



OSPEDALI DI BOLOGNA
Ente Ospedaliero Regionale

OSPEDALE POLICLINICO S. ORSOLA

ISTITUTO DI ONCOLOGIA «FELICE ADDARIO»

Direttore: Prof. Cesare Maltoni

Viale Ercolani 4/2 - 40138 BOLOGNA
Tel. 393824

File 17

Bologna, March, 16, 1974

Prot. N.

Mrs. JEANNE FERRONE
OSHA
Room 240
1726 M Street, N. W.
U. S. Department of Labor
WASHINGTON, D.C., 20210
U.S.A.

Dear Mrs. Ferrone,

herewith enclosed you will find the text of my testimony to OSHA, of February 15, 1974, with related tables and figures, as it was requested to me.

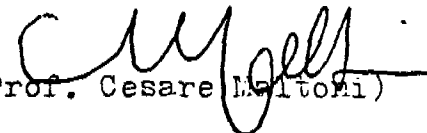
I hope that everything is as you expected.

When published on your records, I would like very much to have a few copies.

My experiments are going on and progressing in the most interesting way.

Thanking you for your collaboration, my best regards and wishes,

Yours sincerely,


(Prof. Cesare Maltoni)

CM/cn

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Tel. 393824

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Istituto di Oncologia "F. Addarii" and Centro Tumori, Bologna, Italy.

Cesare Maltoni, Giuseppe Lefemine and Luciano Gualano.

PRELIMINARY REPORT ON THE CARCINOGENICITY BIO-ASSAYS OF VINYL CHLORIDE.

(This research has been supported by the European Cooperative Group (ECG) which includes Montedison (Italy), ICI (U.K.), Solvay (Belgium), Rhone-Pe
gil (France)).

The project of investigating the oncogenic potential of Vinyl Chloride (VC) followed the preliminary results of the pioneering work of Professor Viola, presented at the X International Cancer Congress (which took place in Houston in 1970) and was then extensively published in "Cancer Research" (1971).

Professor Viola's results indicated that the exposure to 30,000 ppm of VC, four hours a day, five times weekly, for 10 months, produced tumours in rats. These tumours were interpreted by Professor Viola as arising in skin, lungs and bones.

Immediately after the report in Houston we got in touch with Professor Viola, who kindly put at our disposal the manuscript of his extensive report still being printed, and several slides of the tumours.

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On the basis of Professor Viola's results and material, we reached the following conclusions:

- 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 were arising in the Zymbal glands, which in rats are responsive to a large spectre of carcinogens (2-ace_tyl-amino-fluorene, benzidine, polycyclic hydrocarbons, aminostilbenes, ethyl-carbamate, etc.);
- 4) the tumours described as lung tumours were most likely metastases from Zymbal glands carcinomas. The pulmonary neoplastic deposits were in fact morphologically similar to the Zymbal glands carcinomas, and all were observed in animals bearing Zymbal glands tumours.

The need, therefore, emerged for an extensive investigation to further clarify the type and the degree of the carcinogenic effect of VC, with particular emphasis on experimental factors related to exposure, such as route, concentration, length, continuity or intermittance, etc., which could give more direct indications about the risk of occupational conditions.

For these purposes, and since in our country the Institute of Oncology of Bologna is particularly orientated towards studies on cancer prevention and control, we were contacted by Prof. Bartolini, Head of the Health Service of Montedison, who guaranteed the backing of his Company for the experimental

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project on the biological effects of VC. Montedison was soon joined by ICI, Solvay and Rhone-Pegil.

To start the operative phase of the research we needed, first of all, to prepare proper conditions for atmospheric exposure. The studying and building of an apparatus for programmed and controlled exposure took us several months. Such an apparatus makes it possible to deliver concentrations varying from 30,000 ppm to 50 ppm, and to treat simultaneously nearly 1,200 experimental rodents. Basically it is built of inoxidable steel and glass (figures 1 and 2).

VC has been supplied by Montedison. Each stock has been analyzed before the use in the chemical research laboratory of Montedison.

The experiments are mainly performed on Sprague-Dawley rats; Wistar rats, Swiss mice and hamsters have also been used. All the animals, except for hamsters, have been bred in our Institute for years and, whatever their use, they are all examined at death by complete autopsy, which means that we know their current pathology quite well.

13 experiments have been started in sequence. Some of them were programmed at the beginning, for some others the need appeared on the basis of the first experimental results. The plan of the experiments and the up-to-date situation is shown in the following table 1.

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Experiment 1 : studies the effect of the atmospheric exposure to 10,000, 6,000, 2,500, 500, 250, 50 ppm of VC, 4 hours daily, 5 days weekly, for 12 months. Two groups of animals were added as control: one untreated, as for all the following experiments, and one treated with Vinyl Acetate (VA) at 2,500 ppm, under the same conditions. This dose of VA appeared to be the maximum possible dose for a chronic exposure.

Experiment 2 : was performed to investigate in a larger number of animals the effect of doses among 250 and 50, that is 200, 150 and 100, under the same conditions as in experiment 1. It started after it was clear that 250 ppm was still showing oncogenic effects.

Experiment 3 : was planned to study the effects of a shorter period of exposure, keeping all the other conditions of experiment 1.

Experiment 4 : studies the effect of the same type of exposure as in experiment 1, in another species, that is mice. The treatment lasted 7 months in consideration of the higher mortality and shorter life span of the mice of our line.

Experiment 5 : was undertaken as a pilot investigation on the possible effects of the atmospheric exposure during pregnancy, on offsprings.

Experiment 6 : we wanted to reproduce the same conditions of Professor Viola's experiments.

Experiment 7 : was planned to study the effects of the same type of exposure as in experiment 1, in another strain of rats, that is Wistar.

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Experiment 8 : studies the effects of the same exposure as in experiment 1 in a third species, that is hamsters, for the same period as in experiment 4.

Experiment 9 : was planned to further assess whether or not inhalation of VC had any effect at a dose level of 50 ppm.

Experiment 10: studies whether a high, but short and/or intermittent atmospheric exposure has any effect.

Experiment 11: was performed to evaluate the possible effects of VC by ingestion. The doses have been chosen on the basis of early data on the release of VC by food containers of PVC, and following the indications of the EEC.

Experiment 12: studies the third general route of exposure.

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

All the animals were kept under observation until spontaneous death. A complete autopsy was made on each animal, and histological examination performed on 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. All the animals exposed to the highest doses (30,000 and 10,000 ppm) with or without tumours, were examined radiologically, during treatment

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and/or at death. Moreover radiological examinations were made on animals bearing tumours, though exposed to the lower doses.

The preliminary results and the other data on the up-to-date situation of the experiments 1, 3, 6 and 5 are given on the following tables 2-5. As far as the other experiments are concerned we still have to wait for the results.

The current macroscopic and microscopic pictures of the induced tumours are shown in figures 3-52.

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

- 1) VC is oncogenic under our experimental conditions: it induces, in rats, carcinomas of Zymbal glands, nephroblastomas and angiosarcomas in the liver and in other sites.
- 2) A direct relationship exists between the dose and the length of treatment, and the neoplastic response.
- 3) Zymbal glands carcinomas and nephroblastomas may be bilateral.
- 4) Liver angiosarcomas are often polycentric.
- 5) Endothelial hyperplasia, associated or not with cellular atypias, is often observed in various organs and tissues in treated animals, with or without angiosarcomas. Therefore the effect of VC on endothelia should be considered systemic.

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Tel. 393824

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6) The onset of two ossifying angiosarcomas suggests a new orientation in the pathogenetic interpretation of acrosteolysis in workers exposed to VC.

7) Up to the present moment no acrosteolytic lesions have been observed on our treated animals.

Zymbal glands carcinomas, nephroblastomas and liver angiosarcomas have never been observed as occurring spontaneously in our breed of Sprague-Dawley rats.

Only three cases of spontaneously occurring Zymbal glands carcinomas have been recorded in rats (Sprague-Dawley) (Tannenbaum et al., 1962). To our knowledge, no spontaneous nephroblastomas and liver angiosarcomas of rats have been reported in literature.

As far as we know kidney nephroblastomas have never been reported as being experimentally induced.

As far as angiosarcomas are concerned, and in particular the hepatic ones, they have never been experimentally induced in rats. In mice, extra-hepatic angiosarcomas have been induced by o-aminoazotoluene (Andervont et al., 1942; Andervont, 1950) and by p-dimethylaminobenzene-1-azo-2-naphtalene (Mulay and Saxén, 1953); some authors claim they have observed liver angiomas in this species, following treatment with urethan. In the rabbit, angiosarcomas have been produced by thorotrast (Zeithofer and Speiser, 1954).

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In man, angiosarcomas are quite rare. 117 accurately documented cases were collected up to 1958 (Landells, 1958), of which only 21 arising in liver.

Two human examples of induction of angiosarcomas have been reported: one deals with a case of a liver angiosarcoma following the insertion of a radium needle (Ross, 1932), the other deals with cases of liver angiosarcomas following administration of thorotrast (MacMahon et al., 1947; Lüdin, 1953).

The results of our investigation have been periodically transmitted to the Members of the European Cooperative Group. When, more than one year ago, it became definitely clear that VC was able to induce angiosarcomas, nephroblastomas and other malignancies, our results were also communicated to the major American Manufacturers of VC and PVC, to orient clinical observations and epidemiological investigations.

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Tel. 393824

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NO. OF THE EXPERIMENTS	TREATMENT			ANIMALS							LENGTH OF THE EXPERIMENTS AT PRESENT (weeks)
	Route	Doses of VC	Length	Species	Strain	Age (weeks)	No.				
							Q	Q ₁	Total	Per group	
BT1	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm. Untreated controls Treated controls: VA 2,500 ppm.	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Sprague-Dawley	13	268	309	577	64-96	127
BT2	Inhalation	200, 150, 100 ppm. Untreated controls	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Sprague-Dawley	13	280	265	545	65-120	31
BT3	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm. Untreated controls	4 hrs. daily, 5 days weekly, 17 weeks	Rat	Sprague-Dawley	21	262	288	550	60-190	56
BT4	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm. Untreated controls	4 hrs. daily, 5 days weekly, 30 weeks	Mouse	Swiss	11	250	260	510	60-150	31
BT5	Transplacental	10,000, 6,000 ppm.	4 hrs. daily, 7 days (from 12th to 18th day of pregnancy)	Rat	Sprague-Dawley	19 Breeders 12 days Embryos	110	36	146	30-54	65
BT6	Inhalation	30,000 ppm.	4 hrs. daily, 5 days weekly, 41 weeks	Rat	Sprague-Dawley	17	30	30	60	60	31
BT7	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm. Untreated controls	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Wistar	11	-	220	220	30-40	31
BT8	Inhalation	10,000, 6,000, 2,500, 500, 250, 50 ppm. Untreated controls	4 hrs. daily, 5 days weekly, 30 weeks	Hamster	Golden	11	-	268	268	32-70	18
BT9	Inhalation	50 ppm. Untreated controls	4 hrs. daily, 5 days weekly, 52 weeks	Rat	Sprague-Dawley	11	200	200	400	100 (c) 300 (t)	3
BT10	Inhalation	10,000, 6,000 ppm. Untreated controls	4 hrs. daily, 5 days weekly, 5 weeks; 4 hrs. daily, 1 day weekly, 25 weeks; 1 hr. daily, 4 days weekly, 25 weeks	Rat	Sprague-Dawley	11	420	420	840	120	3
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	3
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	3
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	3

TABLE 2
EXPERIMENT BT1: RESULTS AFTER WEEKS

GROUPS AND TREATMENT	ANIMALS (SPRAGUE-DAWLEY RATS)		ANIMALS WITH TUMOURS					Tot No
	Total	Survivors	Zymbal glands carcinomas (a)	Nephrobla- stomas (b)	Angiosarcomas		Other type and/or site	
			No.	No.	Liver (c)	Other sites	No.	
I VA 2,500 ppm.	96	-	-	-	-	-	-	-
II VC 10,000 ppm.	69	-	13	3	6	-	5 (h)	27
III VC 6,000 ppm.	72	-	5	3	11	1 (d)	1 (i)	21
IV VC 2,500 ppm.	74	-	2	6	9	3 (e)	1 (l)	21
V VC 500 ppm.	67	-	3	3	7	2 (f)	1 (m)	16
VI VC 250 ppm.	67	1	-	5	2	2 (g)	2 (n)	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) Angiosarcomas in subcutaneous fibrosing angioma.
- e) 2 intrabdominal angiosarcomas (1 next to spleen and 1 next to ovary); 1 ossifying angiosarcoma of neck.
- f) 1 pulmonary angiosarcoma; 1 angiosarcoma of uterus.
- g) 1 intrabdominal angiosarcoma (next to spleen); 1 intrathoracic ossifying angiosarcoma.
- h) 2 Zymbal glands adenomas; 1 neurilemmoma of the ear; 1 mammary carcinoma; 1 cystadenocarcinoma of ovary.
- i) Sebaceous gland carcinoma of skin.
- l) Zymbal glands adenoma.
- m) Minimal deviation hepatoma.
- n) 1 Zymbal glands adenoma; 1 salivary glands carcinoma.

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TABLE 3

EXPERIMENT BT3: RESULTS AFTER 56 WEEKS (1)

GROUPS AND TREATMENT	ANIMALS (SPRAGUE-DAWLEY RATS)		ANIMALS WITH TUMOURS					
	Total	Survivors	Zymbal glands carcinomas	Nephrobla- stomas	Angiosarcomas		Other type and/or site	Total
			No.	No.	Liver	Other sites		
I VC 10,000 ppm.	60	36	3 (11)	- (1)	- (1)	-	- (4)	3 (7)
II VC 6,000 ppm.	60	48	1 (3)	- (1)	- (3)	- (1)	-	1 (8)
III VC 2,500 ppm.	60	54	- (2)	- (1)	- (1)	-	- (1)	- (5)
IV VC 500 ppm.	60	56	- (1)	-	- (1)	-	- (1)	- (3)
V VC 250 ppm.	60	44	-	-	-	-	-	-
VI VC 50 ppm.	60	50	-	-	-	-	-	-
VII No Treatment	190	183	-	-	-	-	-	-
TOTAL	550	471	4 (17)	- (3)	- (6)	- (1)	- (6)	4 (35)

(1) Between brackets are recorded the tumours found in experiment BT1 after 56 weeks.

TABLE 4

EXPERIMENT BT6: RESULTS AFTER 31 WEEKS

GROUPS AND TREATMENT	ANIMALS (SPRAGUE-DAWLEY RATS)			ANIMALS WITH TUMOURS				
	Total	Survivors	Zymbal glands carcinomas	Nephrobla- stomas	Angiosarcomas		Other type and/or site	Total
					Liver	Other sites		
			No.	No.	No.	No.	No.	No.
I VC 30,000 ppm.	60	60	2	-	-	-	-	-

TABLE 5

EXPERIMENT BT5: RESULTS AFTER 65 WEEKS

GROUPS AND TREATMENT	ANIMALS (SPRAGUE-DAWLEY RATS)		ANIMALS WITH TUMOURS					Total No.
	Total	Survivors	Zymbal glands carcinomas No.	Nephrobla- stomas No.	Angiosarcomas		Other type and/or site No.	
					Liver No.	Other sites (1) No.		
I VC 10,000 ppm. Breeders	30	28	-	-	-	-	-	-
II VC 6,000 ppm. Breeders	30	28	-	-	-	-	-	-
III VC 10,000 ppm. Offsprings	34	30	-	-	-	1	-	1
IV VC 6,000 ppm. Offsprings	32	30	-	-	-	1	-	1
TOTAL	126	116	-	-	-	2	-	2

(1) In subcutaneous tissue.



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Direttore: Prof. Cesare Maltoni

Viale Ercolelli 4/2 - 40138 BOLOGNA
Tel. 393824

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Figure legends

- Fig. 1 The inhalation chamber.
- Fig. 2 The laboratory unit for inhalation.
- Fig. 3 Rat with Zymbal gland carcinoma.
- Fig. 4 Rat with Zymbal gland carcinoma.
- Fig. 5 Rat with bilobated Zymbal gland carcinoma.
- Fig. 6 Rat with hemorrhagic Zymbal gland carcinoma.
- Fig. 7 Normal Zymbal gland, in rat. Hematoxilin and Eosin stain (H.-E.), x 46.
- Fig. 8 Zymbal gland in an old rat. H.-E., x 46.
- Fig. 9 Zymbal gland carcinoma with squamous pattern, in rat. H.-E., x 185.
- Fig. 10 Zymbal gland carcinoma with solid pattern, in rat. H.-E., x 185.
- Fig. 11 Zymbal gland carcinoma with anaplastic pattern, in rat. H.-E., x 185.
- Fig. 12 Zymbal gland carcinoma with polimorphic pattern, in rat. H.-E., x 470.
- Fig. 13 Zymbal gland carcinoma with glandular pattern, in rat. H.-E., x 185.
- Fig. 14 Zymbal gland carcinoma with glandular pattern and abundant stroma, in rat. H.-E., x 185.
- Fig. 15 Pulmonary metastasis from Zymbal gland carcinoma, in rat. H.-E., x 46.
- Fig. 16 Pulmonary metastasis from Zymbal gland carcinoma, in rat. H.-E., x 185.
- Fig. 17 Pulmonary metastasis from Zymbal gland carcinoma with abundant stroma, in rat. H.-E., x 185.
- Fig. 18 Rat with nephroblastoma.
- Fig. 19 Rat with nephroblastoma.
- Fig. 20 Rat with nephroblastoma metastasising to liver.

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Direttore: Prof. Cesare Maltoni

Viale Ercolani 4/2 - 40138 BOLOGNA
Tel. 393824

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- Fig. 21 Nephroblastoma with characteristic pattern, in rat. H.-E., x 185.
- Fig. 22 Nephroblastoma, in rat: nephrogenic blastema differentiating in glomerulus. H.-E., x 470.
- Fig. 23 Liver metastasis from nephroblastoma, in rat. H.-E., x 185.
- Fig. 24 Splenic metastasis from nephroblastoma, in rat. H.-E., x 470;
- Fig. 25 Pulmonary metastasis from nephroblastoma, in rat. H.-E., x 185.
- Fig. 26 Pulmonary metastasis from nephroblastoma, in rat, at a higher magnification. H.-E., x 470.
- Fig. 27 Rat with liver angiosarcoma metastasising to lung.
- Fig. 28 Rat with liver angiosarcoma.
- Fig. 29 Rat with liver angiosarcoma.
- Fig. 30 Liver angiosarcoma with characteristic pattern, in rat. H.-E., x 185.
- Fig. 31 Liver angiosarcoma with characteristic pattern, in rat. H.-E., x 185.
- Fig. 32 Liver angiosarcoma, in rat. H.-E., x 185.
- Fig. 33 Pulmonary metastasis from liver angiosarcoma, in rat. H.-E., x 185.
- Fig. 34 Pulmonary metastasis from liver angiosarcoma, in rat. H.-E., x 185.
- Fig. 35 Rat with liver angiosarcoma and nephroblastoma.
- Fig. 36 Intrabdominal angiosarcoma near to spleen, in rat. H.-E., x 185.
- Fig. 37 Intrabdominal angiosarcoma near to spleen, in rat. H.-E., x 185.
- Fig. 38 Intrabdominal angiosarcoma near to spleen, in rat. H.-E., x 185.
- Fig. 39 Rat with intrabdominal angiosarcoma near to ovary.
- Fig. 40 Intrabdominal angiosarcoma near to ovary, in rat. H.-E., x 185.
- Fig. 41 Rat with angiosarcoma of uterus.
- Fig. 42 Angiosarcoma of uterus, in rat. H.-E., x 470.



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- Fig. 43 Angiosarcoma of lung, in rat. H.-E., x 470.
- Fig. 44 Rat with laterocervical ossifying angiosarcoma.
- Fig. 45 Non ossifying area of laterocervical ossifying angiosarcoma, in rat. H.-E., x 470.
- Fig. 46 Laterocervical ossifying angiosarcoma, in rat. H.-E., x 185.
- Fig. 47 Pulmonary metastasis from laterocervical ossifying angiosarcoma, in rat. H.-E., x 46.
- Fig. 48 Rat with subcutaneous angiosarcoma.
- Fig. 49 Angiosarcoma of subcutaneous tissue, in rat (offspring born from breeders exposed to VC). H.-E., x 185.
- Fig. 50 Cutaneous sebaceous carcinoma, in rat. H.-E., x 185.
- Fig. 51 Rat with salivary gland adenocarcinoma.
- Fig. 52 Adenocarcinoma of salivary gland, in rat. H.-E., x 185.

g. 1

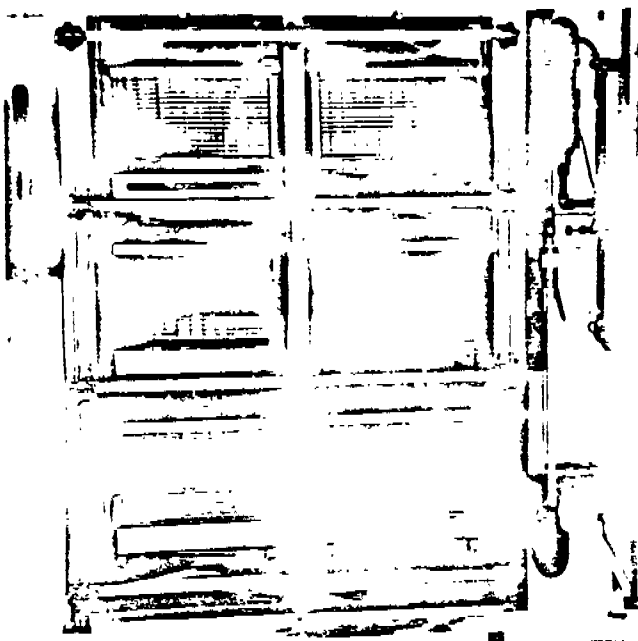


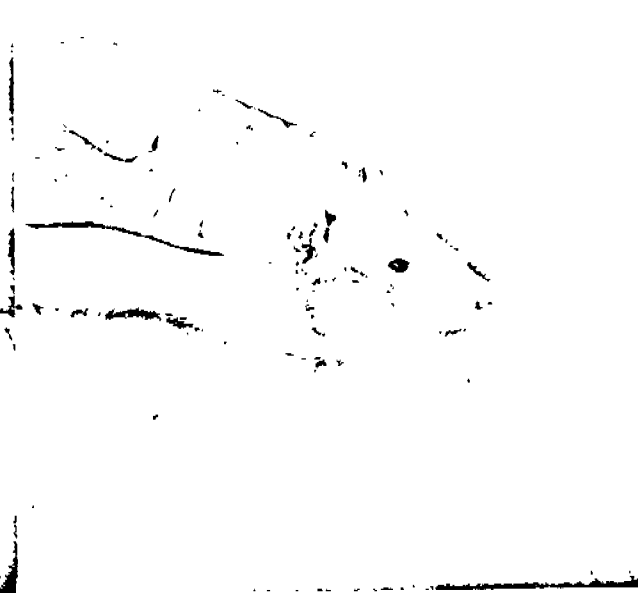
Fig. 2



g. 3



Fig. 4



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g. 5

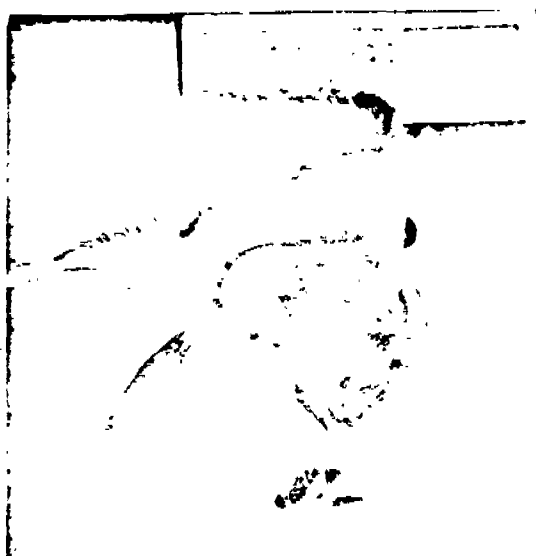
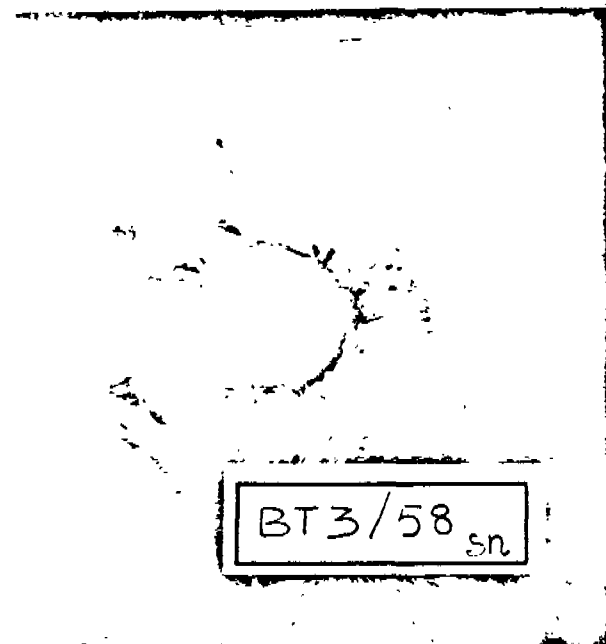


Fig. 6



g. 7



Fig. 8

fig. 9

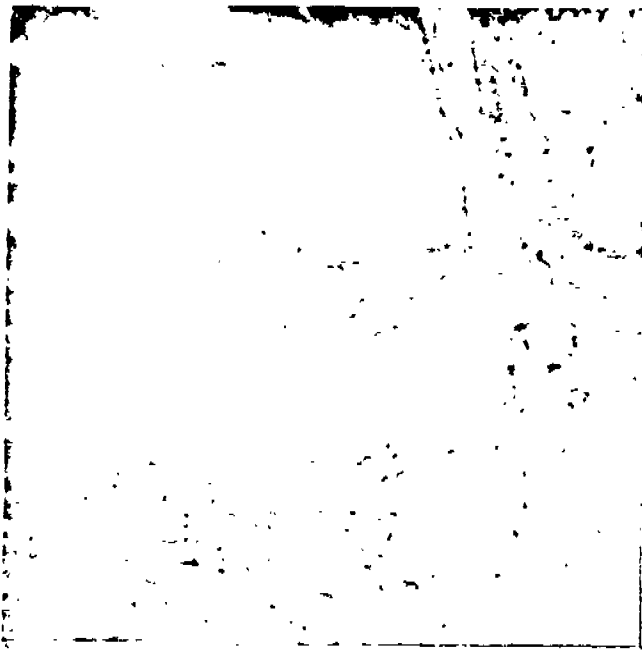


Fig. 10



g. 11



Fig. 12



g. 13

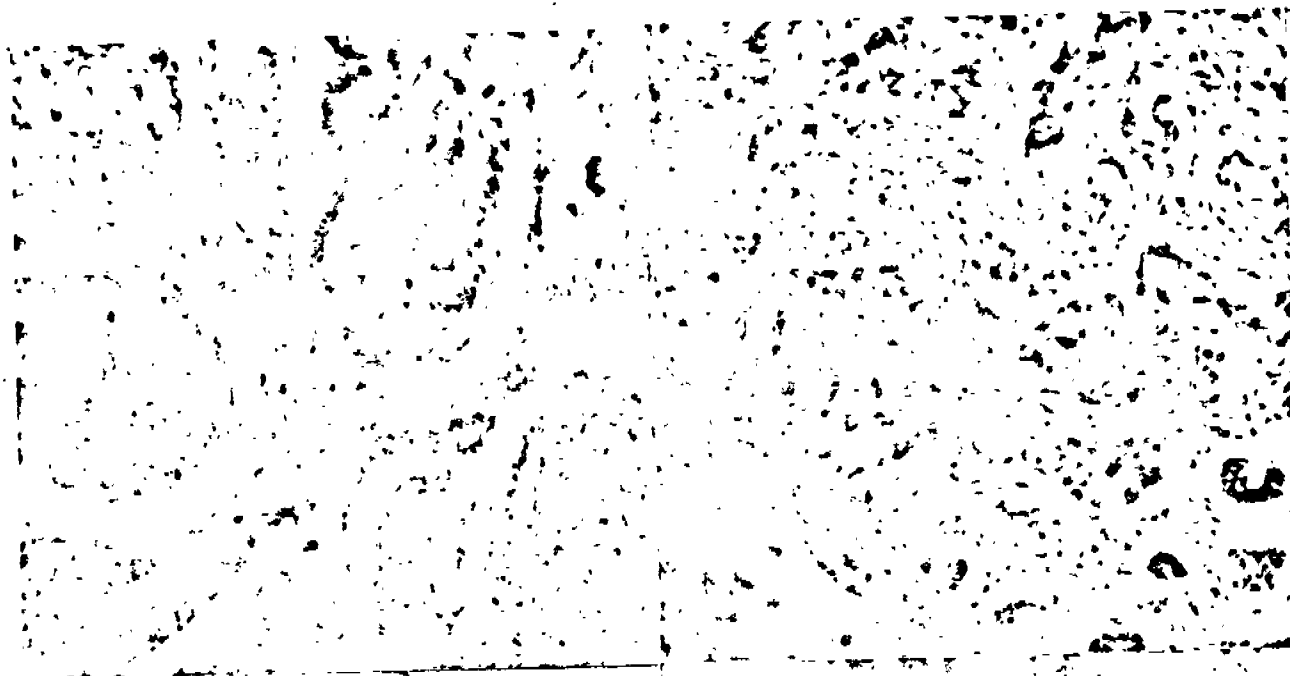


Fig. 14

ig. 15



Fig. 16

Fig. 17

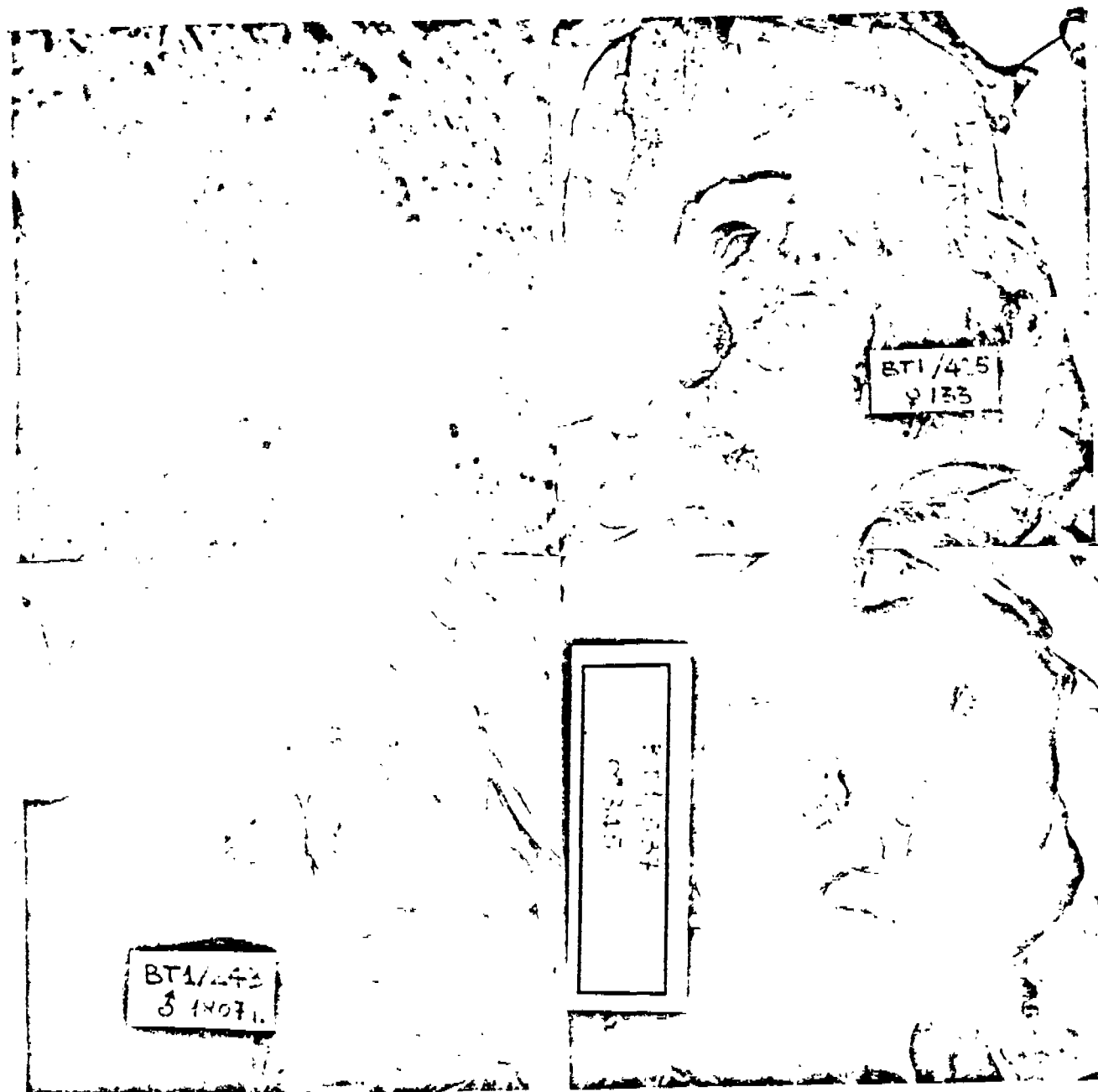
Fig. 18

18

Fig. 19

Fig. 20

2c



g. 21

Fig. 22

ig. 23

Fig. 2.

ig. 25

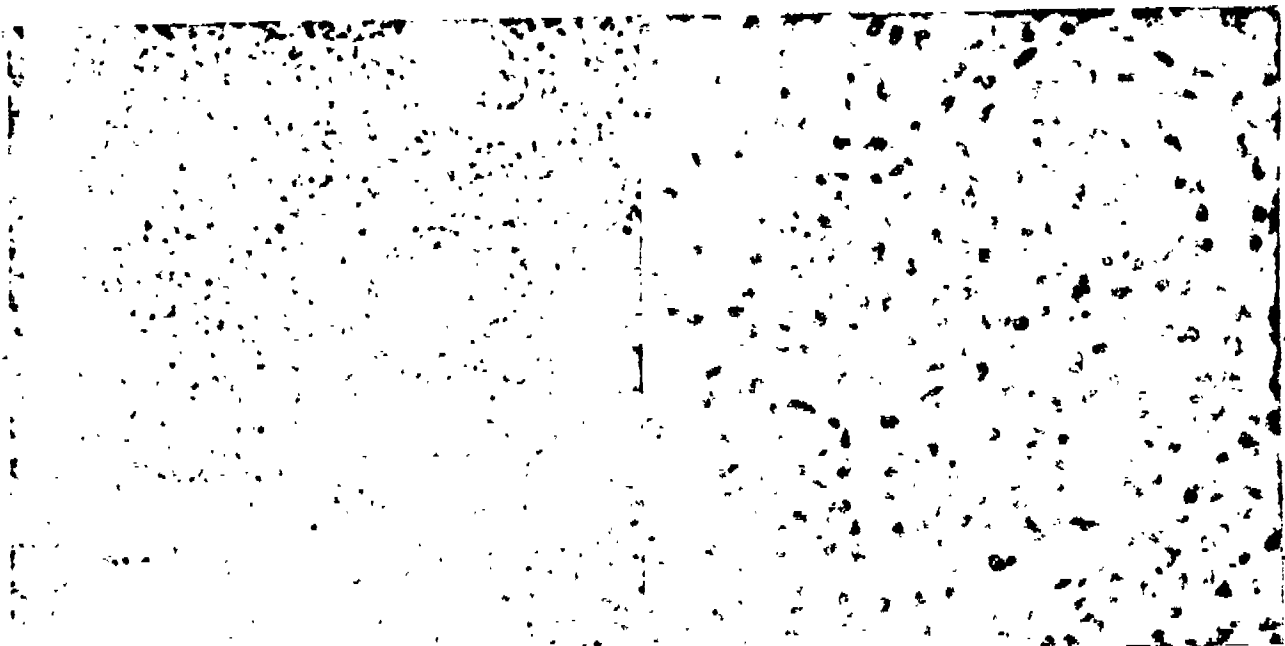


Fig. 26

ig. 27

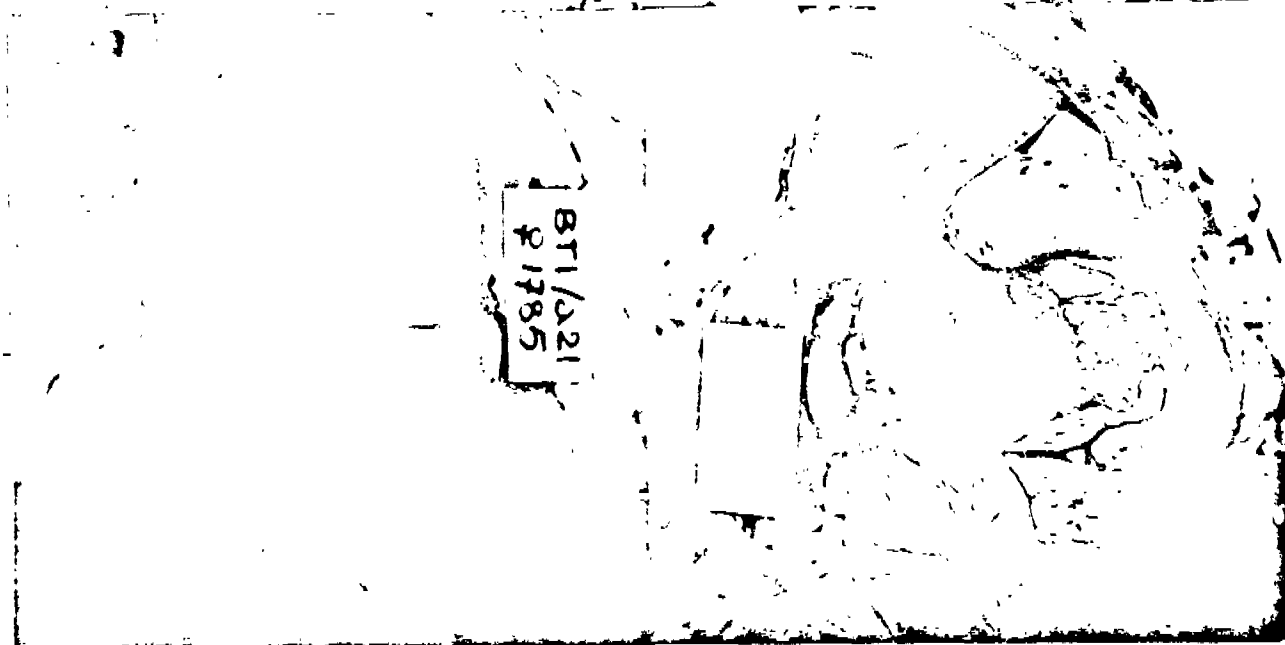


Fig. 28

Fig. 29

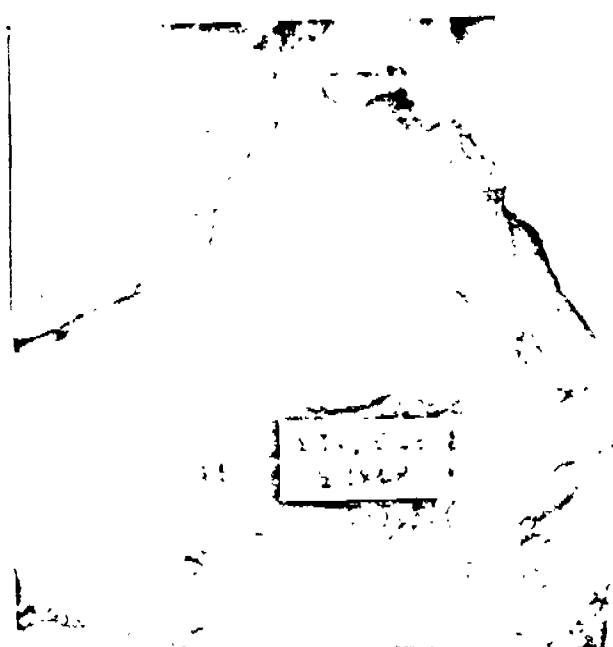


Fig. 30

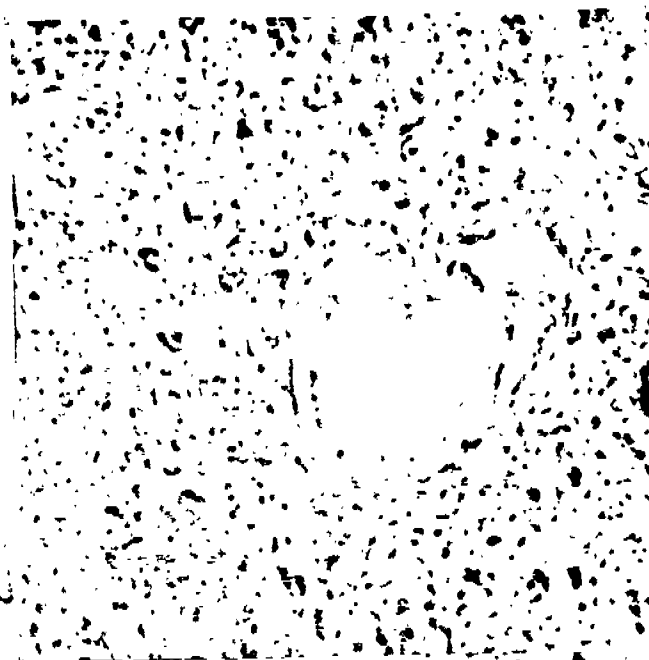


Fig. 31

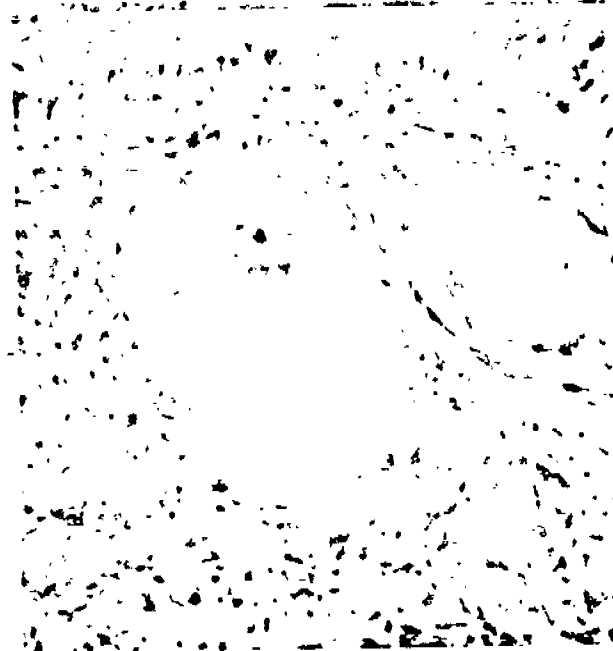


Fig. 32

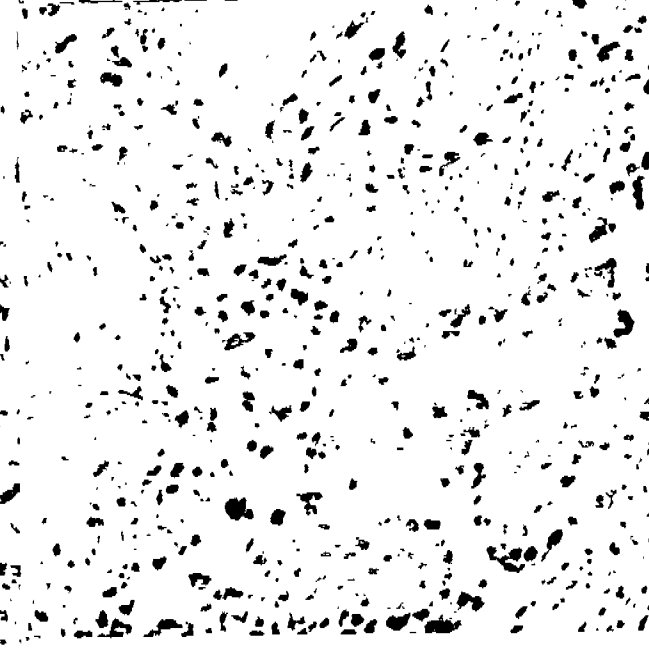


Fig. 33

Fig. 34

Fig. 35

Fig. 36

Fig. 37

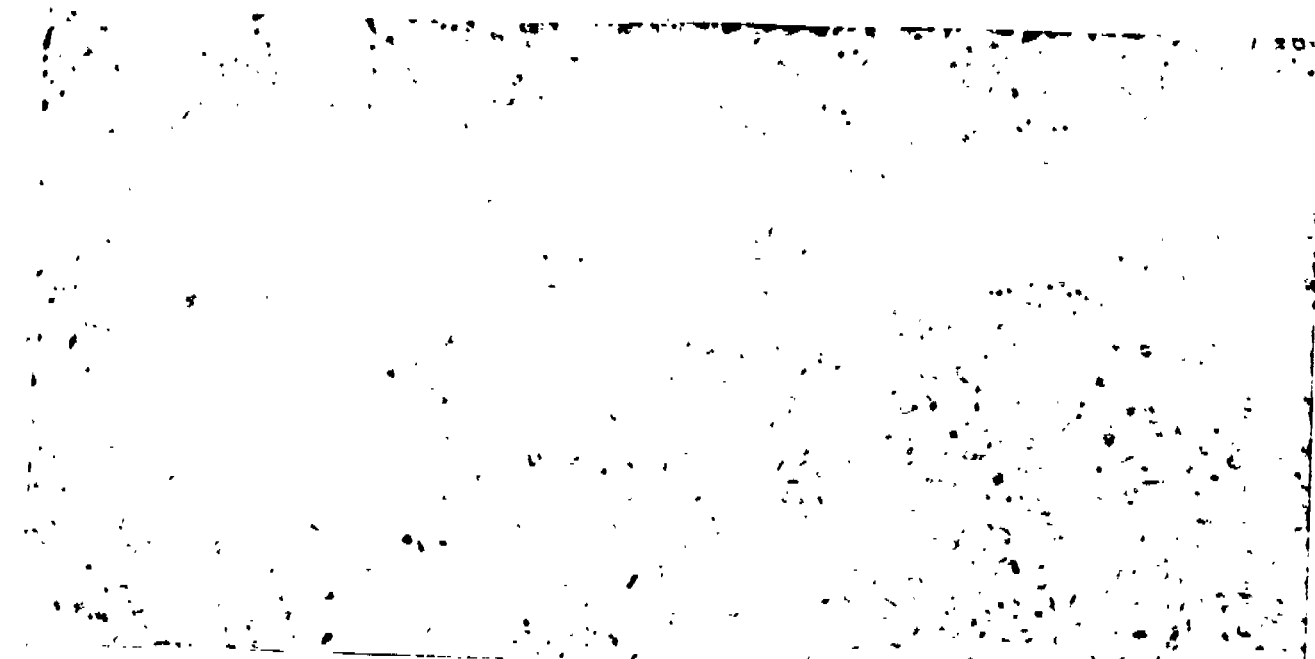


Fig. 39



g. 41

Fig. 42

ig. 43

Fig. 44

g. 45

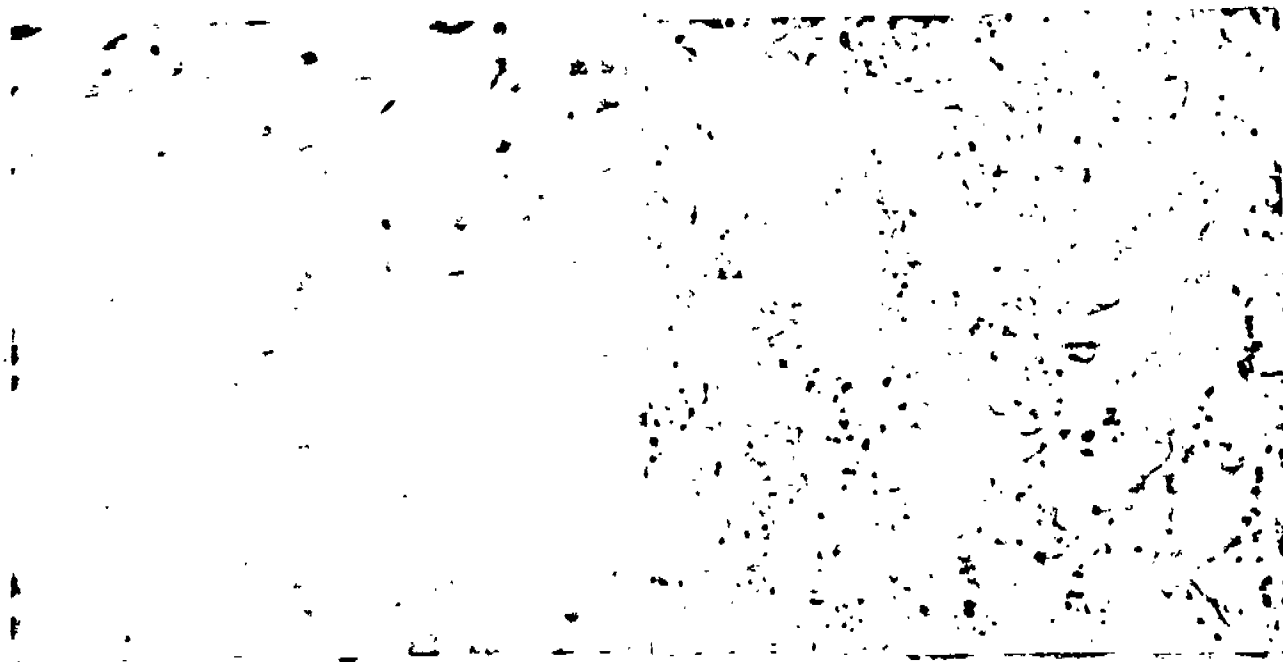


Fig. 46

g. 47



Fig. 48

BOR 011171

g. 49

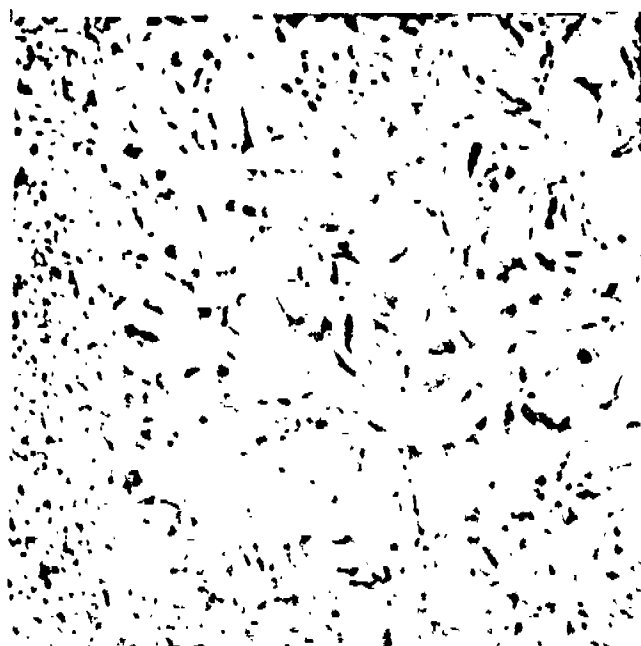


Fig. 50

g. 51



Fig. 52

