellular pleomorphism and several mitotic figures (Fig. 5). A few tumors showed little nests of isolated pale cells (Figs. 6 and 7) of 3 types: mucin-producing cells (originating from the duct epithelium of sweat glands or salivary glands); squamous cells; and intermediate cells with minor tendencies towards differentiation.

Respiratory Tract. These tumors, although occurring rarely, were mainly adenocarcinomatous. Only in 1 rat did we observe an epidermoid tumor originating from the epithelium-covering cells. Sometimes, the tumors were seen in their early development and consisted predominantly of cubic or columnar cells arranged as regular or irregular tubular and papillary elements (Fig. 8) and supported by poorly developed fibrous stroma (Fig. 9).

In other cases, glandular structures were often imperfectly formed and appeared as sheet-like proliferations of undifferentiated or pleomorphic character. The cells showed a tendency to extend into the pulmonary parenchyma, thus simulating the microscopic features of the so-called alveolar cell carcinoma (Fig. 10). Sometimes, this was the prevailing pattern. The pulmonary air sacs were limited by 1 or more layers of cubic, columnar, or polyhedral cells with abundant cytoplasm that was faintly eosinophilic (Fig. 11), frequently, adenopapillary excrescences spreading into the alveolar spaces were present.

In some areas, foci of cellular polymorphism with hyperchromatic nuclei were noticed; mucin was produced in varying amounts and secreted into the lumen of the tubules and acini. There were small pools of mucin in which signet ring cells occurred, either alone or in small clusters (Fig. 12). The alveolar walls were often quite thick and, at times, showed an inflammatory infiltration.

As mentioned before, a single tumor showed squamous structures and appeared to have been formed mainly by spindle and oval undifferentiated cells (Fig. 12).

Bones. In the metacarpal and metatarsal regions of the 4 limbs, a large proliferation of cartilaginous tissues arose outward from the periosteum and, from the appearance of its cells, seemed to derive directly from the cortical bone (Fig. 14). The periosteum also grew and in some areas spread as finger-like prolongations into the newly formed cartilage (Fig. 15). In these places, a gradual transition between fibrous cartilage, periosteum, and bone could be noticed.

The newly formed cartilage appeared irregular with atypical areas; the cells, which had nuclei larger than the normal chondrocytes, lay in well-formed, capsulated lacunae. The cells occurred singly, in pairs, or in tetrads and, although of different size and shape, they usually contained a single, darkly stained nucleus. The cartilaginous growth was not homogeneous, as shown by the extension of the finger-like prolongations into the boundary of newly formed tissue. Besides the chondroblastic, chondrocytic, and angiomatous areas which indicated a rapid growth, there were also cartilaginous zones possessing regressive features, such as fibrosis and hyalinosis. The perichondrium appeared often as a compressed and structurally altered fibrous tissue.

In some cases, the tumor growth was related to the stage of the endochondral ossification occurring below the "epiphysial plate." Ossification was irregular, so that osseous trabeculae varied greatly in thickness and contours. In other cases, foci of active cellular proliferation, cartilaginous areas, chondroid developmental nests, and calcified bones occurred in the deeper portions of the trabeculae (Fig. 18).

The new formation appeared to be an osteochondroma and consisted essentially of a bony protuberance capped by cartilage and a fibrous layer, which represented the perichondrium.

The fibrous layer was continuous with the periosteum of the adjacent cortical bone and extended inward to form septa separating and enclosing lobules of cartilage.

Control Animals. The control rats were kept under the same conditions as the experimental rats and at the appropriate time were subjected to a constant flow of air without vinyl chloride. None of these animals developed tumors or the types of parenchymal lesions developed by the rats that inhaled vinyl chloride. In a very few of the control rats, there was a swelling of the liver and kidneys.

DISCUSSION

As in many carcinogenesis studies in which multiple tumors arise in different tissues and organs, the data must be evaluated in terms of a more prompt positive response to be obtained with the ideal concentration of the carcinogenic compound. The cutaneous system is the most susceptible to the oncogenic effects of vinyl chloride.

Our experimental data do not explain why the cutaneous tumors developed in the same site, *i.e.*, the region including the area in which the submaxillary and parotid glands are located. It is possible that the salivary glands may be involved in the concentration or excretion of vinyl chloride or some of its active decomposition products. This hypothesis is strongly supported by morphological findings showing the specific tendency of the developed tumor to appear as a mucoepidermoid carcinoma, which indicates the active contribution of the mucus glandular cells to the tumorous growth. Such kinds of histotypes are often related to some glandular aggregates, and, therefore, the histogenesis of human mucoepidermoid carcinoma has been restricted to the cells of intercalated ducts. This hypothetical interpretion must be confirmed by future experiments in which the action of the vinyl chloride should be restricted to the salivary system. As the concentrations used, saturation and wetting of the fur might well be expected. Under these circumstances, the natural cleansing habit of the rat might add a significant ingestion problem with subsequent concentration of vinyl chloride in the salivary glands. The local extreme concentration could be the result of the difficulty of complete cleansing by the rat.

The neoplastic response of the lower respiratory tract although of lesser magnitude, is of relevant interest, since some

...the tumors ... morphologically similar to ... described for the lung. The hypothesis that mucus-produ... cells may be capable of retaining vinyl chloride or its decomposition products seems to be relevant once more. Obviously, a different interpretation is required for the pathogenesis of the liver tumors and for their simultaneous incidence at the level of the limbs.

REFERENCES

1. Banerjee, M., and Bates, R. Prevalence of Heteroploidy in Plastic Film-induced Primary Sarcomas. Brit. J. Cancer, *20:* 555–563, 1966.
2. Brand, G., and Buoen, L. Polymer Tumorigenesis: Multiple Preneoplastic Clones in Priority Order with Clonal Inhibition. Proc. Soc. Expl. Biol. Med., *128:* 1153–1157, 1968.
3. Brand, G., Buoen, L., and Brand, I. Malignant Transformation and Maturation in Non-dividing Cells during Polymer Tumorigenesis. Proc. Soc. Expl. Biol. Med., *174:* 675–678, 1967.
4. Brand, G., Buoen, L., and Brand, I. Carcinogenesis from Polymer Implants: New Aspects from Chromosomal and Transplantation Studies during Premalignancy. J. Natl. Cancer Inst., *39:* 663–679, 1970.
5. Druckrey, H. Experimentelle ... ritraepe vum Mechanismus der Carcinogenen Wirkung. Arzneimittel-Forsch., *1:* 383–395, 1951.
6. Hueper, W. C. Cancer Induction by Polyurethan and Polysilicone Plastics. J. Natl. Cancer Inst., *33:* 1005–1027, 1964.
7. Johnson, K., Buoen, L., ... and, I., and Brand, G. Polymer Tumorigenesis Clonal Determination of Histopathological Characteristics during Early Preneoplasia: Relationships to Kar... type, Mouse Strain, and Sex. J. Natl. Cancer Inst., *44:* 785–793, 1970.
8. Kegan, A. Experimental Blastomogenesis Caused by Synthetic Polymers (Plastics). Meditsina, Moscow, *1:* 215–237, 1965.
9. Mastromatteo, E., Fisher, A. M., Christi, H., and Danziger, D. Acute Inhalation Toxicity of Vinyl Chloride to Laboratory Animals. Am. Ind. Hyg. Assoc. J., *21:* 394–397, 1960.
10. Torkerson, T. R., Oyen, F., and Rowe, V. K. The Toxicity of Vinyl Chloride as Determined by Repeated Exposure of Laboratory Animals. Ind. Hyg. J., 354–361, October 1961.
11. Van Duren, B. L., Sivak, A., Goldschmidt, B. M., Katz, C., and Melchionne, S. Carcinogenicity of Halo-Ethers. J. Natl. Cancer Inst., *43:* 481–486, 1969.
12. Viola, P. L. Pathology of Vinyl Chloride. 16th International Congress of Occupational Health. (Communication No. 38), Tokyo, 1969.

Photomicrographs of the original article are not being distributed with this copy because of the poor quality of their reproduction.

...gs. 1 to 18. All sections were stained with H & E.

...g. 1. Squamous cell papilloma of the skin. × 25.

...g. 2. Transitional stage from papilloma to infiltrative type of cancer. × 80.

...g. 3. Finger-like trabeculae branch to form secondary processes showing horny pearl formation (*arrows*). × 25.

...g. 4. Dyskeratotic area. Few epithelial cells with a tendency to form whorls. Little capacity to develop into horny pearls. × 250.

...g. 5. Atypical cells partly lacking prickles and showing considerable variation in size, shape and many mitotic figures. × 250.

...g. 6. Epidermoid skin tumor. Occurrence of hydropic epidermoid cells, basal cells, columnar cells, and basophilic cells in various ... × 100.

...g. 7. Non-epidermoid skin tumor, showing differentiation of masses of squamous epithelium from columnar cells, lining and proliferating into ... tubular spaces. × 100.

...g. 8. Bronchiolar adenocarcinoma of the lung arising from a segmental bronchus. × 25.

...g. 9. Detail of Fig. 8 showing tubular aggregates made up by cells with hyperchromatic nuclei.

...g. 10. Acinar bronchiolar alveolar mucus-secreting adenocarcinoma. × 100.

...g. 11. Detail of Fig. 10, showing an alveologenic pattern. × 250.

...g. 12. Mucus-producing cells with hyperchromatic and pleomorphic nuclei and occurrence of signet ring cells. × 250.

...g. 13. Squamous cell carcinoma of the lung. × 100.

...g. 14. Osteochondroma developing as a protuberance from the small bones of metacarpus and metatarsus. × 25.

...g. 15. Magnification of Fig. 14. The protuberance consists of bone trabeculae, capped by cartilage, and a fibrous layer functioning as ... perichondrium. × 100.

...g. 16. Osteochondroma. Cartilaginous growth characterized by finger-like proliferation. × 100.

...g. 17. Osteochondroma. Area of endochondrial ossification. × 100.

...g. 18. Cellular area of an osteochondroma showing the transition from cartilage to osteoid. × 100.

L. W. Zielek

FOSTER GRANT CO. INC.

Nippon Shohi Keizai Shinbun
(Nippon Consumer Economy Press) - Jan. 26, 1976

Seminar on Safety of Food Containers to be held by Association of Housewives on 28th

The Association of Housewives (Shuhuren) which has been boycotting polyvinylchloride food containers plans to take up the problem of food containers as a subject of this year's 19th annual Consumer's Seminar and look into the safeties of plastic food containers not limited to those of polyvinylchloride.

This Seminar is held in late January every year by the delegates representing various branching organizations that exist in the country and it carries out a thorough research and discussion on a subject that is most important in that year. In the past the subject of the Seminar not only became the main theme of the Shuhuren's movement for the year but also put important influences on the movements of other organizations.

In this year's Seminar which will be held on 28th between 10:30 and 3:30 p.m. the theme will be focused on the problems of safety, label specification and disposal treatment of the plastic containers upon which the concern has rapidly built up in connection with the carcinogenicity of vinylchloride monomer.

Representatives from the related government offices such as Department of Health, Department of Industry and Commerce and Department of Agriculture will attend the Seminar. From the industry side the Polyvinylchloride Association and Polyolefin Association will attend. Also including the experts, they will pursue a comprehensive investigation of the problem of food containers.

Nippon Consumer Economy Press - 1/26/76

Shuhuren has been boycotting foods in polyvinylchloride containers since last year on the ground that they have a risk of containing the monomer which is regarded as carcinogenic. The organization has decided to hold this special seminar in order to investigate whether the containers made of other materials than polyvinylchloride, such as polyethylene and polystyrne, are actually safe or not.

Some of the people have the opinion that not only polyvinylchloride but also other poly-type containers contain toxic materials. Thus the opinion has begun to emerge that a direction has to be taken in the future toward the ban of all the plastic food containers. In view of this it is noteworthy that Shuhuren has started aserious study of the safety problem of the plastic containers.

It seems that the safety problem of the plastics is going to be a major topic of the consumer's movements this year.

tients with normal cycles. We do suspect that their hyperandrogenism arises from the ovaries (even with normal menstrual cycles), since we do not find high androgen gradients in their adrenal veins, we do find androgen gradients in their ovaries and we cannot account for the testosterone coming from prehormone metabolism.

I agree with Dr. Rosenfield that it would be very helpful if we could catheterize these women before and after dexamethasone; however, "horse sense" prevents us from doing multiple catheterizations.

MARVIN A. KIRSCHNER, M.D.
Newark Beth Israel
Newark, NJ Medical Center

1. Bardin CW, Hembree WC, Lipsett MB: Suppression of testosterone and androstenedione production rates with dexamethasone in women with idiopathic hirsutism and polycystic ovaries. J Clin Endocrinol Metab 28:1300, 1968
2. Kirschner MA, Zucker IR, Jespersen D: Idiopathic hirsutism: an ovarian abnormality. N Engl J Med 294:637-640, 1976
3. Huq MS, Pfaff M, Jespersen D, et al: Concurrence of aldosterone, androgen, and cortisol secretion in adrenal venous effluents. J Clin Endocrinol Metab 42:230, 1976
4. Rosenfield RL, Ehrlich EN, Cleary ER: Adrenal and ovarian contributions to the elevated free plasma androgen levels in hirsute women. J Clin Endocrinol Metab 34:92, 1972

INDUSTRIAL EXPOSURE TO VINYL CHLORIDE

To the Editor: The recent article by Wegman et al. entitled "Vinyl Chloride: Can the worker be protected?" (N Engl J Med 294:653, 1976) clearly describes one of the most serious health hazards faced by American workers today. Indeed, the incidence of occupational diseases has been rising, and the passage of the Occupational Health and Safety Act of 1970 has done little to thwart the trend. Today, five years after the Act, there are only about 2000 safety inspectors to inspect four million workplaces.[1] At the current rate of inspection, it would take 230 years to visit each plant once!

Moreover, protective clothing, masks and adequate safety education are rarely provided; when they are, they are often severely inadequate or interfere enough with work as to create new dangers. Fines levied for violations of safety standards are such that it is often much cheaper for a company to pay the fine than attempt to correct the violation. The example given by Boden of compensation costs for workers dead of polyvinyl-chloride-associated disease amounting to a mere fraction of profits vividly illustrates the problem.[2]

Another particularly disturbing fact that readers of the *Journal* must realize all too well is that training for physicians in occupational diseases is virtually nonexistent in medical-school curricula.

Though in no way solving the problems of occupational diseases, efforts by physicians and students to obtain training in diagnosis of such problems, and support of workers' efforts to have legal protections enforced by the Occupational Safety and Health Administration will help to improve the health of millions of American people.

DAVID C. CHRISTIANI
Tufts University School
Boston, MA of Medicine

1. Facts and Analysis: Occupational health and safety. Industrial Union Department of the AFL-CIO, December, 1974
2. Wegman DH, Peters JM, Jaeger RF, et al: Vinyl chloride: can the worker be protected? N Engl J Med 294:653-657, 1976

MANAGEMENT OF HEMOPHILIA WITH ATRIAL CATHETER

To the Editor: The letter from Flessa et al. (N Engl J Med 294:1240, 1976) describes the use of the Cimino arteriovenous fistula as a method of circulatory access for the chronic self-administration of clotting factors to patients with hemophilia. In the event that the vasculature becomes so damaged that it becomes impossible to construct an arteriovenous fistula, the all-silicone rubber right atrial catheter,[1] which we use for self-administered home parenteral nutrition,[2] will serve very well as a safe, semipermanent route of injection of these clotting factors into the bloodstream.

BELDING H. SCRIBNER, M.D.
Seattle, WA University of Washington

1. Broviac JW, Cole JJ, Scribner BH: A silicone rubber atrial catheter for prolonged parenteral alimentation. Surg Gynecol Obstet 136:602-606, 1973
2. Broviac JW, Scribner BH: Prolonged parenteral nutrition in the home. Surg Gynecol Obstet 139:24-28, 1974

"JOGGERS' TOXICOSIS"

To the Editor: The recognition of thyrotoxicosis is usually not difficult when many features of the hypermetabolic state are present. The tachycardia and other hemodynamic changes are the most common and frequently stressed clinical manifestations of the thyrotoxic patient. In fact, hyperthyroidism is often not apparent, especially in elderly persons, except for tachyarrhythmias and congestive heart failure.[1] Cardiovascular changes may be less marked, however, in young, physically active persons, and if relied upon too strongly, could prevent proper diagnosis, particularly in those who jog for physical fitness.

A 37-year-old physician, accustomed to jogging a total of 60 km per week for several years, was seen by his own physician because of weight loss, heat intolerance, fatigue, muscle weakness and loose stools. On examination he had no lid lag or stare, and no tremor or thyrotoxic skin changes, and his thyroid gland was barely palpable. The heart rate was 80 per minute and was assumed to be "normal" even though he reported that his usual resting pulse was 48 to 52 per minute. After a gastrointestinal work-up, a second physician, impressed with the "relative" tachycardia, ordered a determination of thyroxine level which was 17.4 μg per 100 ml. An additional history obtained by still a third physician suggested a viral prodrome with some initial thyroid tenderness, and further studies confirmed a diagnosis of subacute thyroiditis: a sedimentation rate of 38 mm per hour; and 24-hour uptake of radioactive iodine (^{131}I) of <1 per cent. The patient recovered after several months with a return in his resting pulse to 56 per minute, thyroxine level of 7.4 μg per 100 ml and a 24-hour uptake of radioactive iodine of 44 per cent.

Although the eventual diagnosis in this patient was subacute thyroiditis, the presenting thyrotoxic features were not immediately recognized in the absence of tachycardia although the heart rate was in fact "relatively" rapid for this jogger. Because athletes and physical-fitness enthusiasts often have slow heart rates at rest,[2] and unlike this physician, may be unaware of their actual resting pulse, and thus unable to provide this useful information, the absence of tachycardia may be used as evidence against the diagnosis of thyrotoxicosis, as initially occurred in the case. Physicians should be aware of their patients' exercise habits so as not to miss a case of what might be called "joggers' toxicosis."

DANIEL L. ARONS, M.D.
Cambridge, MA Mount Auburn Hospital

1. Davis PJ, Davis FB: Hyperthyroidism in patients over the age of 60 years. Medicine (Baltimore) 53:161-181, 1974
2. Frick MH: Coronary implications of hemodynamic changes caused by physical training. Am J Cardiol 22:107-116, 1968

MULTIPHASIC SCREENING

To the Editor: The issue of April 22 provides a rare insight into a common medical problem that deserves comment: data collection uncoupled from predefined actions.

Olsen et al. — "A Controlled Trial of Multiphasic Screening" (N Engl J Med 294:925-930, 1976) — speak of a "collusion of indifference between patient and physician" in interpreting the lack of effect of screening on health attitudes or status. Their analysis unfortunately precludes identification of obesity or dental caries because the authors view height/weight ratio and dental survey as of "questionable value or not easily related to any specific medical problem" even though these two problems are among the most

jected exceeded the lethal dose. With the exception of EF and DMF, which appeared to increase growth rate, the compounds tested retarded growth. Haematological examination revealed an increase in leucocytes but no effects on erythrocytes, haemoglobin or haematocrit were observed. The level of calcium in the blood was increased, sodium and potassium were eventually decreased, and analysis of serum proteins revealed in most cases a decrease in the γ-globulin fraction. Levels of calcium, sodium and potassium in the urine were decreased. Microscopic examination revealed no lesions in any of the organs examined.

In view of these results the authors suggested that some caution should be exercised in the use of formamide and its N-alkyl derivatives as solvents for pharmacologically active materials.

2335. HAZARD TO RATS FROM VINYL CHLORIDE SNIFFING

Viola, P.L., Bigotti, A. & Caputo, A. (1971). Oncogenic response of rat skin, lungs, and bones to vinyl chloride. Cancer Res. 31, 516.

Vinyl chloride monomer does not seem to have been associated in the past with any indication of carcinogenic potential. The inhalation study reported here, however, suggests that this monomer has some tumour-inducing capacity in rats.

Rats were exposed to 30,000 ppm vinyl chloride vapour for 4 hr daily for 5 days/wk for 12 months. After 10 months, some rats had a hard epidermal mass in the skin over the para-auricular region and this gradually enlarged and broke down after a further 1-2 months to an ulcer, which discharged necrotic debris and formed tumour tissue on its surface. Tumours developed in nearly all the treated rats, usually unilaterally although they occurred bilaterally in a few animals. Many of the rats also developed a fibrous inflammation of the pleure and pericardium, and their lungs became covered with hard white adenocarcinomatous nodules. In a few rats a proliferation of cartilaginous tissue (osteochondroma) developed in the metacarpal and metatarsal regions of the limbs. Certain other lesions were found in the treated animals, notably a disappearance of granular and Purkinje cells, degeneration of the cerebellum, severe chronic hepatitis and interstitial pneumonia. Swelling of the liver and kidneys was seen in a few of the control rats as well as in some of the treated animals, but otherwise the control rats were free of the tumours and lesions reported in the rats exposed to vinyl chloride.

The authors suggest that, in view of the concentration of skin carcinomas and papillomas over the region of the submaxillary and parotid glands, it is possible that the salivary glands of the rat concentrate or excrete vinyl chloride or its active metabolites.

NATURAL PRODUCTS

2336. THE GREEN POTATO TOXIN

Nishie, K., Gumbmann, M.R. & Keyl, A.C. (1971). Pharmacology of solanine. Toxic. appl. Pharmac. 19, 81.