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# CARCINOGENICITY BIOASSAYS OF VINYL CHLORIDE
## I. RESEARCH PLAN AND EARLY RESULTS





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ENVIRONMENTAL RESEARCH 7, 387–405 (1974)

# Carcinogenicity Bioassays of Vinyl Chloride

## I. Research Plan and Early Results[1]

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*Received March 11, 1974*

These investigations are concerned with determining the oncogenic potentialities of vinyl chloride (VC) in experimental animals. The effect of this compound is being studied in relation to various experimental factors, such as route of administration, dose level, length of treatment, species, strain, and age of the animals.

Preliminary results are presented. When given by inhalation, VC induces in rats, Zymbal gland carcinomas, nephroblastomas, and angiosarcomas of the liver and of other anatomical sites; and in mice, pulmonary adenomas, mammary carcinomas and liver angiosarcomas.

A direct relationship has been found between dose and length of treatment and neoplastic response.

Vinyl chloride (VC)($CH_2 = CHCl$) is a chemical compound of increasing industrial importance. It is used in the production of polyvinyl chloride resin, as a copolymer in Saran and other plastics, as a chemical intermediate, as a solvent, and as a propellent; in the past, for a short period, it was also used as anaesthetic. It is at present produced at a rate of near 12 million tons per year.

The following population groups may be exposed to VC: (1) workers engaged in the production of polyvinyl chloride (PVC) and of VC, and in the use of VC for other industrial purposes; (2) workers manufacturing PVC; (3) residents about factories producing PVC and VC; and (4) to a much lesser extent, people undergoing contact with resins made with VC, with materials containing these resins or consumer products containing VC, as some propellant sprays.

The present research includes a series of correlated and integrated experiments dealing with carcinogenicity bioassays of this monomer. This research followed the preliminary results of the pioneering work of P. L. Viola, presented at the X International Cancer Congress (Houston, 1970) and published in 1971 (Viola *et al.*, 1971).

Viola's results indicated that exposure to 30,000 ppm of VC, 4 hours a day, 5 times a week for 10 months, produced tumours in rats, and that these occurred in skin, lungs and bones.

Immediately after the report in Houston, we communicated with Professor Viola, who kindly put at our disposal the manuscript of his extensive report, then in press, and several slides of the tumours.

On the basis of his results and material, we reached the following conclusions.

[1] This project has been supported by the European Cooperative Group (ECG) which includes Montedison (Italy), ICI (U. K.), Solvay (Belgium), Rhone-Progil (France).

(1) Under Professor Viola's experimental conditions, VC definitely showed a carcinogenic effect on rats;
(2) 30,000 ppm of VC was an extremely high level of exposure;
(3) The tumours described as cutaneous arose from Zymbal glands, which in rats are responsive to a large spectrum of carcinogens: e.g., 2-acetylamino-fluorene (Wilson *et al.*, 1941), benzidine (Spitz *et al.*, 1950), 3,2-dimethyl-4-aminobiphenyl (Walpole *et al.*, 1952), 4-aminostilbenes (Haddow *et al.*, 1948), 9,10-dimethyl-1,2-benzanthracene (Geyer *et al.*, 1953), 3-methoxy-4-aminoazobenzene (Miller and Miller, 1961), urethan (Tannenbaum *et al.*, 1962), and others.
(4) The pulmonary tumours were most likely metastases from Zymbal gland carcinomas. These lesions were in fact morphologically similar to the Zymbal gland carcinomas, and all were observed in animals bearing Zymbal gland tumours.

It appeared useful to further investigate the nature and extent of the carcinogenic effect of VC, with particular emphasis on experimental factors related to exposure, such as route, concentration, duration, continuity or intermittence, etc., which could give more direct information concerning the risk of occupational and environmental exposure, and other factors related to the animals studied, such as species, strain, sex, and age. For these reasons, we were contacted by Professor Bartalini, Director of the Health Services of Montedison who offered the support of his Company for an experimental study of the biological effect of VC. Montedison was soon joined by ICI, Solvay and Rhone-Progil.

## MATERIALS AND METHODS

The construction of an apparatus for programmed and controlled exposure took several months. The chambers were designed to deliver concentrations varying from 30,000 ppm to 50 ppm and to simultaneously treat nearly 1200 experimental rodents. Basically, it is built of stainless steel and glass. The control of VC concentrations is by gas chromatography.

VC has been supplied by Montedison. Each batch has been analyzed in the chemical research laboratory of Montedison before use to assess its degree of purity (99.99%).

The experiments largely utilized Sprague–Dawley rats. Wistar rats, Swiss mice, and hamsters have also been used. All the animals, except the hamsters, have been bred in our Institute for years and, whatever their use, are all examined at death by complete autopsy, giving us extensive information concerning their current pathology.

The animals have been weaned and classified by sex when 4–5 weeks old, at which time they have been numbered by ear punch, and divided into groups by litter distribution. From weaning, the animals have been fed, *ad libitum*, an adequate commercial diet. During the period of treatment, the animals are housed in groups of 10 in stainless steel wire cages with a solid bottom of the same metal. After the period of experimental treatment, the animals are kept in groups of 5 in makrolon cages, with tops made of stainless steel wire. A

shallow layer of white wood shavings served as bedding. The animals were kept in a temperature controlled laboratory at 19–20°C.

Fourteen experiments have been started in sequence. Some were programmed at the onset. The need for others appeared on the basis of initial experimental results. The plan of the experiments is shown in Table 1.

*Experiment 1*

Experiment 1 was to investigate the effect of the atmospheric exposure to 10,000. 6000, 2500, 500, 250, and 50 ppm of VC, 4 hours daily, 5 days weekly, for 12 months. Two groups of animals were added as controls: one untreated, as with all the following experiments, and one treated with vinyl acetate (VA) at 2500 ppm, under the same conditions. This dose of VA appeared to be the maximum possible dose for a chronic exposure.

*Experiment 2*

Experiment 2 was performed to obtain data in a larger number of animals on the effect of doses between 250 and 50 ppm, i.e., 200, 150, and 100 ppm, under the same conditions as in Expt 1. It was begun after it became clear that 250 ppm still showed oncogenic effects.

*Experiment 3*

This was planned to study the effects of a shorter period of exposure, keeping constant the other conditions of Expt 1.

*Experiment 4*

Experiment 4 studies the effect of the same type of exposure as in Expt 1, in another species, i.e., mice. The treatment lasted 7 months in view of the higher mortality, and the shorter life span of the mice of our line.

*Experiment 5*

This was undertaken as a pilot investigation on the possible effects of the atmospheric exposure during pregnancy, on offspring.

*Experiment 6*

Experiment 6 reproduced the conditions of Viola's experiments.

*Experiment 7*

This experiment was designed to study the effects of the same type of exposure as in Expt 1 in another strain of rats, i.e., Wistar.

*Experiment 8*

Experiment 8 studies the effects of the same exposure as in Expt 1 in a third species, i.e., hamsters, for the same period as in Expt 4.

*Experiment 9*

This was planned to further assess whether or not inhalation of VC has any effect at a dose level of 50 ppm in experimental animals.

TABLE 1

PLAN OF THE EXPERIMENTS TO MARCH 11, 1974

| No. of experiment | Treatment | | | Animals | | | | | | | Length of experiments (weeks) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | No. | | | | |
| | Route | Doses of VC | Length | Species | Strain | Age (weeks) | ♀ | ♂ | Total | Per group | |
| BT1 | Inhalation | 10,000, 6000, 2500, 500, 250, 50 ppm<br>Untreated controls<br>Treated controls: VA 2500 ppm | 4 hours daily, 5 days weekly, 52 weeks | Rat | Sprague-Dawley | 13 | 268 | 309 | 577 | 64–96 | 131 |
| BT2 | Inhalation | 200, 150, 100 ppm<br>Untreated controls | 4 hours daily, 5 days weekly, 52 weeks | Rat | Sprague-Dawley | 13 | 280 | 265 | 545 | 120–185 | 35 |
| BT3 | Inhalation | 10,000, 6000, 2500, 500, 250, 50 ppm<br>Untreated controls | 4 hours daily, 5 days weekly, 17 weeks | Rat | Sprague-Dawley | 21 | 262 | 288 | 550 | 60–190 | 60 |
| BT4 | Inhalation | 10,000, 6000, 2500, 500, 250, 50 ppm<br>Untreated controls | 4 hours daily, 5 days weekly, 30 weeks | Mouse | Swiss | 11 | 250 | 260 | 510 | 60–150 | 35 |
| BT5 | Transplacental | 10,000, 6000 ppm | 4 hours daily, 7 days of pregnancy | Rat | Sprague-Dawley | 19 Breeders<br>12 days Embryos | 110 | 36 | 146 | 30–51 | 69 |
| BT6 | Inhalation | 30,000 ppm | 4 hours daily, 5 days weekly, 52 weeks | Rat | Sprague-Dawley | 17 | 30 | 30 | 60 | 60 | 35 |
| BT7 | Inhalation | 10,000, 6000, 2500, 500, 250, 50 ppm<br>Untreated controls | 4 hours daily, 5 days weekly, 52 weeks | Rat | Wistar | 11 | -- | 220 | 220 | 30–40 | 35 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Untreated controls | | | | | | | | | | |
| BT5 | Trans-placental | 10,000, 6000 ppm | 4 hours daily, 7 days of pregnancy | Rat | Sprague-Dawley | 19 Breeders 12 days Embryos | 110 | 36 | 146 | 30 54 | 69 |
| BT6 | Inhalation | 30,000 ppm | 4 hours daily, 5 days weekly, 52 weeks | Rat | Sprague-Dawley | 17 | 30 | 30 | 60 | 60 | 35 |
| BT7 | Inhalation | 10,000, 6000, 2500, 500, 250, 50 ppm Untreated controls | 4 hours daily, 5 days weekly, 52 weeks | Rat | Wistar | 11 | -- | 220 | 220 | 30 40 | 35 |
| BT8 | Inhalation | 10,000, 6000, 2500, 500, 250, 50 ppm Untreated controls | 4 hours daily, 5 days weekly, 30 weeks | Hamster | Golden | 11 | — | 268 | 268 | 32-70 | 22 |
| BT9 | Inhalation | 50 ppm (*t*) Untreated controls (c) | 4 hours daily, 5 days weekly, 52 weeks | Rat | Sprague-Dawley | 11 | 200 | 200 | 400 | 100 (c) 300 (*t*) | 7 |
| BT10 | Inhalation | 10,000, 6000 ppm Untreated controls | 4 hours daily, 5 days weekly, 5 weeks; 4 hours daily, 1 day weekly, 25 weeks; 1 hour daily, 4 days weekly, 25 weeks | Rat | Sprague-Dawley | 11 | 420 | 420 | 840 | 120 | 7 |
| BT11 | Ingestion | 16,6 mg; 3,32 mg; 50 mg/kg body weight in olive oil Controls: olive oil | 5 times weekly, 52 weeks | Rat | Sprague-Dawley | 13 | 160 | 160 | 320 | 80 | 7 |
| BT12 | Endoperitoneal injection | 4,25 mg in 1,0 cc olive oil Controls: 1,0 cc olive oil | 4, 3, 2, times by two months, and once | Rat | Sprague-Dawley | 13 | 150 | 150 | 300 | 60 | 7 |
| BT13 | Subcutaneous injection | 4,25 mg. in 1,0 cc olive oil Controls: 1,0 cc olive oil | 1 injection | Rat | Sprague-Dawley | 21 | 80 | 70 | 150 | 75 | 7 |
| BT14 | Inhalation | 10,000, 6000 ppm | 4 hours daily, 5 days weekly, 5 weeks | Rat | Sprague-Dawley | 1 day | 45 | 44 | 82 | 43-46 | 2 |

*Experiment 10*

Experiment 10 studies the effect of a high, but [illegible] intermitt[illegible] ... spheric exposure.

*Experiment 11*

This was performed to evaluate possible effects of VC by ingestion. Doses have been chosen on the basis of early data on the release of VC from food containers made of PVC, and following suggestions of EEC.

*Experiment 12*

This experiment studies a third general route of exposure namely the peritoneal cavity.

*Experiment 13*

Experiment 13 was started to assess whether the VC acts on tissues directly or through metabolites.

*Experiment 14*

This experiment has been included to study the responsiveness of newborn animals.

The animals are examined weekly, and weighed every 2 weeks during the period of treatment, and monthly after the treatment is completed. All detectable gross pathological changes are recorded during examination. All animals are kept under observation until spontaneous death. Moribund animals are isolated, in order to avoid cannibalism.

A complete autopsy is made of every animal. Histological specimens include Zymbal glands, interscapular brown fat, salivary glands, tongue, lungs, liver, kidneys, spleen, stomach, different segments of the intestine, bladder, brain, bones of the legs and feet, and any other organ with pathological lesions. The tissues are fixed in alcohol, processed, sectioned, and routinely stained by hematoxylin and eosin and with Van Gieson's method; in selected cases, other staining techniques have also been used.

All animals exposed to the highest doses (30,000 and 10,000 ppm) with or without tumours, are examined radiologically, during treatment and/or at death. Moreover, radiological examinations are made of all animals bearing tumours, even if exposed to the lower doses.

## RESULTS

Preliminary results and other current data of Expts BT1, BT3, and BT4 are given in Tables 2–4.

Special aspects of Expt BT5 and BT6 are discussed in the text. Insofar as the other experiments are concerned, results are awaited.

In Table 2 are listed the observations on the oncogenic effect of graded concentrations of VC within a range of 50–10,000 ppm. It is evident that the overall occurrence of tumours decreases with decreasing concentrations from 39% tumour

TABLE 2
EXPERIMENT BT1: RESULTS AFTER 131 WEEKS

| Groups and treatment | Animals (Sprague–Dawley rats) Total | Survivors | Animals with tumours: Zymbal glands carcinomas[a] No. | Nephroblastomas[b] No. | Angiosarcomas: Liver[c] No. | Angiosarcomas: Other sites No. | Other type and/or site No. | Total No.[m] |
|---|---|---|---|---|---|---|---|---|
| I VA 2500 ppm | 96 | — | — | — | — | — | — | — |
| II VC 10,000 ppm | 69 | — | 13 | 3 | 6 | — | 5[h] | 27 |
| III VC 6000 ppm | 72 | — | 5 | 3 | 11 | 1[d] | 1[i] | 21 |
| IV VC 2500 ppm | 74 | — | 2 | 6 | 9 | 3[e] | 1[j] | 21 |
| V VC 500 ppm | 67 | — | 3 | 3 | 7 | 2[f] | 1[k] | 16 |
| VI VC 250 ppm | 67 | 1 | — | 5 | 2 | 2[g] | 2[l] | 11 |
| VII VC 50 ppm | 64 | 3 | — | — | — | — | — | — |
| VIII No treatment | 68 | 1 | — | — | — | — | — | — |
| Total | 577 | 5 | 23 | 20 | 35 | 8 | 10 | 96 |

[a] Metastases to lung.
[b] Metastases to liver and/or to lung and spleen.
[c] Metastases to lung.
[d] Angiosarcoma in subcutaneous fibrosing angioma.
[e] Two intra-abdominal angiosarcomas (1 contiguous to spleen and 1 to ovary); 1 ossifying angiosarcoma of neck.
[f] One pulmonary angiosarcoma; 1 angiosarcoma of uterus.
[g] One intra-abdominal angiosarcoma (near to spleen); 1 intrathoracic ossifying angiosarcoma.
[h] Two Zymbal gland adenomas; 1 neurilemmoma of the ear; 1 mammary carcinoma; 1 cystoadenocarcinoma of ovary.
[i] Sebaceous gland carcinoma of skin.
[j] Zymbal gland adenoma.
[k] Minimal deviation hepatoma.
[l] One Zymbal gland adenoma; 1 salivary gland carcinoma.
[m] Total No. of tumours.

incidence at 10,000 ppm, 29% at 6000 and 2500 ppm to 24% and 16% at 500 and 250 ppm, respectively. Fifty (50) ppm did not cause tumour development in the limited number of animals so exposed, and no neoplasms were found in untreated controls and in rats exposed to VA 2500 ppm. Zymbal gland carcinomas, nephroblastomas and angiosarcomas of the liver and other sites were the prevailing tumours. The development of the latter 2 neoplasms was not always dependent on the concentration of the toxic agent, but to a higher degree on the duration of exposure. If exposure time was reduced from 52 weeks (Table 2) to 17 weeks (Table 3) the number of tumours after 60 weeks is markedly smaller: their per-

TABLE 3
EXPERIMENT BT5: RESULTS AFTER 60 WEEKS[a]

| Groups and treatment | Animals (Sprague-Dawley rats) | | Animals with tumours | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Survivors | Zymbal glands carcinomas No. | Nephroblastomas No. | Angiosarcomas Liver No. | Angiosarcomas Other sites No. | Other type and/or site No. | Total No.[b] |
| I VC 10,000 ppm | 60 | 36 | 3 (11) | — (1) | — (1) | — | — (4) | 3 (17) |
| II VC 6000 ppm | 60 | 48 | 1 (3) | — (1) | — (3) | — (1) | — | 1 (8) |
| III VC 2500 ppm | 60 | 54 | — (2) | — (1) | — (1) | — | — (1) | — (5) |
| IV VC 500 ppm | 60 | 56 | — (1) | — | — (1) | — | — (1) | — (3) |
| V VC 250 ppm | 60 | 44 | — | — | — (1) | — | — | — (1) |
| VI VC 50 ppm | 60 | 50 | — | — | — | — | — | — |
| VII No treatment | 190 | 183 | — | — | — | — | — | — |
| Total | 550 | 471 | 4 (17) | — (3) | — (7) | — (1) | — (6) | 4 (34) |

[a] Tumours found in experiment BT1 after 60 weeks are recorded in parenthesis.
[b] Total No. of tumours.

centage is 5% at VC 10,000 ppm and 1.7% at 6000 ppm; at this time no tumours were found after administration of the lower concentrations. It is also worthy of note that all malignancies in this series were Zymbal gland carcinomas. After 35 weeks of exposure to 30,000 ppm (Expt BT6) 2 Zymbal gland carcinomas have been observed among 60 rats (58 survivors). In Expt BT5, two groups of 30 mature breeder rats were exposed to VC 10,000 ppm and 6000 ppm for 7 days during pregnancy. No tumours were observed after 69 weeks among the 28 survivors of each group. Angiosarcomas of the subcutaneous tissue occurred in their offspring; one tumour in one of the 54 rats of the 10,000 ppm group at the age of 24 weeks; the other tumor in one of the 36 animals of the 6000 ppm group was found at 22 weeks of age. Fifty and 30 rats, respectively, of the litters are still alive and under observation.

Table 4 indicates that mice respond to VC inhalation of 10,000–50 ppm in a similar manner as rats. While 50 ppm is again ineffective after 35 weeks, 30%, 15%, and 8.4% neoplasms were found after 10,000–6000, 2500–500, and 250 ppm, respectively. It is perhaps not surprising that in mice, pulmonary and mammary tumors were more frequent than other localizations, but the presence of angiosarcomas of the liver also occurred in this genus.

At present, 5 distinct types of tumours induced by VC have been observed; i.e., angiosarcomas, particularly of the liver (in rats and mice), nephroblastomas (in rats), Zymbal gland carcinomas (in rats) and pulmonary adenomas, some of

TABLE 4
EXPERIMENT BT4: RESULTS AFTER 35 WEEKS

| Groups and treatment | Animals (Swiss mice) | | | | | | Animals with tumours | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Treated | | | Survivors | | | Pulmonary tumours | Mammary carcinomas[a] | Liver angiosarcomas | Other type and/or site | Total |
| | ♂ | ♀ | Total | ♂ | ♀ | Total | No. | No. | No. | No. | No.[d] |
| I VC 10,000 ppm | 30 | 30 | 60 | 6 | 18 | 24 | 12 | 4 | — | 3[b] | 19 |
| II VC 6000 ppm | 30 | 30 | 60 | 11 | 18 | 29 | 12 | 3 | 1 | 2[c] | 18 |
| III VC 2500 ppm | 30 | 30 | 60 | 11 | 22 | 33 | 7 | 2 | — | — | 9 |
| IV VC 500 ppm | 30 | 30 | 60 | 13 | 25 | 38 | 7 | — | 2 | — | 9 |
| V VC 250 ppm | 30 | 30 | 60 | 22 | 19 | 41 | 4 | 1 | — | — | 5 |
| VI VC 50 ppm | 30 | 30 | 60 | 13 | 24 | 37 | — | — | — | — | — |
| VII No treatment | 80 | 70 | 150 | 61 | 61 | 122 | — | — | — | — | — |
| Total | 260 | 250 | 510 | 137 | 187 | 324 | 42 | 10 | 3 | 5 | 60 |

[a] In females.
[b] One skin squamocellular carcinoma; 1 skin invasive acanthoma; 1 subcutaneous hemangioma;
[c] One skin squamocellular carcinoma; 1 thymic lymphosarcoma.
[d] Total No. of tumors.

which undergo malignant transformation and mammary carcinomas (in mice).

Macroscopic and microscopic illustrations of the tumours induced are shown in Figs. 1–25.

The frequent Zymbal gland carcinomas can reach considerable size (Fig. 1*),[2] are sometimes bilobated and show a tendency to hemorrhages. Their structure can show different patterns. The arrangement of the normal Zymbal gland (Fig. 2) appears often in a disorganized form in the tumours. The carcinomas present various different histological patterns, e.g., glandular (Fig. 3), solid (Fig. 4*), squamous, anaplastic, and polymorphous. The frequent pulmonary metastases carry the characteristics of the primary lesion, (Fig. 5). The nephroblastomas (Figs. 6–8) lead to numerous metastases in the liver (Figs. 9*, 10*) but can also involve spleen and lungs. The frequently found angiosarcomas of the liver in rats (Figs. 11*, 12*, 13*, and 14) are characterized by the vascular growth and hemorrhagic appearance which is also present in pulmonary metastases (Fig. 15*). Occasionally, both angiosarcoma of the liver and nephroblastoma occurred in the same animal (Fig. 16*). Angiosarcomas of other sites appear generally as more or less hemorrhagic masses developing in the ab-

[2] Figures marked by asterisks (*) appear on the color plates.

dominal cavity (Fig. 17), in the subcutaneous tissue (Fig. 22*) in the uterus (Fig. 18), or in the lung (Fig. 19). The ossifying angiosarcoma (Figs. 20*, 21*) and the salivary gland carcinoma (Figs. 23 and 24) occurred rarely (see Table 2, group VI). Figure 25 shows a liver angiosarcoma of a mouse.

## CONCLUSIONS AND DISCUSSION

From the results presented in the tables, from the pathological and histological observations, the following early conclusions may be drawn.

(1) VC is oncogenic under our experimental conditions. It induces, in rats, carcinomas of the Zymbal glands, nephroblastomas and angiosarcomas in liver and other sites; in mice, liver angiosarcomas, pulmonary adenomas and mammary carcinomas.
(2) A direct relationship exists between the dose and length of treatment, and the neoplastic response.
(3) Zymbal gland carcinomas and nephroblastomas may be bilateral.
(4) Liver angiosarcomas are often multicentric.
(5) Blood vessel ectasias and endothelial hyperplasia, associated or not with cellular atypia, are often observed in liver and in other organs and tissues in treated animals, with or without angiosarcomas. Therefore, the effect of VC on blood vessels and endothelia should be considered systemic.
(6) The onset of 2 ossifying angiosarcomas suggests a new orientation in the pathogenetic interpretation of acroosteolysis in workers exposed to VC.
(7) To the present no acroosteolytic lesions have been observed in our exposed animals.
(8) No tumours have been observed in rats exposed to VA (2500 ppm).

Zymbal gland carcinomas, nephroblastomas and liver angiosarcomas have never been observed to occur spontaneously in our breed of Sprague–Dawley rats.

Although Zymbal glands, in rats, are responsive to a large number of carcinogens, only 3 spontaneously occurring cases of Zymbal gland carcinomas have been recorded in this species (Tannenbaum *et al.*, 1962). To our knowledge, no spontaneous nephroblastomas and liver angiosarcomas of rats have been reported

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FIG. 1. Rat with Zymbal gland carcinoma.
FIG. 4. Zymbal gland carcinoma, solid pattern; in rat. H–E × 158.
FIG. 9. Rat with nephroblastoma; metastases in liver.
FIG. 10. Liver metastasis from nephroblastoma; in rat. H–E × 158.
FIG. 11. Rat with liver angiosarcoma.
FIG. 12. Rat with liver angiosarcoma with lung metastasis.
FIG. 13. Liver angiosarcoma; characteristic pattern; in rat. H–E × 158.
FIG. 15. Pulmonary metastasis of liver angiosarcoma; in rat. H–E × 158.
FIG. 16. Liver angiosarcoma + nephroblastoma in rat.
FIG. 20. Laterocervical ossifying angiosarcoma; in rat. H–E × 158.
FIG. 21. Pulmonary metastasis of ossifying angiosarcoma; in rat. H–E × 40.
FIG. 22. Rat with subcutaneous angiosarcoma.

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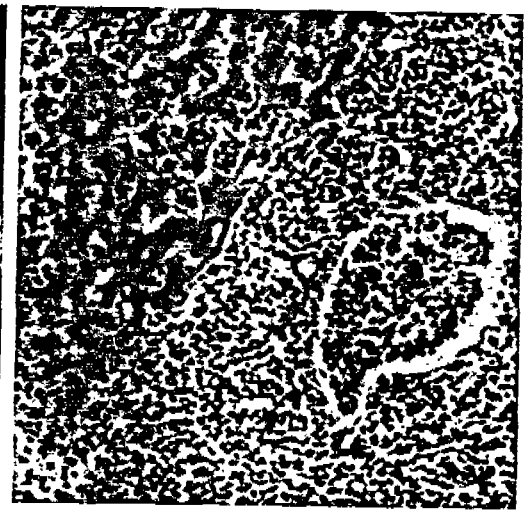
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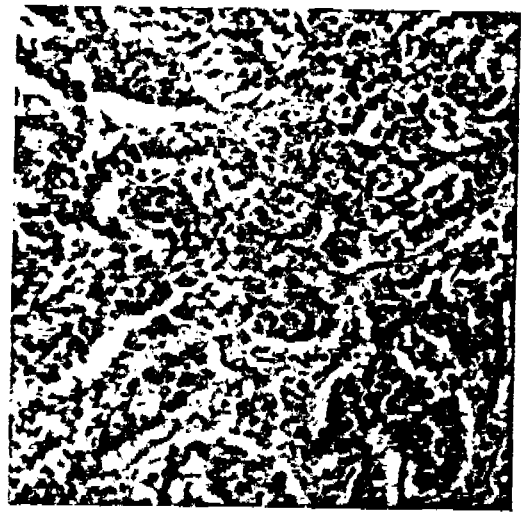
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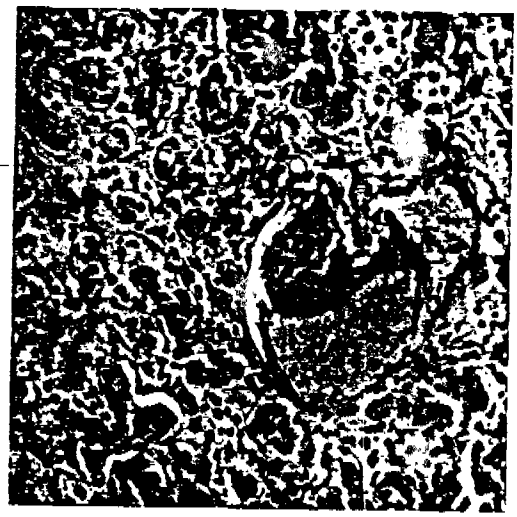

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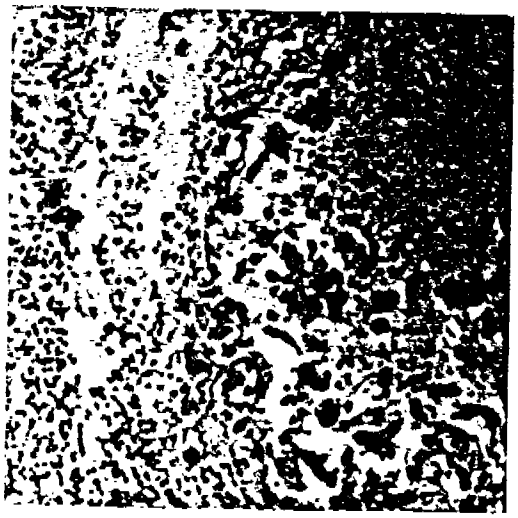

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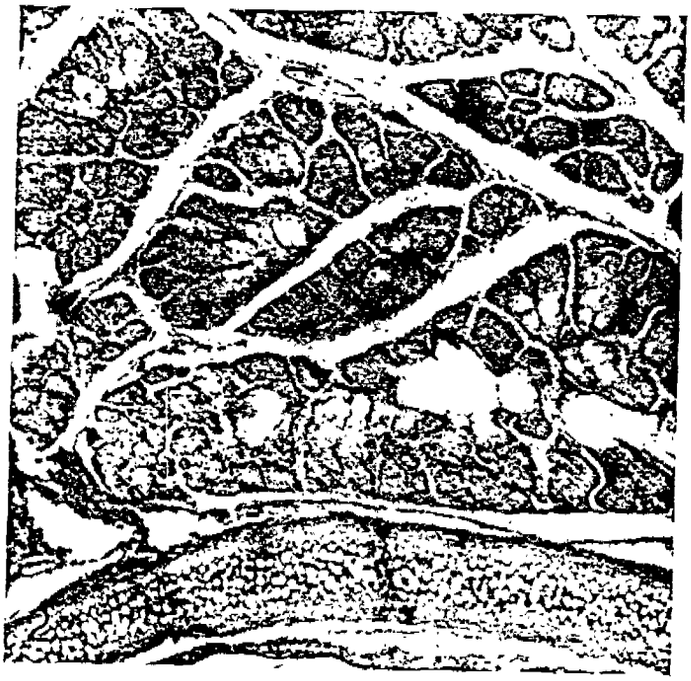

FIG. 2. Normal Zymbal gland of rat. H–E × 46.

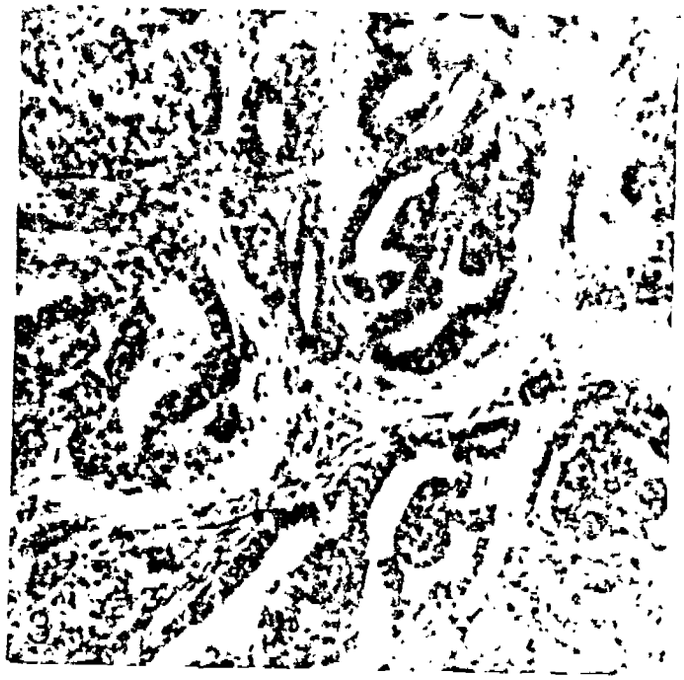

FIG. 3. Zymbal gland carcinoma, glandular pattern: in rat. H–E × 185.

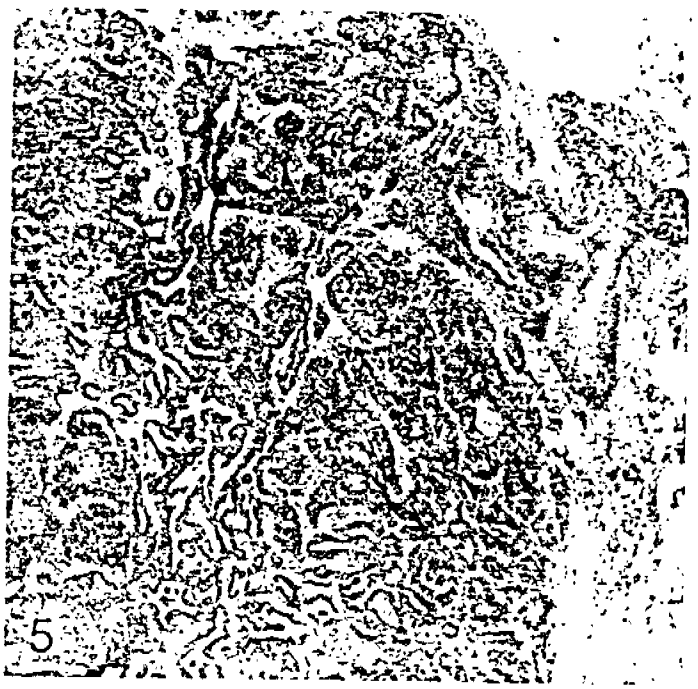

FIG. 5. Zymbal gland carcinoma; pulmonary metastasis; in rat. H–E × 46.


FIG. 6. Nephroblastoma in rat.

rat. H–E × 46.

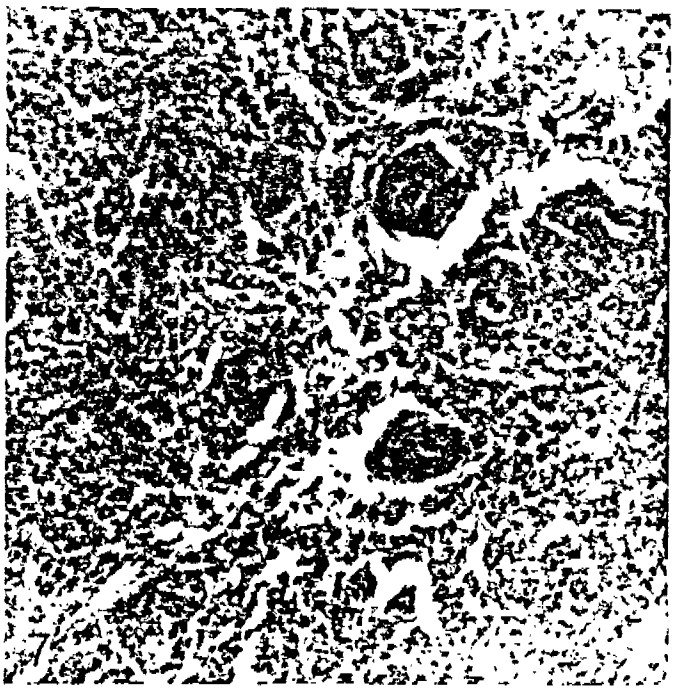

FIG. 7. Nephroblastoma of rat; characteristic pattern; H–E × 185.

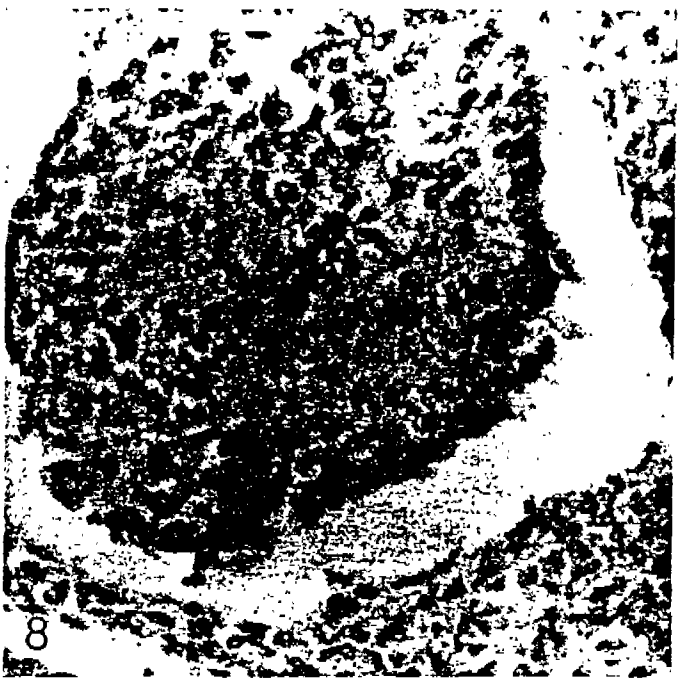

FIG. 8. Nephroblastoma of a rat; nephrogenic blastema differentiating in a glomerulus H–E × 470.

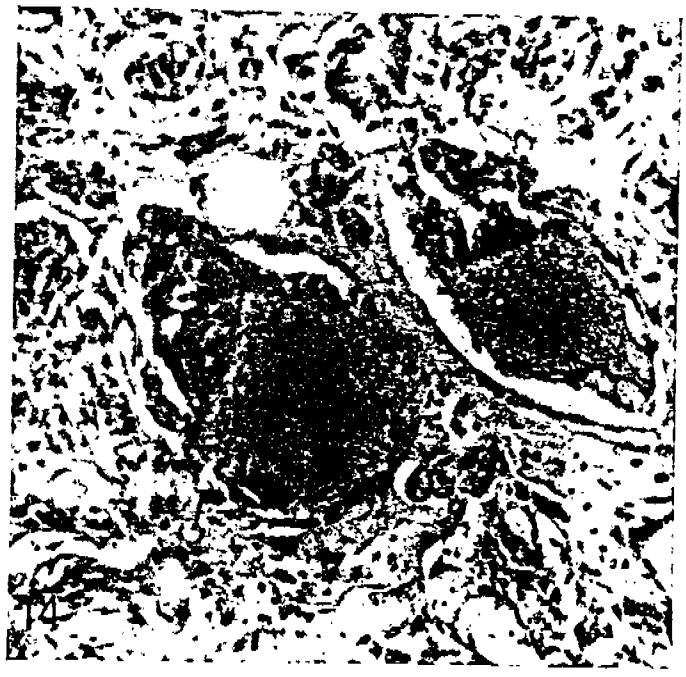

FIG. 14. Liver angiosarcoma; characteristic pattern in a rat. H-E × 185.

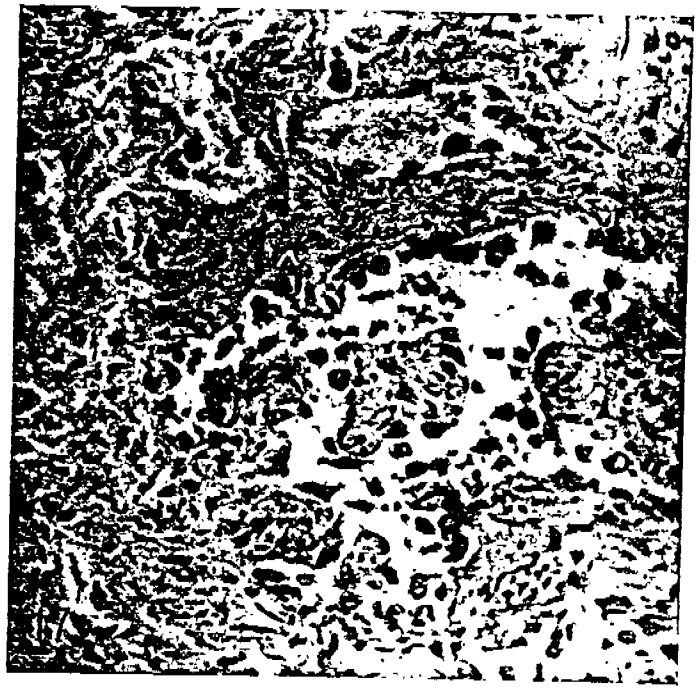

FIG. 17. Intra-abdominal angiosarcoma near the spleen; in rat. H-E × 185.

rat. H–E × 185.

at. H–E × 185.

FIG. 18. Uterus angiosarcoma; in rat. H–E × 470.

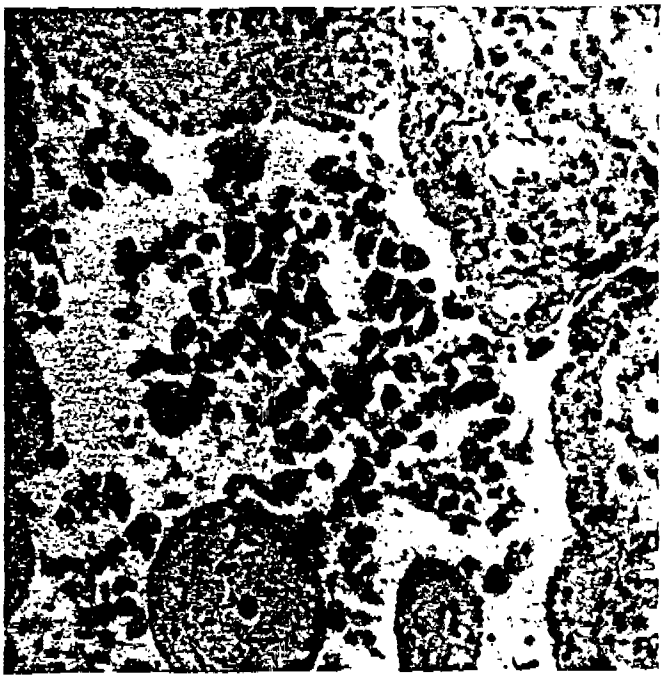

FIG. 19. Angiosarcoma of lung, in rat. H–E × 185.


FIG. 23. Rat with salivary gland adenocarcinoma.

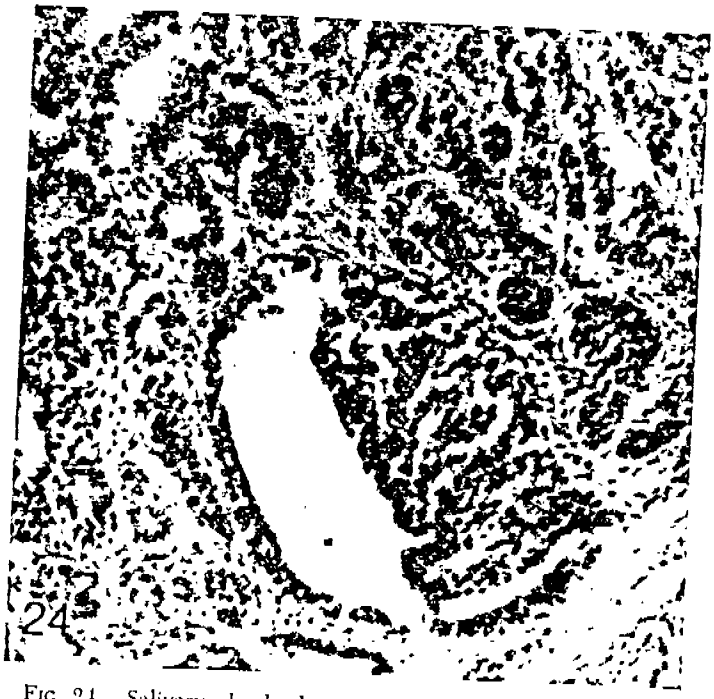


FIG. 24. Salivary gland adenocarcinoma; in rat. H–E × 185.

nd adenocarcinoma.

n r –E × 185.



FIG. 25. Liver angiosarcoma in a mouse. H–E × 185.

in literature and as far as we know, kidney nephroblastomas have never been reported as being experimentally induced.

Hepatic angiosarcomas have been experimentally induced in rats (Reuber and Lee, 1968; Hadjiolov, 1972), in mice (Roe and Salaman, 1954; Cardesa *et al.*, 1973) and in hamsters (Toth, 1972). In mice, extrahepatic angiosarcomas have been induced by *o*-aminoazotoluene (Andervont *et al.*, 1942; Andervont, 1950) and by *p*-dimethylaminobenzene-1-azo-2-naphthalene (Mulay and Saxén, 1953). In the rabbit, angiosarcomas have been produced by thorotrast (Zeitlhofer and Speiser, 1954).

In man, angiosarcomas are quite rare. One hundred-seventeen documented cases were collected to 1958 (Landells, 1958), of which only 21 arose in the liver.

Induction of liver angiosarcomas have been reported in humans. In one case, a liver angiosarcoma followed the insertion of a radium needle (Ross, 1932). Cases of liver angiosarcomas have been reported following administration of thorotrast (MacMahon *et al.*, 1947; Lüdin, 1953; Baserga *et al.*, 1960; Da Silva Horta *et al.*, 1965) and exposure to arsenic (Roth, 1957).

The results of our investigations have been periodically transmitted to the members of the European Cooperative Group. When, approximately a year and a half ago, it became definitely clear that VC was able to induce angiosarcomas, nephroblastomas and other malignancies, our results were also communicated to major American manufacturers of VC and PVC, to orient clinical observations

and epidemiological investigations, and to guide industrial hygiene measures needed for prevention of diseases which might be associated with VC exposure.

## SUMMARY

This project of investigations is concerned with determining the oncogenic potentialities of vinyl chloride (VC). The effect of this compound is studied in relation to various experimental factors, such as route of administration, dose level, length of treatment, and species, strain and age of the animals.

The preliminary results are presented. When given by inhalation VC induces, in rats, Zymbal gland carcinomas, nephroblastomas and angiosarcomas of the liver and of other anatomical sites, and in mice, pulmonary adenomas, mammary carcinomas, and liver angiosarcomas.

A direct relationship between dose and length of treatment, and neoplastic response has been found.

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# Announcements

## René Barthe International Prize 1975

The René Barthe Prize is awarded for a recent original paper on a topic of Occupational Medicine or Industrial Hygiene. Personal papers by authors of any nationality may be submitted.

The award, amounting to 8000 French Francs, is made every three years, on occasion of the International Congress on Occupational Health, organized under the auspices of the Permanent Commission and International Association on Occupational Health.

The next award will be made in September 1975 in conjunction with the 18th International Congress on Occupational Health which will be held in Brighton, England.

Regulations concerning the award may be obtained from:

Comité du Souvenir du Docteur René Barthe
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75008 Paris, France

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