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CARCINOGENICITY OF VINYL CHLORIDE AND
VINYLIDENE CHLORIDE

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ABSTRACT

Carcinogenicity of Vinyl Chloride and Vinylidene Chloride.

Lee, C. C., Bhandari, J. C., Winston, J. M., House, W. B., Dixon, R. L., and Woods, J. S. (1977). Toxicol. Environ. Health 00:00-00. Exposure of mice to 50, 250 or 1,000 ppm of vinyl chloride (VC) in the air, 6 hrs/day and 5 days/wk, caused a high incidence of bronchiolo-alveolar adenoma, mammary gland tumors and hemangiosarcoma. Mammary gland tumors occurred only in the female and included ductular adenocarcinoma, squamous and anaplastic carcinomas with metastasis to the lung. Hemangiosarcoma occurred in the liver, and, to a lesser extent, in various other organs. The incidence and severity of these tumors increased with the VC level and the length of exposure. Malignant lymphoma involving various organs was observed in several mice. Rats were more resistant to the carcinogenic effects of VC. Exposure of rats to 250 or 1,000 ppm of VC caused hemangiosarcoma in the liver. Many rats with hepatic hemangiosarcoma also developed hemangiosarcoma in the lung. Extrahepatic hemangiosarcoma also occasionally occurred in other organs. Exposure to 55 ppm of vinylidene chloride (VDC) caused hepatic hemangiosarcoma and probably bronchiolo-alveolar adenoma in mice. Hemangiosarcoma also occurred in the mesenteric lymph node or subcutaneous tissue in two rats exposed to 55 ppm of VDC.

Key Words: Carcinogenicity
Vinyl chloride
Vinylidene chloride

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In 1974, four cases of hepatic angiosarcoma were reported in polyvinyl chloride workers (Creach and Johnson). The first case of hepatic angiosarcoma occurred in 1961 (Heath et al., 1965). Further cases of hepatic angiosarcoma and other hepatic diseases, notably portal fibrosis and portal hypertension, were identified among VC polymerization workers (Block, 1974; Falk, et al., 1974; Lee and Warren, 1974; Maki et al., 1974; Block et

tumors at multiple sites developed in VC and polyvinyl chloride workers (Monson and Peters, 1974; Tabershaw and Gaffey, 1974; Nicholson et al., 1975; Byren et al., 1976; Waxweiler et al., 1976). This report summarizes the carcinogenic effects of 50, 250 or 1,000 ppm of VC in rats and mice and compares the effect of vinylidene chloride (VDC) at concentration of 55 ppm.

METHODS

Inhalation Chambers and Air Supply: Five stainless steel cubical type exposure chambers of 3.5 m³ volume were used. VC or VDC was introduced through the top of the chamber. Each chamber contained a plenum, a diffusion plate and two small squirrel cage fans (2.85 m³/min), mounted on opposite sides of the top cone above the diffusion plate, to ensure complete mixture of the gas with air. The outside air supply passed through a coarse filter, over coils for heating, cooling and dehumidifying, and then through an absolute filter (99.97-99.99% retention of 0.3 μ particles) into the plenum of the chamber. Air flow rates were measured initially at the inlet side of the chamber with a pitot tube connected to a magnahelix gauge and later at the exhaust outlet with a orifice plate and magnahelix gauge. The orifice plate was calibrated with an air flow transducer (Autotronics 100-SXX). These measurements indicated air flow rates of about 12 chamber volumes (0.70 m³/min) per hour.

Generation of VC and VDC Vapor: VC gas (99.8% pure, Matheson Products) was metered with rotameters into the chamber air supply. VDC (99% pure, Aldrich Company) was heated to 37°C to generate the vapor. All VDC lines and the rotameter were heated to 40°C to prevent condensation.

Chamber Monitoring and Sampling: Chamber concentrations were monitored using a gas chromatograph (Varian-2700) with a flame ionization detector. A 6 ft x 1/8 in. stainless steel column packed with 0.4% Carbowax 1500 on Carbowax A was used with a nitrogen carrier flow rate of 80 ml/min.

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The injection, column and detector temperatures were 135°C, 65°C, and 170°C, respectively. VC standards at dilutions of 10, 50 and 100 ppm were obtained in lecture bottles (Supelco, Inc., Bellefonte, PA), and a 1,000 ppm primary standard was obtained from Matheson Gas Products (Joliet, IL). VDC standards were prepared by a serial dilution (weight/volume) of VDC in carbon tetrachloride.

Each chamber was fitted with 10 sampling ports on two sides. Polyethylene tubes were positioned through the ports at the center and near the periphery of the chamber. Samples were withdrawn with a syringe and introduced into the gas chromatograph. A valid sample could be withdrawn by pumping the syringe three times on the short sampling lines and five times on the long lines. All sampling was performed in triplicate. Distribution studies at all parts of the chamber were compared with a reference point in the center. The results indicated that average chamber concentrations were $\pm 3\%$ of the desired concentration and the reference point averages were 98.4% to 100.4% of the chamber averages. During the study, chambers were routinely sampled from the reference point three to four times a day.

An automatic sampling system was used later during the experiment. A polyfluoroethylene (Teflon®, DuPont) line (1/4 in. diameter) connected each chamber to the automatic sampler. These lines were purged constantly. Periodically, a sample was directed to the gas chromatograph where it was injected via a sampling valve with twin 1-ml sampling loops. The readout was processed by a Varian CDS 111 electronic integrator. The integrator

was programmed to measure peak area and to calculate ppm by an external standards program. A chart recorder connected to the integrator was occasionally used to visualize the chromatogram.

Experimental Design: Albino CD-1 mice and CD® rats (Charles River Breeding Lab) about 2 months old were used. For each species, a total of 360 animals were divided into five groups, each consisting of 36 males and 36 females. Each group of both species was exposed to 50, 250 or 1,000 ppm of VC, 55 ppm of VDC, or uncontaminated air for 6 hrs/day and 5 days/wk. All animals were kept in the same stainless steel cages with wire bottoms both during exposure and when outside of the chambers. Mice were housed six to eight/cage and rats two/cage. During exposure, the position of cages was constantly rotated throughout the study. Pulverized or block laboratory chow (Wayne Lab Blox) was provided except during exposure. Water was available ad libitum. A 12-hr light cycle was maintained. The temperature in the chamber and in the room averaged $24 \pm 1.3^{\circ}\text{C}$. The relative humidity ranged from 25 to 60% at the start of the experiment and was later regulated at $50 \pm 10\%$.

Four animals of each species, sex and exposure level were terminated for various laboratory tests, and gross and histopathologic examinations at the end of 1, 2, 3, 6 and 9 months. The surviving animals were terminated at the end of 12 months.

Laboratory Evaluations: All animals were observed throughout the study for adverse signs. Food consumption was recorded weekly and body

weight biweekly at a uniform time of day. Various clinical laboratory tests and specific studies were performed as described elsewhere (Lee et al., 1977). When moribund or at terminations, all animals were euthanized for necropsy after the collection of blood. Gross examination, especially for any appearance of abnormal growth or other lesions, was carefully performed on all tissues including the brain, pituitary, thyroids, respiratory tract, alimentary canal, urogenital organs, thymus, heart, liver, pancreas, spleen, mesenteric lymph nodes, and other tissues with pathological lesions. Tumors with adjacent normal tissues and the other tissues without tumors were fixed, processed, sectioned, and stained for microscopic examination. All external and internal tumors were carefully examined and identified histologically.

RESULTS

Chamber Concentrations: For VC, the average weekly concentration in the 1,000 ppm and 250 ppm chambers did not vary more than $\pm 5\%$ from the desired concentrations except during the third week when the average concentrations were about 10% lower. The variations in the 50 ppm chamber were slightly greater during the second, 7th and 8th weeks. With a few exceptions, no sample varied more than 10% from the desired concentration. It was planned that the exposure concentration for VDC would be 50 ppm. However, the slightly higher concentration of 55 ppm was obtained and maintained throughout the experiment.

MICE

General Condition: A few mice exposed to various levels of VC started to exhibit toxic signs including rough hair coat, lethargy, anorexia and rapid weight loss during the 6th month. Some mice died or were terminated before their imminent death. Thereafter, the general health of the remaining mice exposed to VC deteriorated. Abdominal distention and/or external tumor masses, especially mammary tumors in the females, occurred. All male and female mice exposed to 1,000 ppm and all females exposed to 250 ppm died or were terminated during the 10th through 12th months. Of the mice exposed to 55 ppm of VDC, two males were terminated during the 9th month and one female during the 10th month. Most mice that died or were terminated ahead of schedule and many mice that were terminated on schedule at various times developed one or more types of tumors. In the control group, two males

died during the 8th or 9th month. One death was due to injury from fighting, the other mouse was found dead with autolysis. No obvious mass was observed in any controls.

Gross Lesions: Gross lesions were observed in several organs of some mice. In the lung, there were raised, tan to greyish white nodules of pinhead size to 0.5 cm or larger. In the liver, there were moderate mottling and small dark hemorrhagic spots varying in size from petechiae to 1 cm in diameter, or dark nodular masses filled with blood or ruptures in several animals. Spleens were slightly to markedly enlarged. Subcutaneous masses occurred at various locations, varying in size from 1 to 3 cm or larger, moderately firm and greyish-white to dark in appearance.

Bronchiolo-alveolar Adenoma: Bronchiolo-alveolar adenomas were found during the second month in the mice exposed to 1,000 or 250 ppm of VC and during the third month in the mice exposed to 50 ppm. The adenoma was characterized by focal areas of acinar or papillary growth, forming small solitary nodules which were well demarcated but not encapsulated (Plate 1). The incidence (Table 1) and severity of the tumor were in direct proportion to the level of VC and to the length of exposure. In more severe tumors, there was an increase in number and in size of nodules by expansion and coalescing to cause consolidation of the affected lobes. There was no sex difference. A total of 12, 22 and 48 mice⁹ exposed to 50, 250 or 1,000 ppm of VC, respectively, developed bronchiolo-alveolar adenoma. This tumor was found in only one male control during the 9th month. In the group exposed to 55 ppm of VDC, a few small nodules of

bronchiolo-alveolar adenoma were found in one male during the 6th month, two males during the 9th month, and three males during the 12th month.

Hemangiosarcoma: Hemangiosarcomas were found in the livers of mice exposed to 1,000 or 250 ppm of VC starting the 6th month. The hemangiosarcoma was characterized by moderate to severe proliferation of endothelial cells lining the sinusoids, dilation of the sinusoids, focal hemorrhage forming small to large cavernous blood spaces, invasion of the hepatic parenchyma with neoplastic cells, and mild to severe necrosis (Plate 2) depending upon the VC level and length of exposure. The incidence of hepatic hemangiosarcoma was also related to the VC levels and to the length of exposure (Table 2). A total of 3, 23 and 31 mice exposed to 50, 250 or 1,000 ppm, respectively, developed hemangiosarcoma in the liver. Hepatic hemangiosarcoma appeared to occur more in females than in males exposed to 250 or 1,000 ppm of VC. However, the differences between sexes were not statistically significant. Extrahepatic hemangiosarcomas occasionally occurred in mammary gland, heart, gastrointestinal tract, pancreas, kidney, epididymis and testis, mesenteric lymph nodes and skeletal muscle. The incidence of extra hepatic hemangiosarcoma was not related to the VC level or to the length of exposure. Hemangiosarcoma was not found in any control mice. In the mice exposed to 55 ppm of VDC, hemangiosarcomas occurred in the livers of two males and one female. There were also hemangiosarcomas in the mediastinum of one female exposed to 50 ppm of VC and in the connective tissue adjacent to the salivary gland of one male exposed to 1,000 ppm.

Mammary Tumors: Mammary gland tumors were observed in females exposed to various levels of VC starting the 6th or 7th month. The tumors consisted of adenocarcinoma, squamous and anaplastic carcinomas (Plate 3). The adenocarcinoma was characterized by proliferation of ductular epithelium with a marked anaplastic and squamous cell metaplasia; the squamous carcinoma was characterized by marked proliferation of stratified squamous epithelium, marked keratinization, marked purulent inflammation and necrosis; and the anaplastic carcinoma was characterized by marked proliferation of undifferentiated cells in large sheets, irregular cords, and packets. These tumors occurred in 9, 3 and 13 females exposed to 50, 250 or 1,000 ppm, respectively (Table 3). Most of these mice had a combination of the various tumors. Metastatic clusters of squamous and/or anaplastic carcinomas were also found adjacent to the pleura and/or in the lung of most of these females (Plate 4). These primary and metastatic mammary gland tumors were more severe in the mice exposed to higher levels of VC and in the mice that died or were terminated at later date. In the group exposed to 1,000 or 250 ppm, the females developed these tumors earlier. Mammary gland tumors were not found in any control mice or mice exposed to 55 ppm of VDC.

Malignant Lymphoma: During the 6th month, a malignant lymphoma characterized by marked disseminated or diffused infiltration of lymphoreticular cells in the epicardium and myocardium, perivascular and interstitial areas of the lung, liver, spleen and kidney was found in one female mouse exposed to 50 ppm of VC. There was loss of splenic architecture (Plate 5). In addition, a malignant lymphoma characterized by a large mass

of lympho-reticular cells and necrotic debris, infiltrating the cervical tissue surrounding the trachea, blood vessels and esophagus was found in one male exposed to 1,000 ppm. During the 9th month, malignant lymphomas involving spleen, liver, lung, heart, subcutaneous tissue in the cervical area, and/or mammary gland were found in two females exposed to 250 ppm and one male and three females exposed to 1,000 ppm. Malignant lymphoma was not found in any control mice or mice exposed to 55 ppm of VDC at any time.

Hepatomas and Other Tumors: A total of three mice exposed to 55 ppm of VDC developed hepatomas. This tumor was found in one male when terminated during the 9th month, in one male and one female during the 12th month. The hepatoma was characterized by a marked proliferation of hepatocytes with a loss of the lobular pattern, except in the male mouse terminated at the 12th month. This mouse had only a tiny focus of the neoplastic cells. Hepatoma was not found in any control mice or mice exposed to any levels of VC. There were a hepatic cell carcinoma, and a renal adenoma in one mouse each exposed to 50 or 1,000 ppm of VC, and skin keratoacanthomas in two mice exposed to 55 ppm of VDC.

RATS

General Conditions: A number of rats had rough hair coat, lost muscular tone and weight, and were lethargic after 7 months. Eight males and 13 females exposed to 1,000 ppm of VC died or were terminated during the 8th through the 12th months. Four males and 10 females exposed to 250 ppm died or were terminated during the same period. Two females exposed to

50 ppm died. No deaths occurred in the control group. One female rat exposed to 55 ppm of VDC was terminated during the 9th month.

Hemangiosarcoma: All the rats that died or were terminated ahead of schedule and a number of the rats that were terminated on schedule during the 9th through 12th months developed hemangiosarcomas. During the 9th month, hemangiosarcomas were found in the livers of two rats exposed to 250 ppm of VC and of four rats exposed to 1,000 ppm. By the end of the 12th month, hepatic hemangiosarcomas were found in the livers of 12 and 21 rats exposed to 250 or 1,000 ppm, respectively. Three of these rats exposed to 250 ppm and thirteen of these rats exposed to 1,000 ppm also had hemangiosarcomas in the lung (Plate 6). As shown in Table 4, hemangiosarcomas in the liver occurred more in the females than in the males at 1,000 ppm. Hemangiosarcomas also occurred in two rats (subcutaneous) exposed to 50 ppm of VC; two rats (omentum or mesentery) exposed to 250 ppm; one rat (omentum) exposed to 1,000 ppm; and two rats (mesenteric lymph node or subcutaneous) exposed to 55 ppm of VDC. Hemangiosarcomas were not found in the liver, lungs or any other organs of any control rats. There were also hemangiomas in the adrenal glands of two rats exposed to 1,000 ppm of VC.

Other Tumors: A few other tumors occasionally occurred in one or several rats. The tumors included: a small nodule of bronchiolo-alveolar adenoma; reticulo-endothelial cell carcinoma or hepatoma in the liver; ductular adenocarcinoma or fibroadenoma in the mammary gland of the female; malignant lymphoma in the spleen or other organs; adenoma in the kidney;

squamous carcinoma, keratoacanthoma or fibroma in the skin; adenocarcinoma in the sebaceous gland; and chromophobe cell adenoma in the pituitary. These occasional tumors were not related to VC or VDC.

DISCUSSION AND CONCLUSIONS

Exposure to 50, 250 or 1,000 ppm of VC, 6 hrs/ day and 5 days/wk, was highly carcinogenic in mice. Bronchiolo-alveolar adenomas, mammary gland tumors, and hemangiosarcomas developed in these mice. The incidence and severity of these tumors were related to the level of VC and to the length of exposure. A few mice exposed to VC also developed malignant lymphomas. The total incidence of various tumors would probably be considerably higher, if some of the mice had not been terminated at early intervals.

Bronchiolo-alveolar adenomas were observed starting the second month. Bronchiolo-alveolar adenoma, bronchiolar adenoma, or pulmonary adenomatosis, has been reported to occur spontaneously in aging mice, mostly over 1 year of age (Amaral-Mendes, 1969; Baillif and Jones, 1973; Deerberg et al., 1974). However, in the present study, large numbers of mice exposed to various levels of VC developed this tumor. In addition, the tumors were observed at a very early age; the incidence and severity were related to the VC level and the length of exposure. On the other hand, only a few small nodules of this tumor occurred at later times in one control and several mice treated with 55 ppm of VDC. Its significance in VC mice is questionable.

Hemanigosarcomas, primarily in the liver, were observed starting the 6th month especially the mice exposed to 250 or 1,000 ppm of VC. Hepatic hemangiosarcomas also occurred in three mice exposed to 55 ppm of VDC. The severity of these tumors and the mammary gland tumors in females exposed to VC probably contributed to the deaths of most of the mice.

Mammary gland tumors were observed only in female mice starting the 6th month and consisted of ductular adenocarcinoma, squamous and anaplastic carcinomas. The mammary gland tumor was the most complex. Observations on several stages and sizes of this tumor suggested that the tumor originated as ductular adenocarcinoma and then in a very early stage underwent an anaplastic and squamous cell metaplasia. The tumor at this stage appeared quite malignant and invasive. In many cases, there were metastases of the anaplastic and squamous carcinomas in the lung. In addition, the ductular or alveolar involvement seemed to be only minimal except in the early stages of some small tumors. This type of pattern is very different from the spontaneously occurring mammary gland tumors in mice.

The incidence and severity of the mammary gland tumors appeared to be greater in mice exposed to higher levels of VC and in those mice exposed for the longest periods of time. This may explain the higher incidence of mammary tumors in the group exposed to 50 ppm as compared to the group exposed to 250 ppm. All females exposed to 250 ppm died by the end of the 9th month, while many females exposed to 50 ppm survived beyond this time. This increased exposure time in the latter group may then account for the greater number of tumors.

The significance of hepatomas in three mice as related to the exposure of VC was considered questionable. These tumors have been reported to occur spontaneously in small numbers at this age (Andervont, 1950; Percy

and Jonas, 1971; Shen, 1974), even though they did not occur in any of the control animals. The other occasional tumors observed in mice were not related to exposure of VC or VDC.

Rats were more resistant to the carcinogenic effects of VC or VDC. Hepatic hemangiosarcomas were observed in rats exposed to 250 or 1,000 ppm of VC starting the 9th month. In contrast to the mice, many of the rats with hepatic hemangiosarcomas also developed hemangiosarcomas in the lung. VC did not cause any other tumors in the rat. Two rats exposed to 55 ppm of VDC developed hemangiosarcomas in the mesenteric lymph node or subcutaneous tissue; these tumors were probably caused by VDC. The rats were also found to be more resistant to the acute or other chronic effects of VC or VDC than mice as reported elsewhere (Lee et al., 1977).

TABLE 1

INCIDENCE OF BRONCHIOLO-ALVEOLAR ADENOMA IN MALE (M) AND
FEMALE (F) MICE EXPOSED TO VC OR VDC

Exposure Time (Months)	VC (ppm)								VDC (ppm)	
	0		50		250		1,000		55	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
1-3	0/12	0/12	1/12	0/12	2/12	0/12	3/12	3/12	0/12	0/12
4-6	0/4	0/4	2/5	0/5	1/4	4/7	6/6	4/5	1/4	0/4
7-9	1/6	0/4	2/7	4/14	5/11	8/15	13/15	19/19	2/6	0/4
10-12	0/4	0/16	3/5	0/3	2/2	0/0	0/0	0/0	3/13	0/15
Total	1/26	0/36	8/29	4/34	10/29	12/34	22/33	26/36	6/35	0/35

Entries indicate No. of incidence/No. of mice examined.

TABLE 2

INCIDENCE OF HEMANGIOSARCOMA IN MALE (M) AND
FEMALE (F) MICE EXPOSED TO VC OR VDC

Exposure Time (Months)	VC (ppm)								VDC (ppm)	
	0		50		250		1,000		55	
	M	F	M	F	M	F	M	F	M	F
<u>In Liver</u>										
6	0/16	0/16	0/17	0/17	0/16	2/19	2/18	3/17	0/16	0/16
7-9	0/6	0/4	1/7	0/14	5/11	14/15	11/15	15/19	1/6	0/4
10-12	0/4	0/16	2/5	0/3	2/2	0/0	0/0	0/0	1/13	1/15
Total	0/26	0/36	3/29	0/34	7 ^a /29	16 ^a /34	13 ^a /33	18/36	2/35	1/35
<u>In Other Organs</u>										
6	0/16	0/16	0/17	0/17	0/16	0/19	0/18	2/17	0/16	0/16
7-9	0/6	0/4	1/7	0/14	1/11	3/15	0/15	7/19	0/6	0/4
10-12	0/4	0/16	4/5	1/3	1/2	0/0	0/0	0/0	0/13	0/15
Total	0/26	0/36	5 ^a /29	1/34	2/29	3/34	0/33	9 ^{a,b} /36	0/35	0/35

Entries indicate No. of incidence/No. of mice examined.

a/ Significantly different from incidence in control group by Fisher exact probability test (Siegel, 1956), $p < 0.05$.

b/ Significantly different from incidence in opposite sex exposed to same concentration by Fisher exact probability test (Siegel, 1956), $p < 0.05$.

TABLE 3

INCIDENCE OF MAMMARY GLAND TUMORS AND METASTASIS
IN THE LUNG IN FEMALE MICE EXPOSED TO VC

<u>Exposure Time</u> <u>(Months)</u>	<u>VC Concentration (ppm)</u>			
	<u>0</u>	<u>50</u>	<u>250</u>	<u>1,000</u>
<u>Mammary Gland Tumors</u>				
6	0/16	0/17	1/19	3/17
7-9	0/4	7/14	2/15	10/19
10-12	0/16	2/3	0/0	0/0
	—	—	—	—
Total	0/36	9/34	3/34	13/36
<u>Metastasis in the Lung</u>				
6	0/16	0/17	1/19	3/17
7-9	0/4	2/14	1/15	5/19
10-12	0/16	0/3	0/0	0/0
	—	—	—	—
Total	0/36	2/34	2/34	8/36

Entries indicate No. of incidence/No. of mice examined.

TABLE 4

NUMBER OF MALE AND FEMALE RATS EXPOSED TO VC OR VDC
WHICH DEVELOPED HEMANGIOSARCOMA

<u>Sex</u>	<u>VC (ppm)</u>				<u>VDC (ppm)</u>
	<u>0</u>	<u>50</u>	<u>250</u>	<u>1,000</u>	<u>55</u>
<u>In the Liver</u>					
Male	0/35	0/36	2/36	6/34	0/36
Female	0/35	0/36	10 ^a /34	15 ^{a,b} /36	0/35
<u>In the Lungs</u>					
Male	0/35	0/36	0/36	4/34	0/36
Female	0/35	0/36	3/34	9 ^a /36	0/35
<u>In Other Organs</u>					
Male	0/35	1/36	2/36	0/34	2/36
Female	0/35	1/36	0/34	1/36	0/35

Entries indicated No. of incidence/No. of rats examined.

a/ Significantly different from incidence in control group by Fisher exact probability test (Siegel, 1956), $p < 0.05$.

b/ Significantly different from incidence in opposite sex exposed to same concentration by Fisher exact probability test (Siegel, 1956), $p < 0.05$.

LIST OF PLATES

<u>Plate</u>	<u>Title</u>
1	Bronchiolo-alveolar adenoma in mice exposed to VC. Top: Showing two small nodules, one with a focus of metastatic squamous cell carcinoma (A) from the mammary gland. H&E x 25. Bottom: Higher magnification, showing Papillary Proliferation. H&E x 160.
2	Hepatic hemangiosarcoma in mice exposed to VC, showing endothelial proliferation (A), invasion of hepatocytes (B) and hemorrhage (C). H&E x 100.
3	Mammary gland tumors in mice exposed to VC. Top: Ductular adenocarcinoma (A) and anaplastic carcinoma (B). H&E x 250. Bottom: Squamous cell carcinoma. H&E x 100.
4	Metastatic mammary gland carcinoma in the lung of mice exposed to VDC. Top: Anaplastic carcinoma, mitotic figures (A). H&E x 250. Bottom: Squamous cell carcinoma, keratinization (A), stratified squamous epithelium (B). H&E x 250.
5	Malignant lymphoma in the spleen of mice exposed to VC, showing proliferation of lymphocytes and loss of splenic architecture. H&E x 160.
6	Hemangiosarcoma in rats exposed to VC. Top: Liver, showing endothelial proliferation (A), invasion of hepatocytes (B) and hemorrhage (C). H&E x 100. Bottom: Lung, showing endothelial proliferation (A), invasion of alveoli (B) and hemorrhage (C). H&E x 160.

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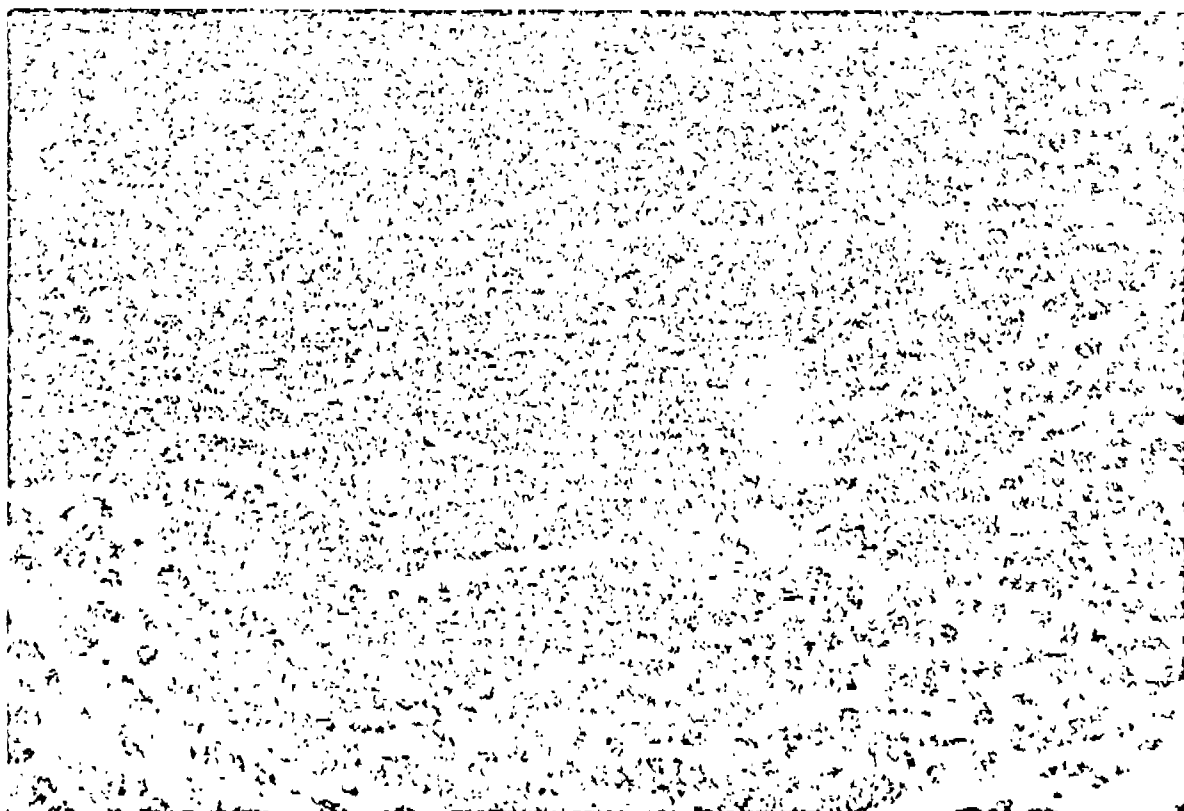
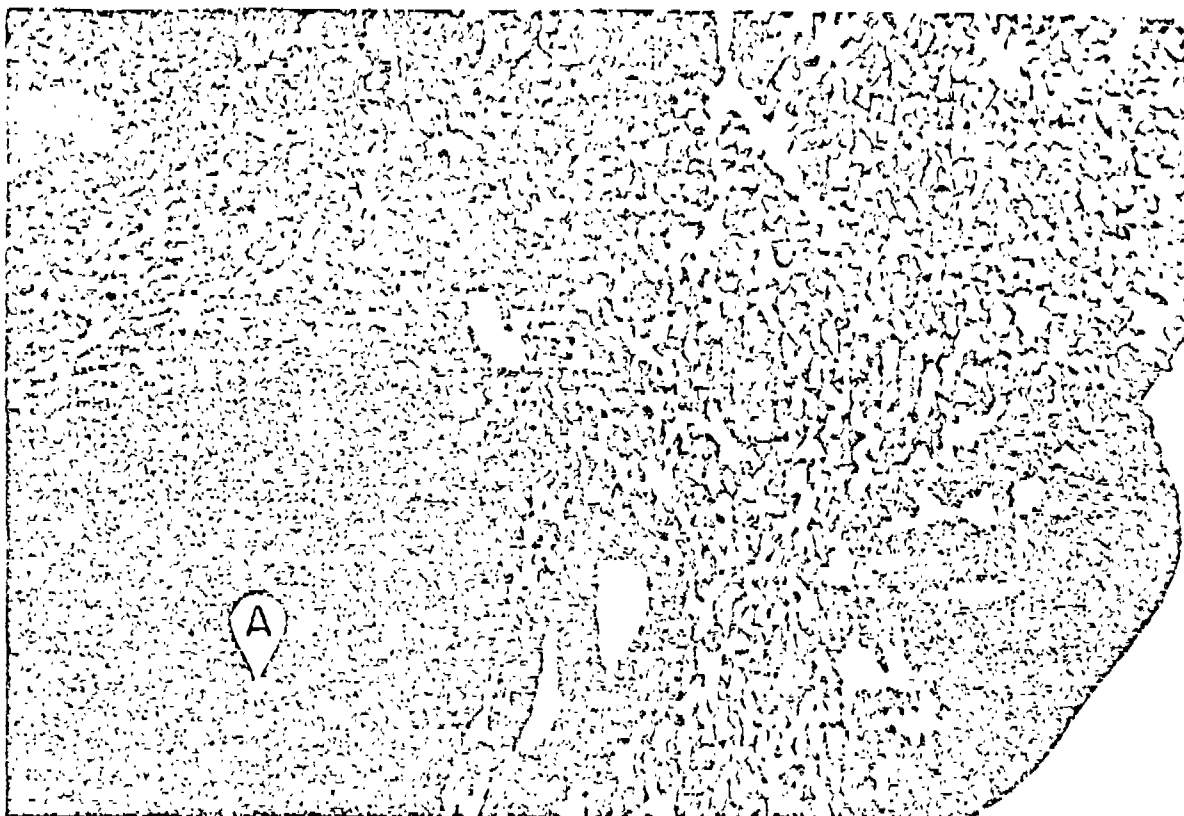


PLATE I

CMA 010918

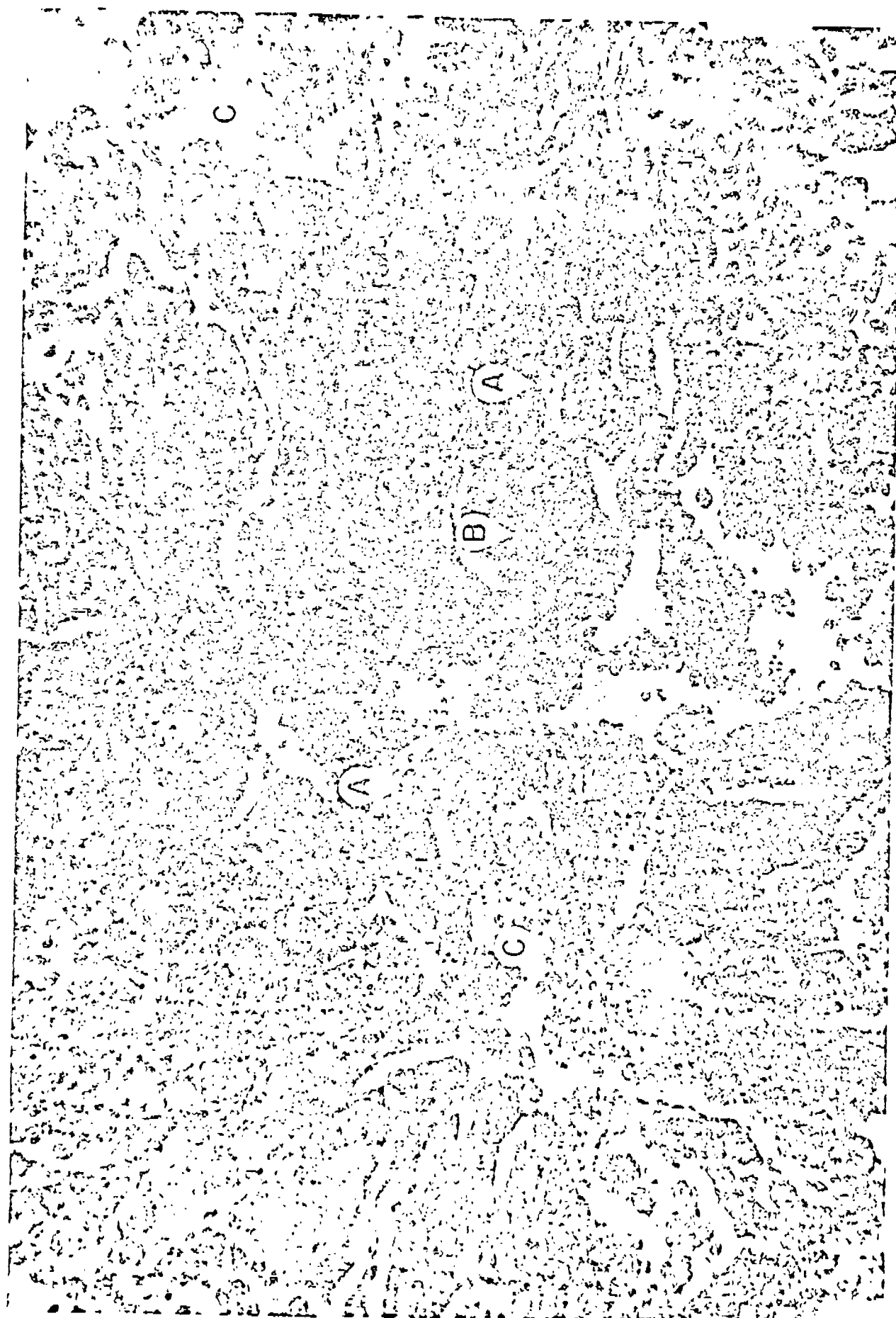


PLATE 2

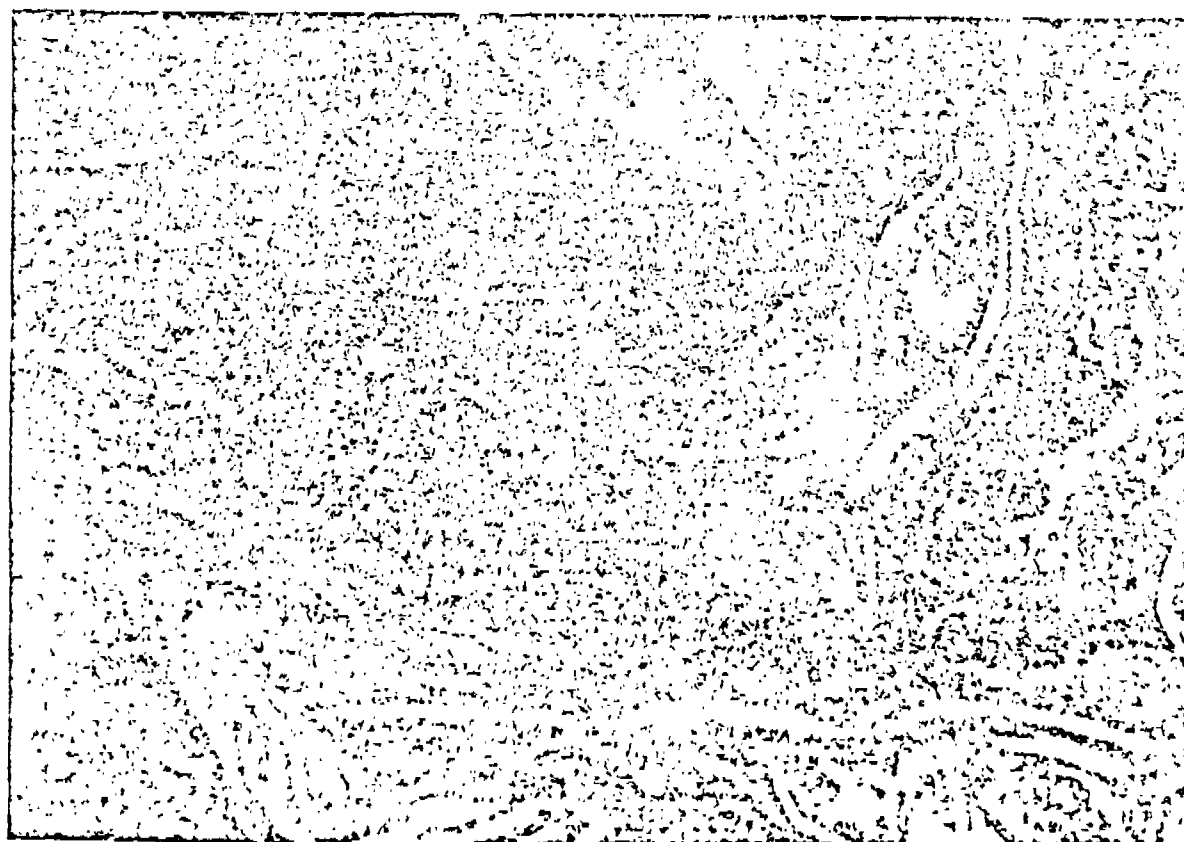
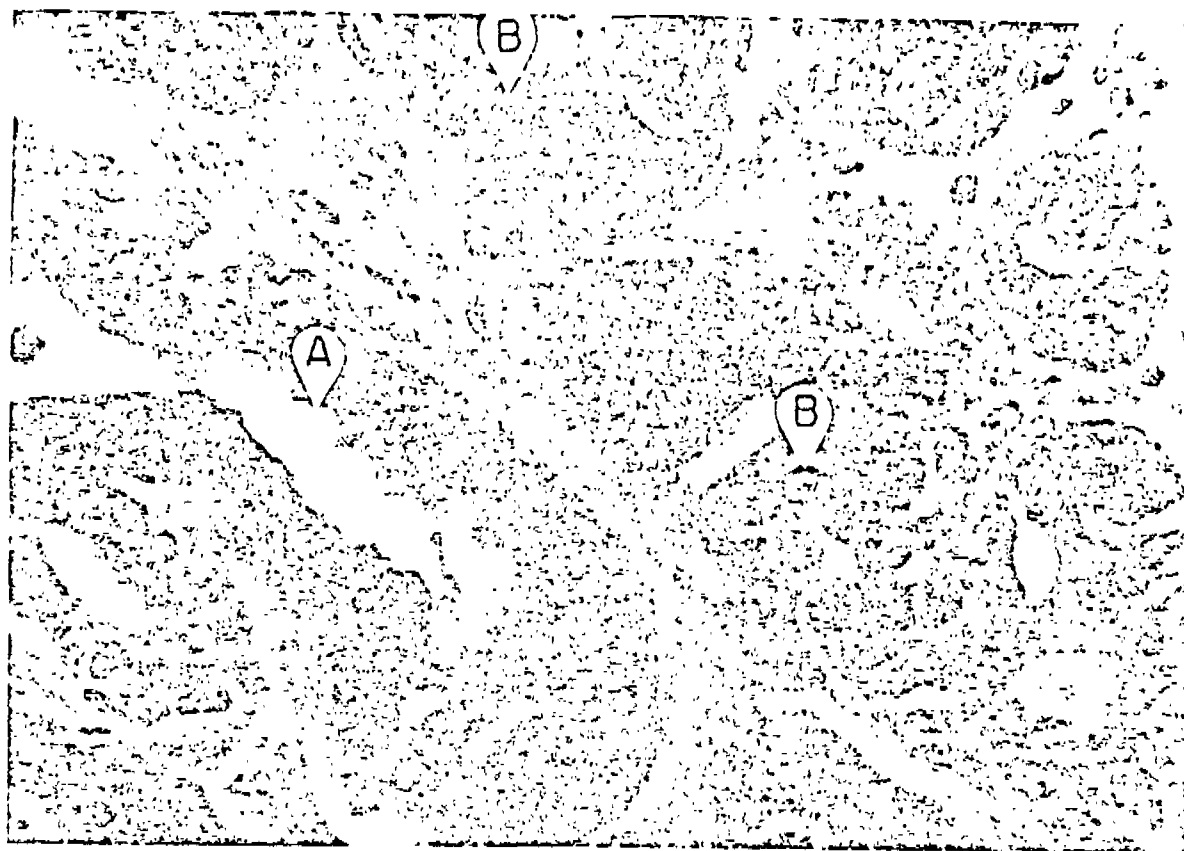


PLATE 3



PLATE 4

CMA 10,921

24 010071

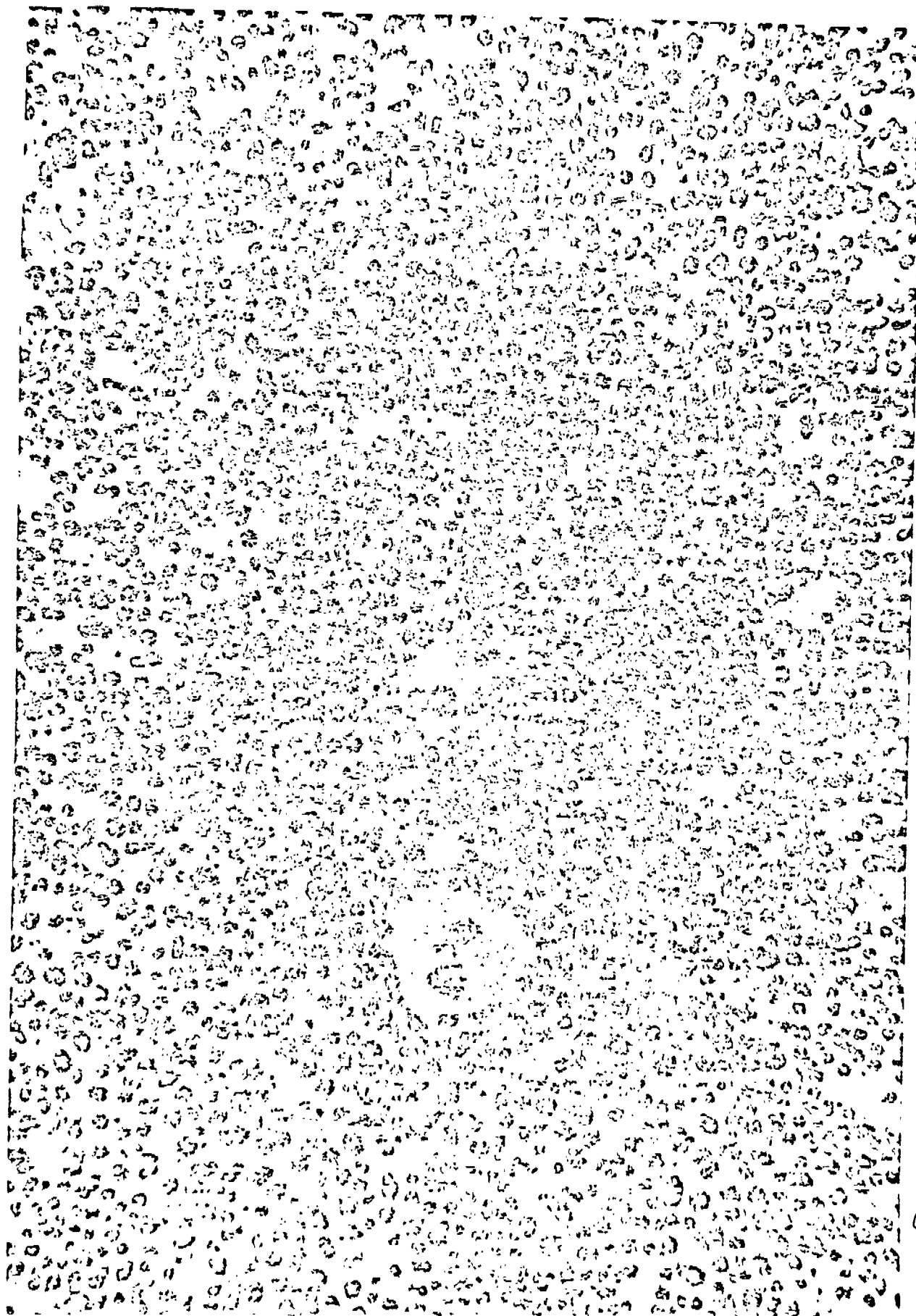
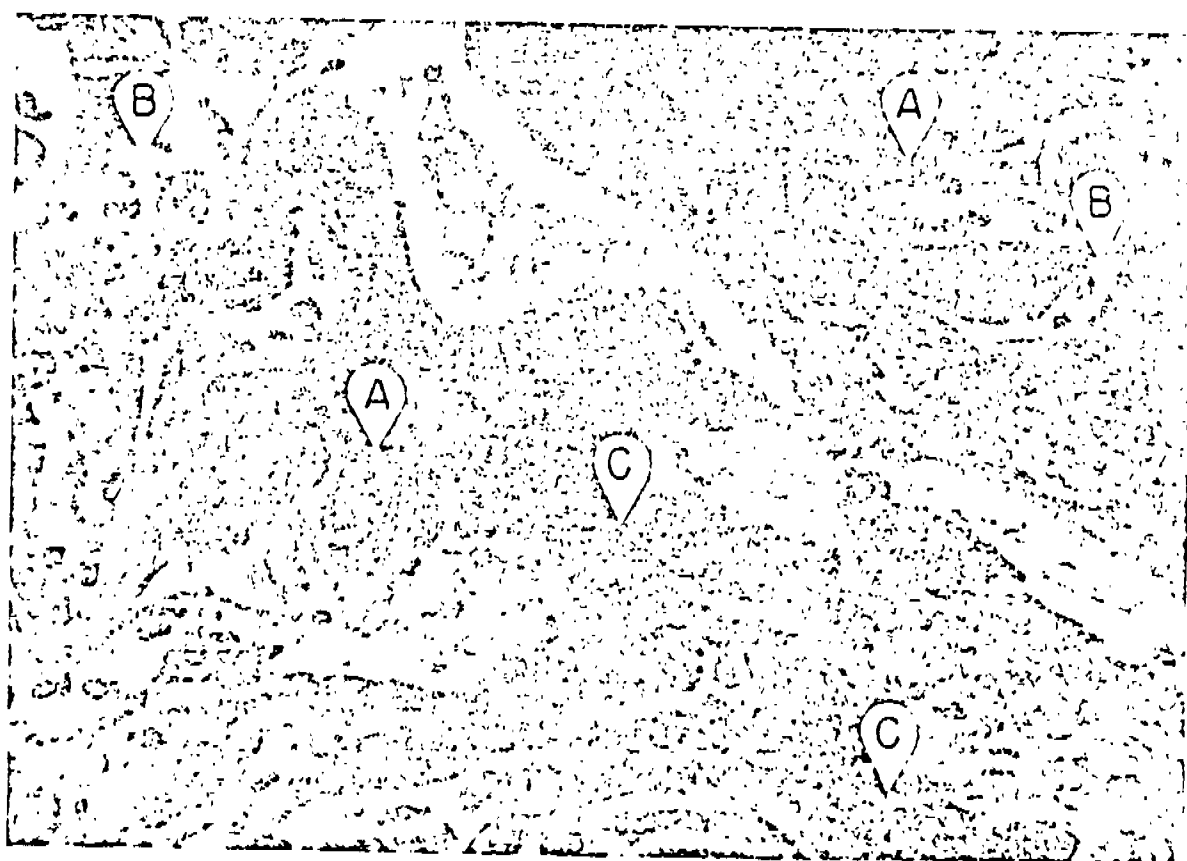
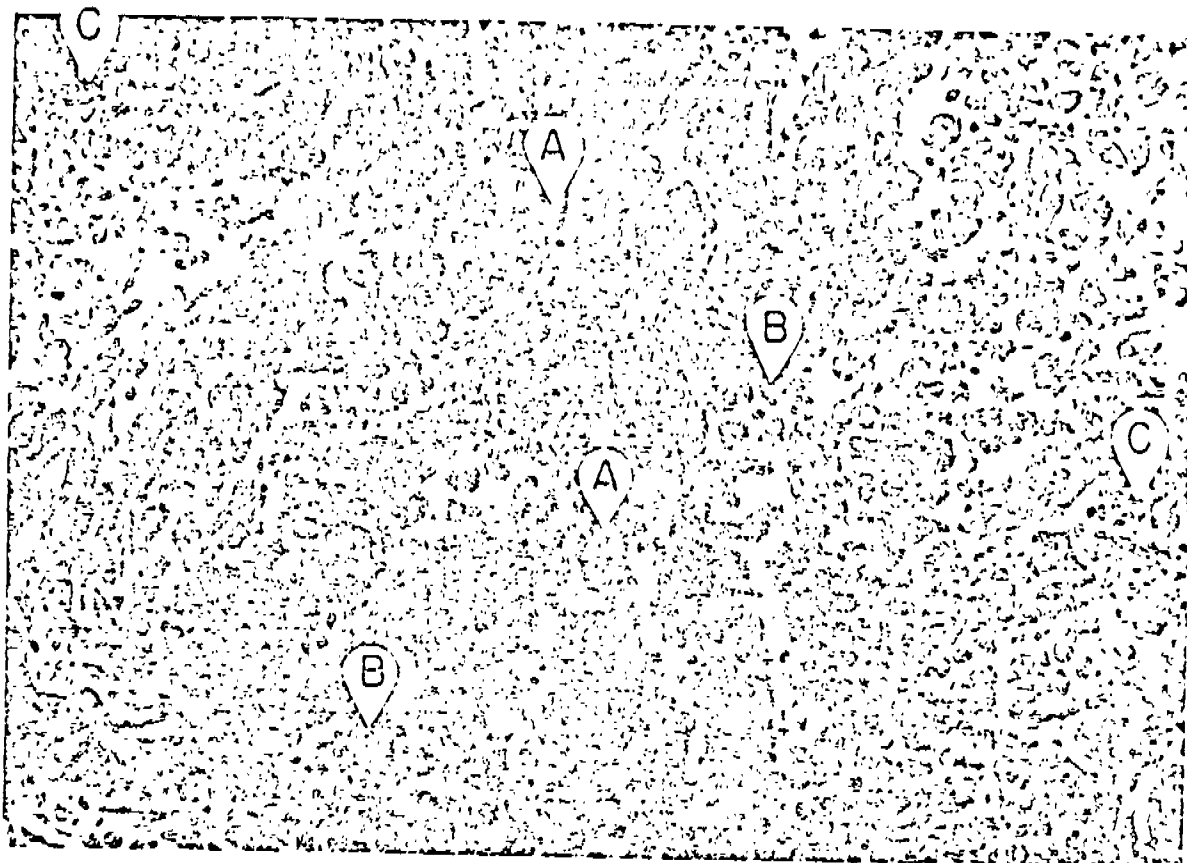


PLATE 5

CMA 10,922



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10,923