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BINGHAMTON STATE OFFICE BUILDING SOOT-INDUCED MORPHOLOGIC ALTERATIONS IN THE LIVERS OF GUINEA PIGS

Preliminary Report submitted to
Dr. D.O. Carpenter
on 1/6/82

by

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Dose level
1, 10, 100, & 500 mg/m³ Soot
— Concentration of mix
— Analyses
— Concentrations in Liver, Fat ?

ABSTRACT

A fire in an office building transformer, cooled with Pyranol which is composed of 65% Aroclor 1254 (containing tri, tetra, penta and hexachlorobiphenyls) and 35% chlorinated benzenes, resulted in contamination of the building with a fine soot. Due to the pyrolysis of the fluid mixture, the soot contains a number of polychlorinated organics, including biphenyls, dioxins, and dibenzofurans. As part of the evaluation of the soot's toxicity, it was dispersed in 0.75% methyl cellulose and administered by gavage to Hartley guinea pigs in a single dose. Animals were sacrificed after forty-two days and liver tissue was examined by light and electron microscopy.

Hypertrophy of hepatocytes, fat infiltration, focal piecemeal necrosis, bile duct proliferation with fibrosclerosis, and hyaline-like bodies were observed by light microscopy. Proliferation of the smooth endoplasmic reticulum (SER), concentric membrane arrays (CMA), mitochondrial alterations, decreased rough endoplasmic reticulum (RER), and autophagolysosomes were observed by electron microscopy. The CMAs frequently surrounded lipid droplets, but also encircled areas of the cytoplasm including mitochondria and degenerating organelles. These CMAs corresponded to the hyaline-like bodies observed by light microscopy.

On February 5, 1981 a fire occurred in the electric service transformer of the New York State Office Building in Binghamton, New York (henceforth referred to as the BSOB). The transformer was cooled and insulated with Pyranol-65% Aroclor 1254 (a mixture of polychlorinated biphenyls-PCBs) and 35% chlorinated benzenes. The building was contaminated with a fine soot subsequently shown to contain a number of PCB, dioxin, and dibenzofuran isomers including the highly toxic 2, 3, 7, 8 - tetrachlorodibenzo-p-dioxin (Schwetz, et al., 1973). Chemical analysis was done and will be reported elsewhere by P. O'Keeffe and co-workers, Division of Laboratories and Research, New York State Department of Health. The dioxin and dibenzofuran isomers were formed by pyroloysis of the Pyranol (Bumb, et al., 1980; Buser, et al., 1978).

A series of animal tests were designed and performed by Dr. L. Kaminsky and co-workers of the Division of Laboratories and Research, New York State Department of Health, to test the soot's toxicity. In one of these experiments, guinea pigs were fed a single dose of BSOB soot, and the morphologic alterations of their livers are reported here. Other experimental data and results will be presented elsewhere by Kaminsky and co-workers. Guinea pigs were selected as the experimental animal because they are more sensitive to dioxin and dibenzofuran intoxication than other laboratory animals including rats, mice, Rhesus monkeys, rabbits, and dogs (Gupta, et al., 1973; Harris, et al., 1973; Schwetz, et al., 1973; McConnell, et al., 1978; Moore, et al., 1979). The liver was of particular interest because it is a target organ for PCBs, dioxin, and dibenzofuran (Litterst, et al., 1972; Harris, et al., 1973; Piper, et al., 1973; Rose, et al., 1976; Gasiewicz and Neal, 1979).

PCBs, and chlorinated dioxins and dibenzofurans all produce similar morphological alterations in the liver (Kimbrough, 1974). At the light microscopic

level the changes are: liver necrosis, fat infiltration, hypertrophy of hepatocytes, proliferation of bile ducts, and hyaline bodies in the cytoplasm of the hepatocytes. These observations have been reported in a number of species - rats (Bennett, et al., 1938; Miller, 1944; Jones and Butler, 1974; Gupta, et al., 1973; Greig and Osborne, 1978; Norback and Allen, 1973; Kasza, et al., 1976; Jonsson, et al., 1981), mice (Nishizumi, 1970; Gupta, et al., 1973), monkeys (Nishizumi, 1970; Norback and Allen, 1973; McConnell, et al., 1978), rabbits (Miller, 1944; Vos and Beems, 1971), and guinea pigs (Miller, 1944; Gupta, et al., 1973). The presence of a yellow-brown or brown pigment sometimes weakly staining for hemosiderin is reported for PCB intoxication, but not for purified dioxins or dibenzofurans (Nishizumi, 1970; Vos and Beems, 1971; Kimbrough, et al., 1972; Buse, et al., 1974; Jonsson, et al., 1981). The pigment is not, however, a consistent finding, and Kimbrough, et al., 1972, reported its presence in rats fed Aroclor 1242, but not in those fed Aroclor 1016. The presence of necrosis is frequently reported as single cell, focal, or piecemeal (Vos and Beems, 1971; Gupta, et al., 1973; Jones and Butler, 1974; McConnell, et al., 1978; Jonsson, et al., 1981), and altered hepatocytes were predominantly in the centrilobular region.

Bile duct proliferation has been reported as a result of feeding both purified dioxin (Norback and Allen, 1973) and PCBs (Kimbrough, et al., 1972; Norback and Allen, 1972; Kasza, et al., 1976; Jonsson, et al., 1981). Adenofibrosis, generally taken to be the result of bile duct proliferation, has also been reported (Kimbrough, et al., 1972, and 1973; Kimbrough and Linder, 1974; Wassermann, et al., 1978). Kimbrough, et al., 1972, reported a higher incidence of adenofibrosis in female rats than in males. Kimbrough, 1973, reported extensive adenofibrosis and the development of pancreatic-type cells in rats chronically fed high levels of Aroclor 1254.

Animals fed purified dioxin have been frequently reported to have multinucleated hepatocytes (Jones and Butler, 1974; Gupta, et al., 1973; Norback and Allen, 1973; Greig and Osborne, 1978; McConnell, et al., 1978). Jones and Butler claim these cells arise by cell fusion as opposed to mitosis. This is supported by the fact that none of the other authors report mitosis of bi or multinucleated cells. Similar cells have not been reported in PCB fed animals.

Ultrastructurally, the livers of animals fed PCB or purified chlorinated dioxins and dibenzenofurans have similar alterations. These changes include proliferation of SER, decreased RER, large numbers of lipid droplets, concentric membrane arrays (CMAs), and mitochondrial alterations. For a review of these changes, see Kimbrough, 1974. Most workers report large numbers of lipid droplets,proliferated SER,and decreased RER (Nishizumi, 1970; Norback and Allen, 1972; Kimbrough, et al., 1972; Allen and Abrahamson, 1973; Jones and Butler, 1974; Kasza, et al., 1976; Jonsson, et al., 1981). CMAs are also frequently reported in hepatocytes (Norback and Allen, 1972 and 1973; Kimbrough, et al., 1973; Allen and Abrahamson, 1973; Jonsson, et al., 1981). Mitochondrial alterations are occasionally reported and range from shape changes,to parallel arranged cristae,to severe deterioration and dense granulation in the matrix (Burse, et al., 1974; Jonsson, et al., 1981). Jones and Butler, 1974 demonstrated multinucleated cells,and Greig and Osborne, 1978 demonstrated areas of lateral plasma membrane fusion.

The morphological alterations of the liver of a wide variety of species fed PCBs,and chlorinated dioxins and dibenzofurans are usually reported as similar to each other and a number of other toxic organic molecules (Kimbrough, 1974). The reports are not, however, completely consistent and may vary with respect to the mixture of compounds, dose,or method of administration.

Cockerham, et al., 1980, for example, reported no liver alterations in beach mice exposed to dioxin.

METHOD

Soot collected from the BSOB was suspended in 0.75% aqueous methyl cellulose, and administered in a single gavage at 1, 10, 100, and 500mgm soot/kgm body weight to Hartley guinea pigs. Each dose group was composed of six males and six females. A fifth group was fed 500mgm activated carbon/kgm body weight in 0.75% methyl cellulose as a control. An additional control group of six males was fed 0.75% methyl cellulose, while a second group of six males served as an untreated control. Female animals were eleven weeks old at the start of the test and the males were eight weeks old. All animals were sacrificed by suffocation in CO_2 42 days after administration of the single dose, and complete necropsy performed. Animals had free access to food and water during the test. This animal experiment was designed and carried out by L.S. Kaminsky, J. Silkworth and D. McMartin of the Toxicology Institute, Division of Laboratories and Research, New York State Department of Health, and results, other than the liver morphology presented here, will be reported elsewhere.

Two other untreated control groups, both composed of ten animals - five males and five females - were used for comparison to the experimental groups. One group was randomly selected from the New York State Department of Health's guinea pig colony. The other group was from an outside commercial supplier (Charles Rivers). These animals were sacrificed and necropsied in the same way as the experimental animals.

Specimens from the liver of 91 guinea pigs (one female in the 500mgm soot/kgm group died during the test) were processed for light microscopy. Samples from all livers were fixed in buffered formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin (H&E), periodic acid - Schiff (PAS), PAS after diastase, and phosphotungstic acid hematoxylin

(PTAH). Samples from 15 livers were quick frozen, cryostat sectioned at 5μm, and stained with oil red O.

Samples for electron microscopy were taken from randomly selected (by means of a random number table) guinea pigs in each dose group, the activated carbon control group, and the untreated control group. Two males and two females were selected from each dose level and from the activated carbon control. Two guinea pigs were selected from the untreated all male group. Samples were also taken from one female pig from the highest dose group which was moribund and sacrificed at day 17 into the test. The livers of 23 guinea pigs were examined by electron microscopy. A thin slice of liver was removed from the animals as soon after death as possible and immediately immersed in 2% glutaraldehyde in 0.1M cacodylate buffer at ph 7.4 and 4°C, and placed into 1-2mm cubes. After overnight fixation at 4°C, post fixation was carried out in 1% OsO_4 in 0.1M cacodylate buffer at ph 7.4 for one hour at room temperature. The samples were dehydrated and embedded in epon 812. Thick sections were cut on 5 to 10 blocks from each animal - a total of 150 blocks were examined after toluidine blue staining. Ultrathin sections were cut on 90 blocks, and were stained with uranyl acetate and Reynolds lead citrate.

RESULTS

Gross Observations and Light Microscopy

At necropsy, single and occasionally multiple focal pale areas were observed on the surface of the livers of guinea pigs from all groups.

Microscopically, morphologic alterations in the hepatocytes were observed in the experimental guinea pigs and in one guinea pig in the activated carbon control group (guinea pig No. 37). These alterations were: hypertrophy of hepatocytes, fat infiltration, focal piecemeal necrosis, bile duct proliferation with fibrosclerosis, and hyaline-like cytoplasmic inclusion bodies.

Fig. 1 is representative of the widespread fat infiltration observed. It is a micrograph of a frozen section stained with oil red O. The fat droplets vary from cytoplasmic microdroplets to confluent globules larger than the nucleus. With the exception of No. 37, the control guinea pigs exhibited fat droplets of normal size, number and distribution.

Fig. 2 illustrates proliferation of bile ductules and fibrosclerosis. Several small duct-like structures intermingled with collagenous proliferation are evident. This alteration was observed in six female guinea pigs, two in the 1 mgm soot/kgm group, three in the 100 mgm soot/kgm group and one in the 500 mgm soot/kgm group, as well as in one male in the 500 mgm/kgm group.

Fig. 3 shows a paraffin section stained with PTAH. Cytoplasmic alteration is reflected in the numerous discrete spherical hyaline-like bodies which stain an intense dark blue. These hyaline-like bodies show greater contrast and detail in PTAH stained than in H&E stained sections. Fig. 4 is a higher magnification of these hyaline-like bodies. They exhibit a wide range of sizes and shapes - some minute, others as large or larger than the nucleus. Single round bodies ranging in size from 1.9 to 5.7μm are observed, some with clear centers (small

arrows), others of solid density (large arrows). Individual cells may contain several bodies or a confluent group. These groups may be as large as 10μm (double arrows).

Fig. 5 illustrates a 1μm toludine blue stained plastic section. Hexagonally shaped hepatocytes appear enlarged and contain round appearing nuclei with prominant nucleoli. Binucleated cells, such as the one in the center of the field, are not uncommon. The hyaline-like bodies present in the cytoplasm display a wide range of sizes, and most have a light center with a dark peripheral annulus consisting of as much as 2/3's the diameter of the body. Multiple bodies are frequently seen in a single cell, and confluent groups as large as 14μm are present. Many small bodies appear uniformly dense.

The PAS and PAS/diastase stained sections showed normal amounts of glycogen in all animals.

Electron Microscopy

Electron microscopic examination of ultrathin sections show the following hepatocyte alterations: proliferated SER, CMAs, mitochondrial degeneration, decreased RER,and margination of organelles. All experimental animals and No. 37 show proliferated SER, frequently causing margination of mitochondria by increasing the cytoplasmic matrix. CMAs were most frequently observed surrounding fat droplets, and occasionally encompassing volumes of cytoplasm, mitochondria and degenerating organelles. CMAs were, on occasion, found in the sinusoidal lumen. The mitochondrial alterations appeared to be of two types, changes in shape and lamination of cristae. All experimental animals and No. 37 showed variations in shape but variations in cristae were observed only in the two highest dose groups.

Fig. 6 is a low magnification electron micrograph of 5 hepatocytes showing nuclei, lipid droplets, proliferated SER and margination of mitochondria.

Two large CMAs surround lipid droplets.

Fig. 7 shows details of two CMAs in which regularly spaced smooth membranes are arranged concentrically about lipid droplets. The outer membranes appear to be continuous with portions of the SER. Fig. 8 more clearly demonstrates this association of the membranes to a large lipid droplet. The membrane layers nearest the lipid droplet are regularly and closely spaced, appearing to continuously surround the droplet. The outer layers are less evenly spaced and are irregularly organized with large protruding areas. The outermost membranes are continuous with portions of the SER as indicated by the arrows, and are present as discrete leaflets that appear to cover only part of the circumference of the CMA.

The sinusoid and associated perisinusoidal space of Disse occasionally contained cellular debris and CMAs as in Fig. 9.

Fig. 10 shows three lipid droplets which are confluent and contain internal membrane fragments. The droplets are membrane bound, but lack concentric arrays as illustrated in Figs. 6, 7, and 8. Fig. 11 shows two lipid droplets with fragmented membranes internally, with concentric membranes associated with part of their circumference.

Random condensations of SER associated with islands of proliferated SER are illustrated in Fig. 12.

Alterations in the shape of mitochondria were occasionally noted. Fig. 13 shows many normal mitochondria, and one irregularly shaped one. A pseudo-inclusion composed of cytoplasmic components is evident in the large central mitochondria. The two highest dose groups show motochondria with parallel cristae. Fig. 14 is an illustration of this alteration.

DISCUSSION

The pale areas on the liver surface observed at necropsy in all groups have been shown to be manifested microscopically as coagulative necrosis, and to be present in otherwise normal guinea pig populations (Wagner and Manning, 1976).

All of the control animals with the exception of guinea pig No. 37 in the activated carbon group showed morphologically normal livers at both the light and electron microscopic levels. The experimental animals in all dose groups exhibited alterations at both microscopic levels, demonstrating a toxic reaction to the ingestion of BSOB soot. Since guinea pig No. 37 was only one of forty-four control animals and only one of twelve in the activated carbon group, the observation of morphologic alterations in its liver was not taken to be significant. An adequate control is, therefore, established and differences between control and experimental guinea pigs have been demonstrated. Comparison of the four dose groups did not produce differences, and to date the only alteration that is a function of the dose level is the parallel mitochondrial cristae observed in the 100 and 500 mgm soot/kgm groups. The morphologic alterations observed are consistent with those found by other workers in the liver of animals fed either PCBs or purified chlorinated dioxins (see Kimbrough, 1974 for a review).

However, the current experiment did not exhibit the multinucleated hepatocytes observed by workers who fed purified dioxins (Gupta, et al., 1973; Norback and Allen, 1973; Jones and Butler, 1974; Greig and Osborne, 1978), nor did other studies of PCB fed animals (Nishizumi, 1970; Kimbrough, et al., 1972; Norback and Allen, 1972; Allen and Abrahamson, 1973; Kasza, et al., 1976; Jonsson, et al., 1981). Since PCBs, dioxins and dibenzofurans are present in the BSOB soot and the PCBs of the other studies were probably contaminated with

dioxins, it appears that multinucleated cells are not formed when a mixture is present.

The observation of bile duct proliferation with fibrosclerosis in seven of forty-seven experimental animals is consistent with a number of other reports in which animals were fed PCBs or dioxins (see introduction for references). It is difficult, however, to compare the various studies since the dose levels, number of doses, and time course of the experiments are different. Kimbrough, et al., 1972 and 1973 report a large percentage of animals with this alteration, but their experiment involved multiple doses over longer time periods. Differences in toxicity of the particular compounds used may also be a variable as Kimbrough, et al., 1972 reported a difference between Aroclor 1254 and 1260. The possibility and extent of dioxin contamination in various PCB mixtures is also an unknown parameter. Kimbrough, et al., 1972 reported an increased incidence in females as opposed to males, and six of the seven animals exhibiting the alteration in this study were females.

Hyaline-like bodies in the cytoplasm of the hepatocytes have been observed in a number of studies for a variety of toxic organic molecules including PCBs, dioxins, and dibenzofurans (Kimbrough, 1974). The CMAs at the ultrastructural level undoubtedly correspond to these bodies at the light microscopic level. This is also suggested by Kimbrough, 1974. The observation of the CMAs is consistent with many other studies in which a variety of species were fed PCBs or dioxins (Kimbrough, 1974, Jonsson, et al., 1981). Jonsson, et al., 1981 suggested that the ejection of CMAs into the sinusoids and bile canaliculi was a mechanism to rid the hepatocyte of toxic materials. The ejection of CMAs and other cell debris into the sinusoids was also observed in this study.

The ultrastructural alterations reported here are in general consistent with other reports, but some variation is also observed. For example, Jonsson, et al., 1981 reported severe degeneration of mitochondria, but we observed few de-

generated mitochondria. The observation of parallel cristae in a small number of mitochondria in the two highest dose groups is in agreement with the results of Burse, et al., 1974. The increased SER and decreased RER is in agreement with all previous studies of PCB, dioxin and dibenzofuran intoxication except Fowler, et al., 1973 who reported an increase in RER in rat hepatocytes following a single oral dose of dioxin. The condensed, laminated SER of Fig. 12 has not been previously reported, but was occasionally observed in some experimental animals.

The morphological differences between control and treated guinea pigs demonstrate a toxic effect due to the ingestion of BSOB soot, but dose level related effects have not been documented. The alterations reported here and in the literature vary in some details, but are generally consistent. The explanation of the variation in morphological alterations cannot be determined at this time, but is probably a complex function of sampling, ingested molecules, dose level, number of doses, time course of the experiment, and animal species.

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FIGURE LEGENDS

Fig. 1 is a photomicrograph of a frozen liver section stained with oil red O. Magnification is 500X.

Fig. 2 is a photomicrograph of an H&E stained paraffin section of liver from an area of bile duct proliferation with fibrosclerosis. Magnification is 800X.

Fig. 3 is a photomicrograph of a PTAH stained paraffin section of the liver. The magnification is 320X.

Fig. 4 is a photomicrograph of a PTAH stained paraffin section of the liver. The hyaline-like bodies are indicated by the arrows: clear centers by the small arrows, dense bodies by the large arrows, and a confluent group by the double arrow. The magnification is 800X.

Fig. 5 is a photomicrograph of a 1μm plastic section of the liver stained with toludine blue. The magnification is 800X.

Fig. 6 is an electron micrograph of an ultrathin section at 5,100 times magnification. The nuclei (N), lipid droplets (Li), concentric membrane arrays (CMA), and mitochondria (Mi) are readily observed.

Fig. 7 is an electron micrograph of three CMAs viewed at 26,192X magnification.

Fig. 8 is an electron micrograph of a portion of a CMA around a lipid droplet (Li). The arrows indicate areas of continuity between the outer CMA membrane and the SER. Magnification is 18,000X.

Fig. 9 is an electron micrograph of a CMA in a liver sinus. A red blood cell (RBC) and Disse space (DS) are seen. Magnification is 18,000X.

Fig. 10 is an electron micrograph of three lipid droplets and their associated membrane systems in a hepatocyte. Magnification is 18,000X.

Fig. 11 is an electron micrograph of two lipid droplets with associated

membrane systems, and some areas of parallel aligned SER in a hepatocyte. Magnification is 18,000X.

Fig. 12 is an electron micrograph of areas of condensed SER in a hepatocyte. Magnification is 18,000X.

Fig. 13 is an electron micrograph of several mitochondria in a hepatocyte. Magnification is 18,000X.

Fig. 14 is an electron micrograph of several mitochondria, two of which have parallel arranged cristae. Magnification is 51,000X.

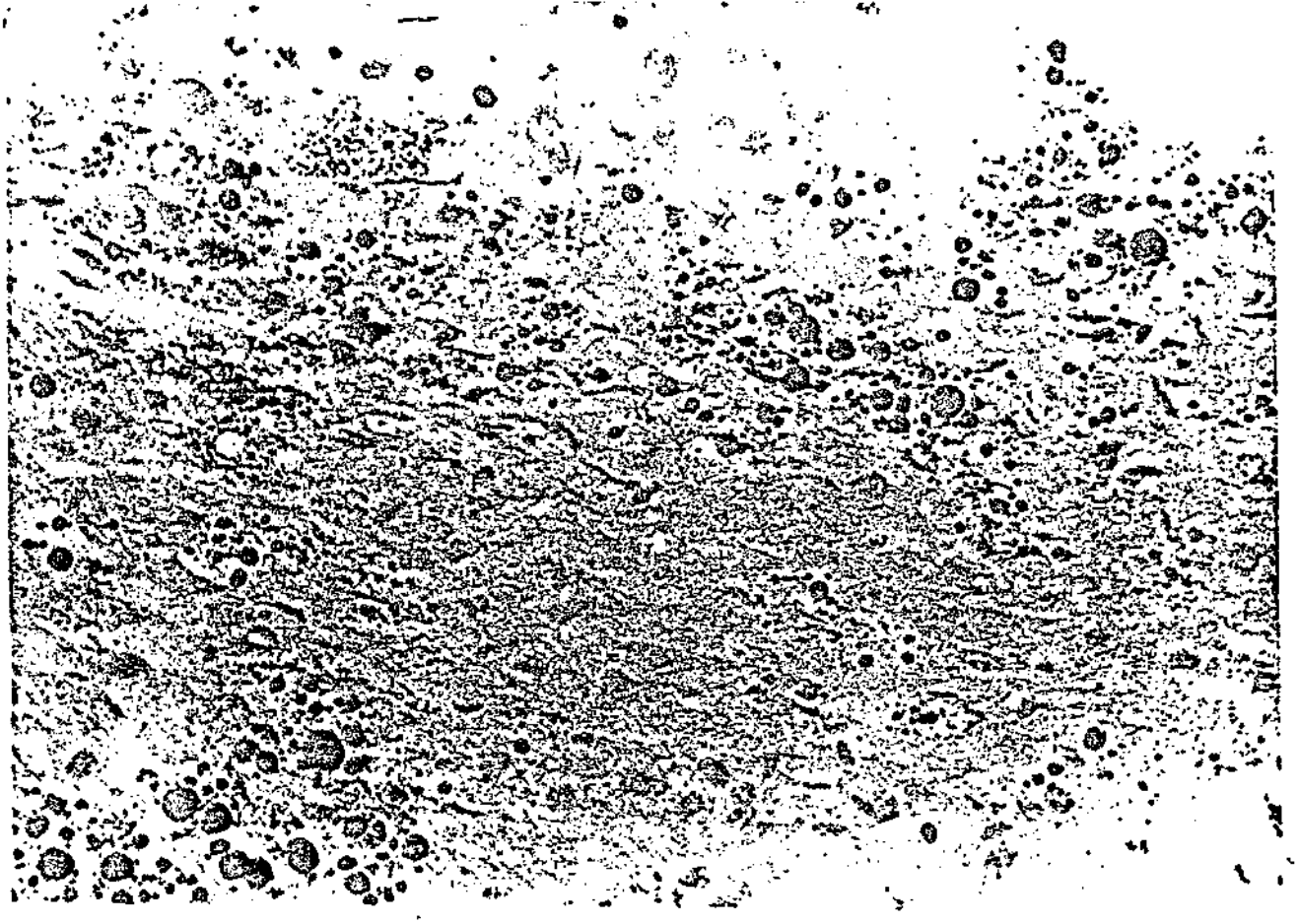

Fig 1

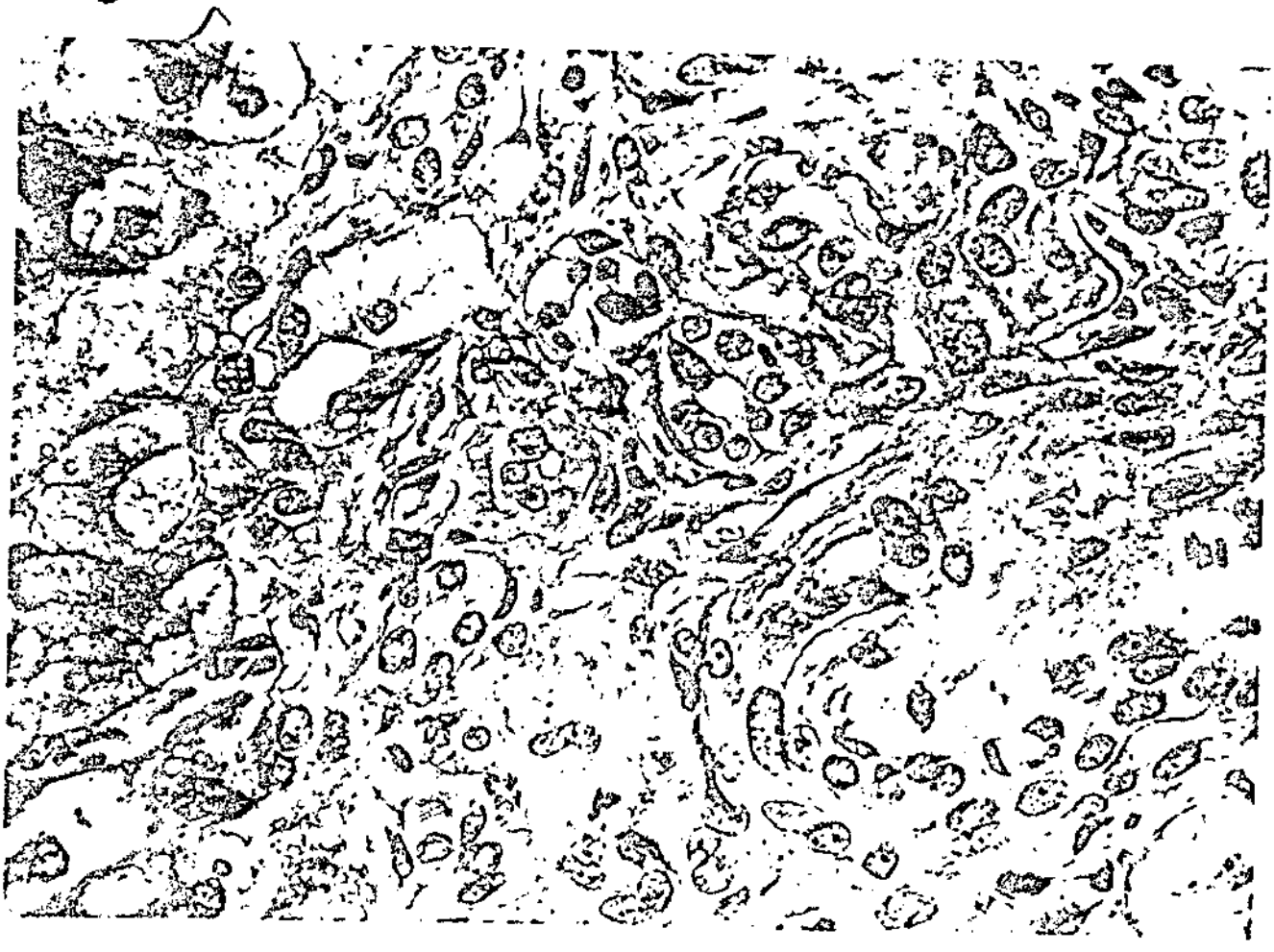

Fig 2

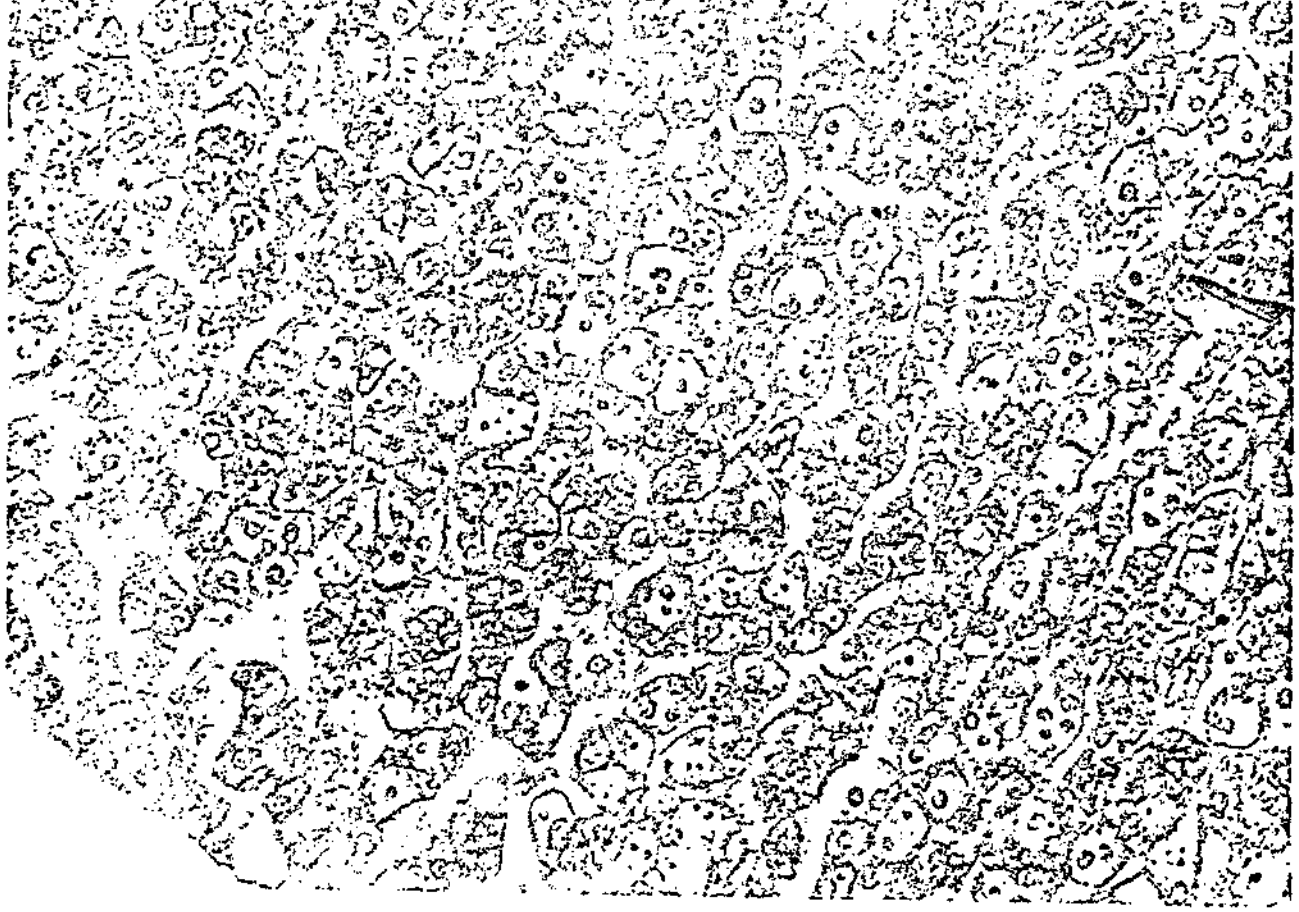

Fig 3

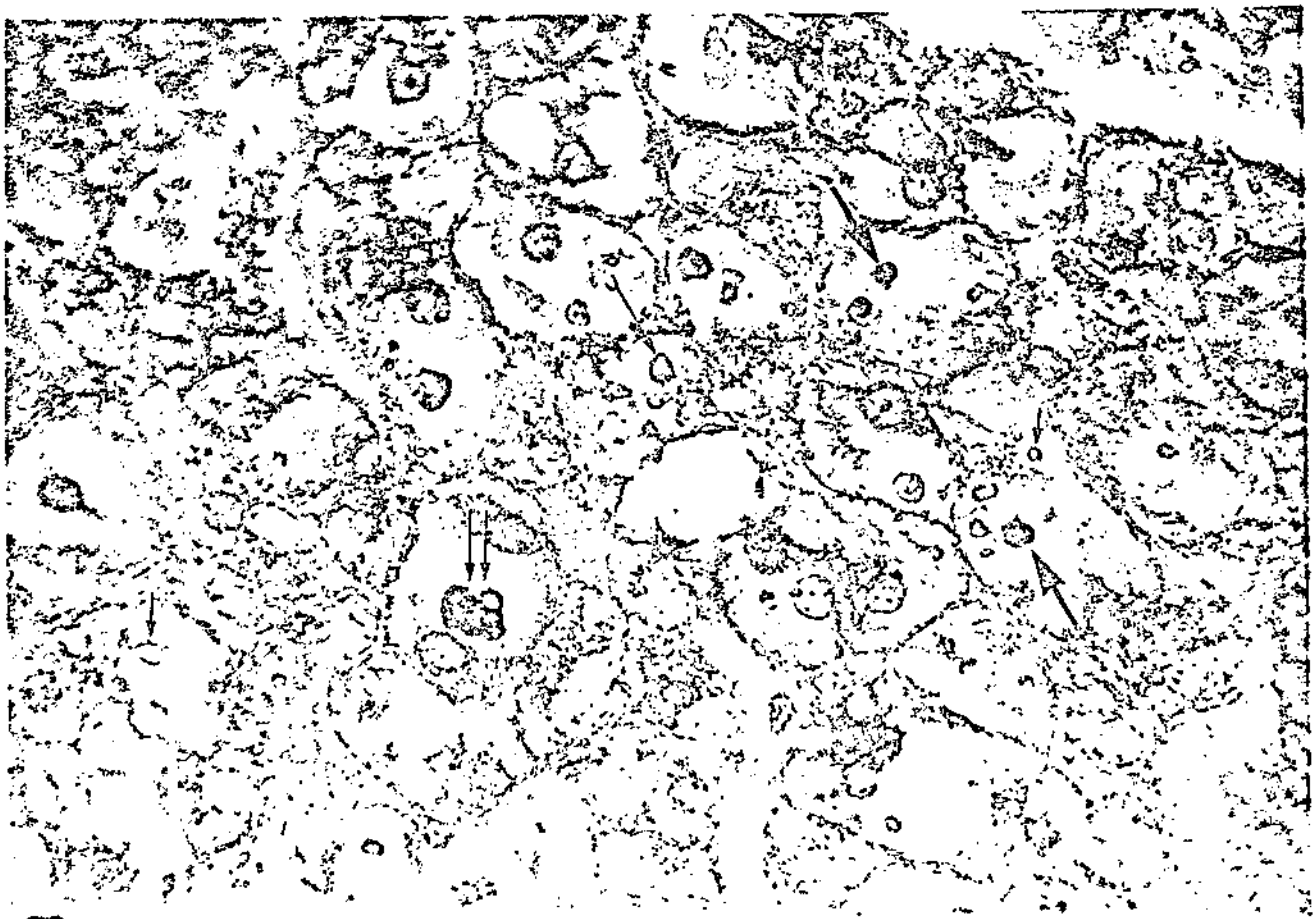

Fig 4

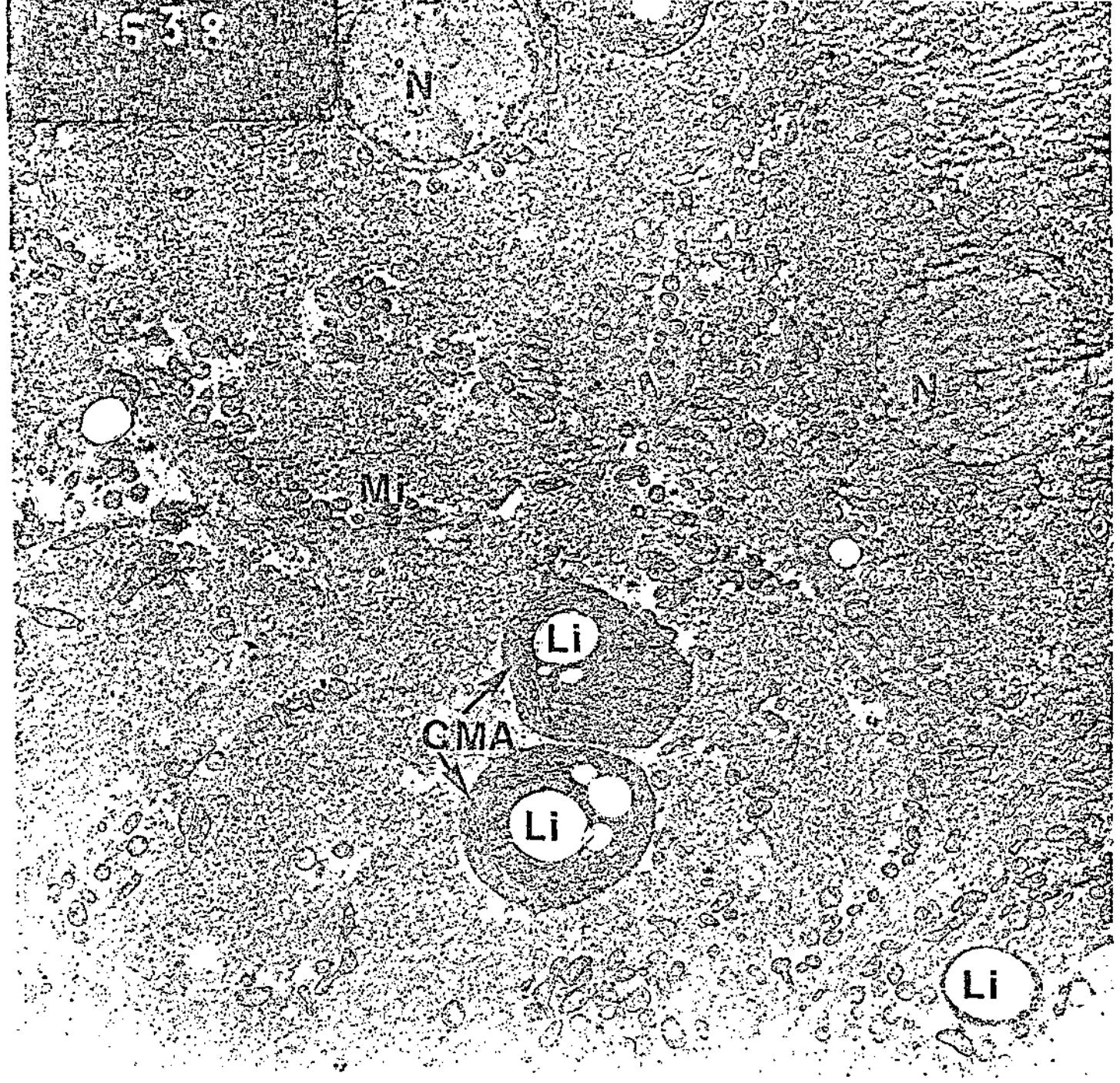

Fig 6

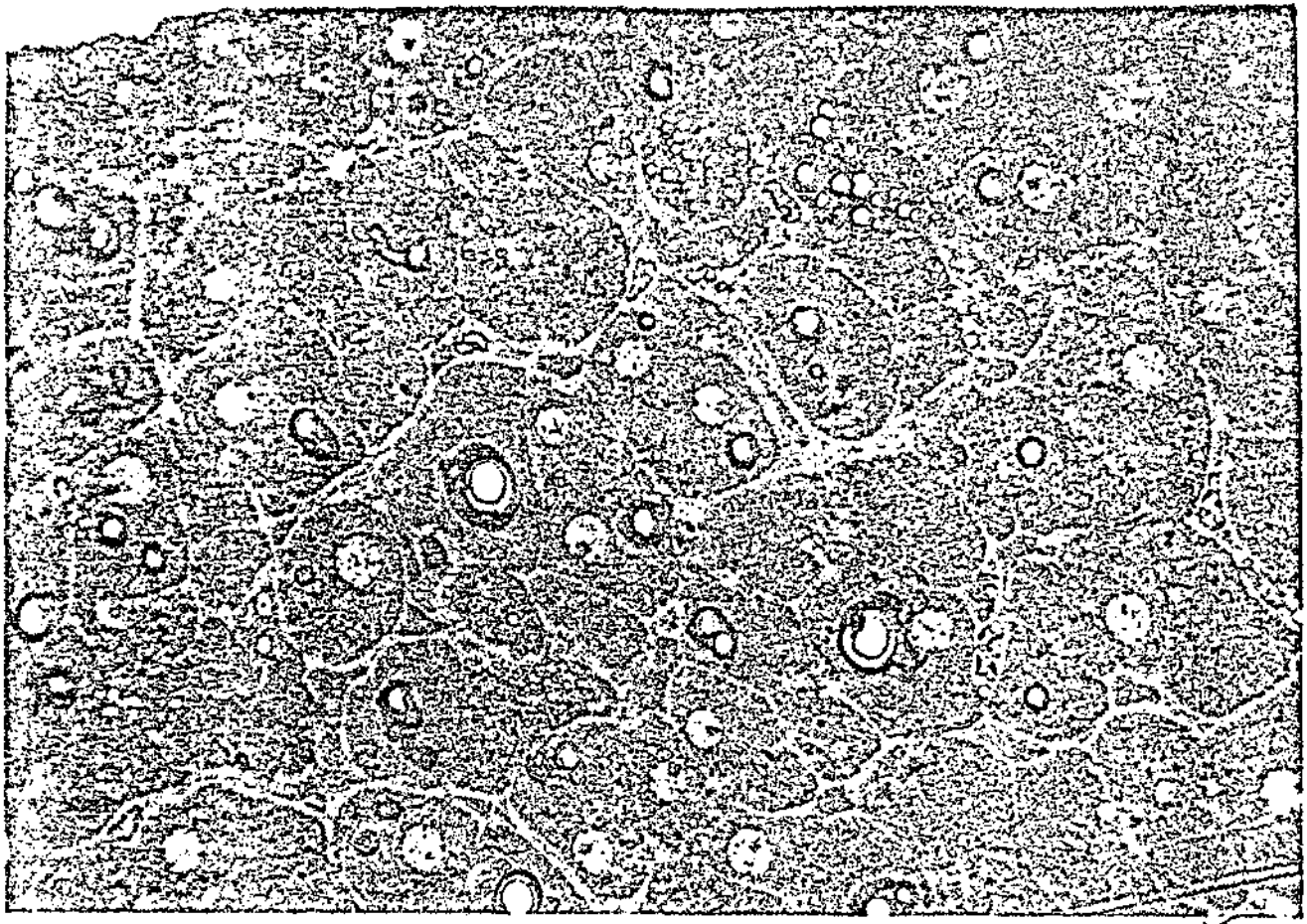

Fig 5

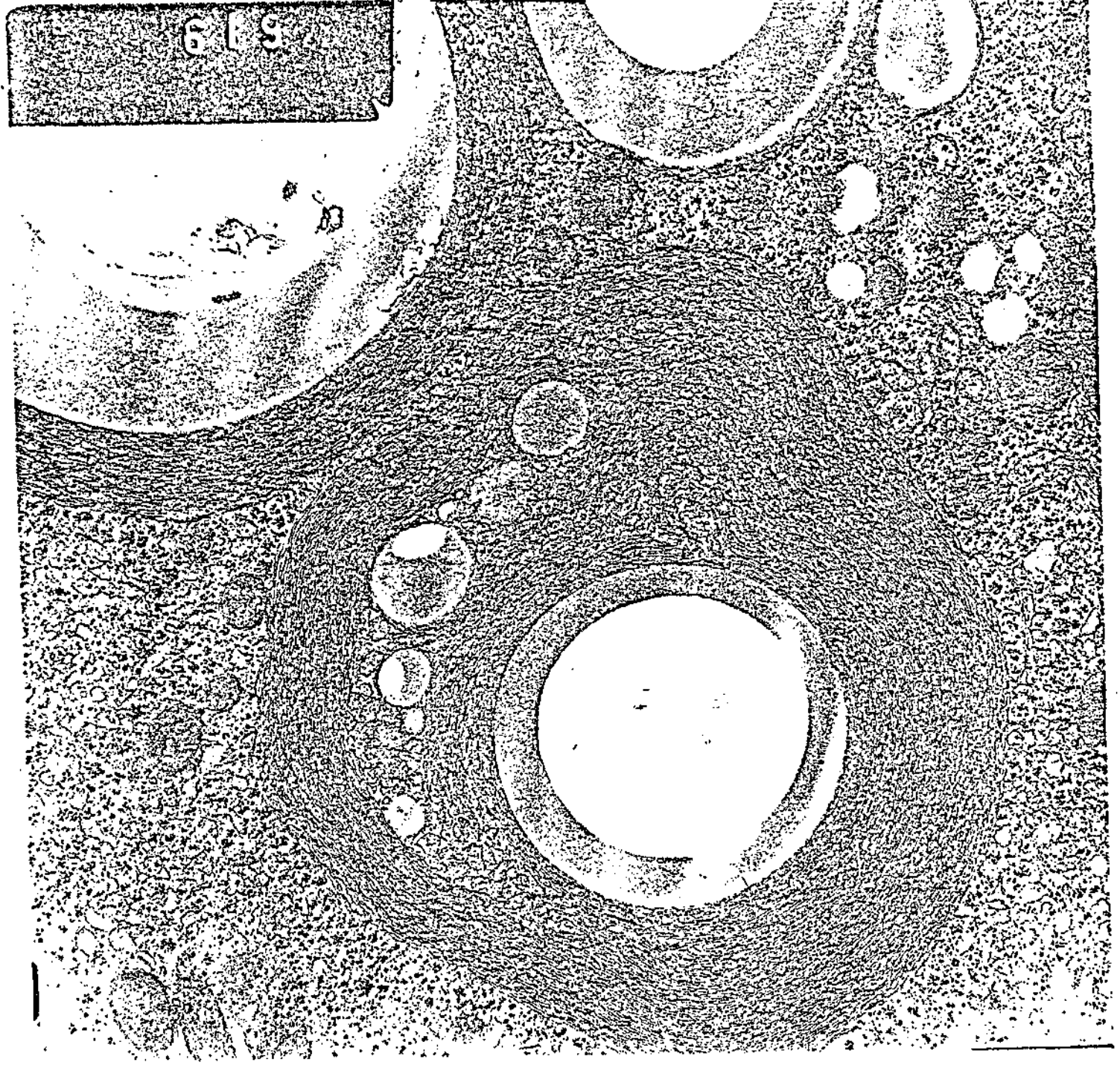

Fig 7

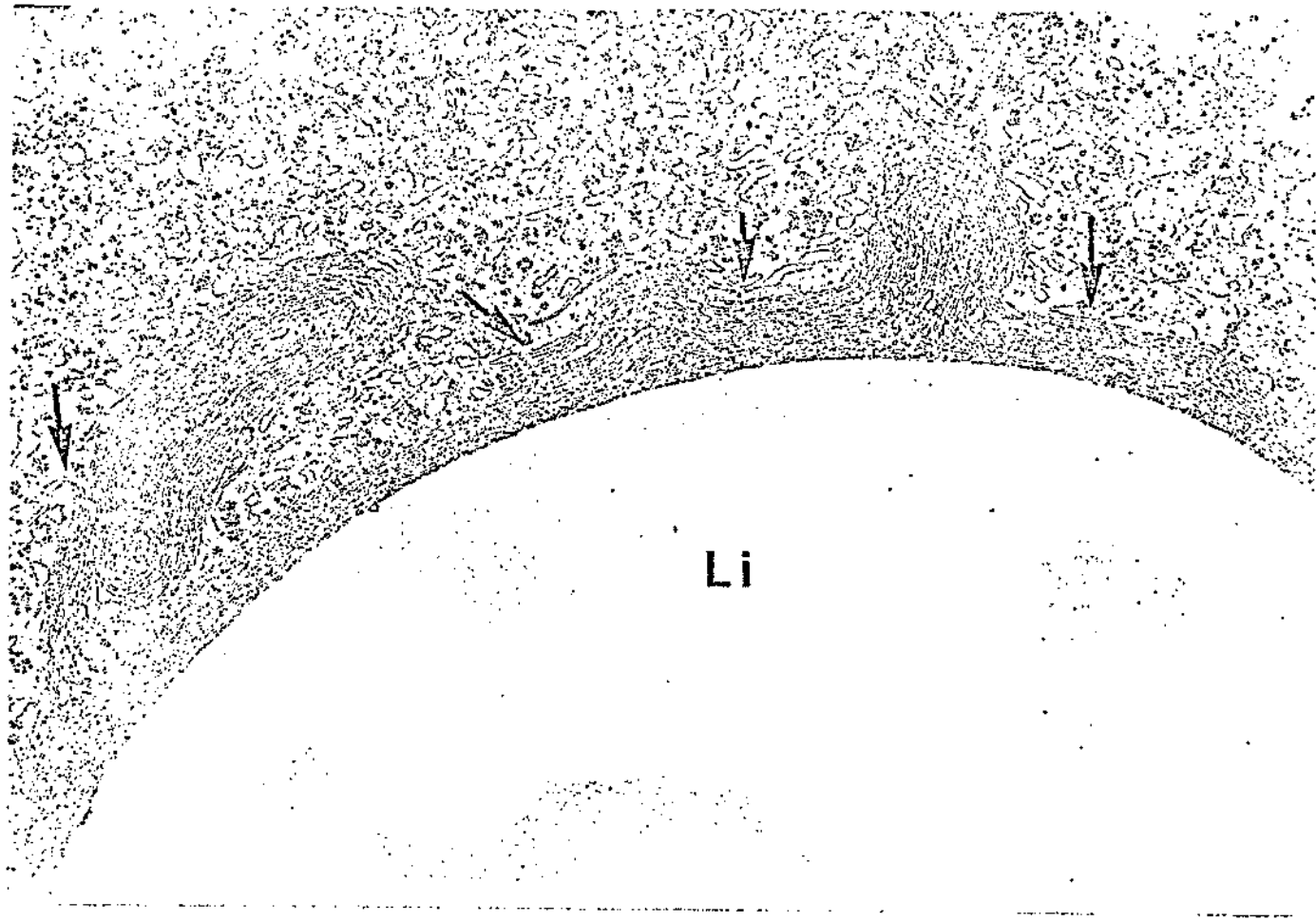

Fig 8

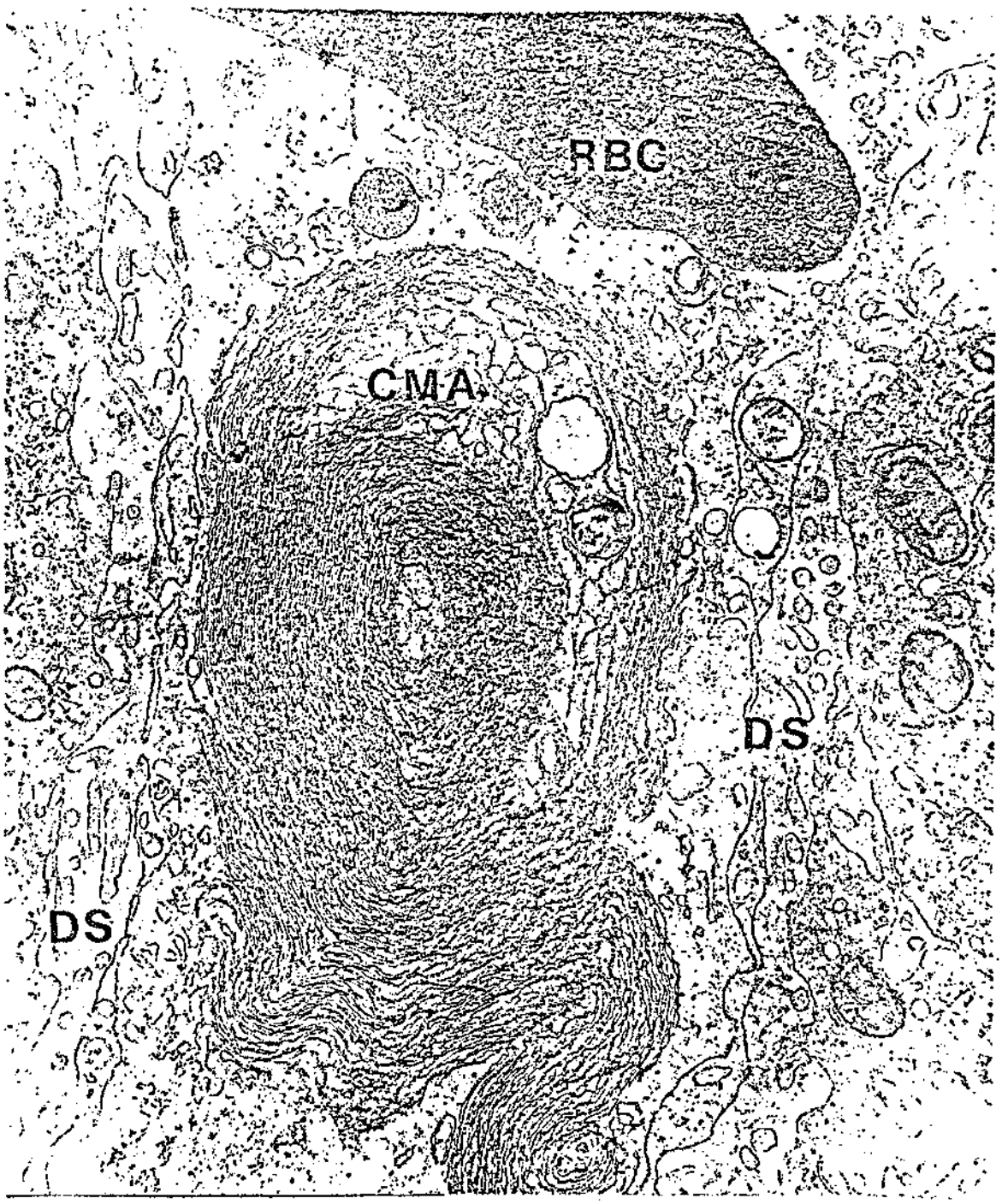

Fig 9

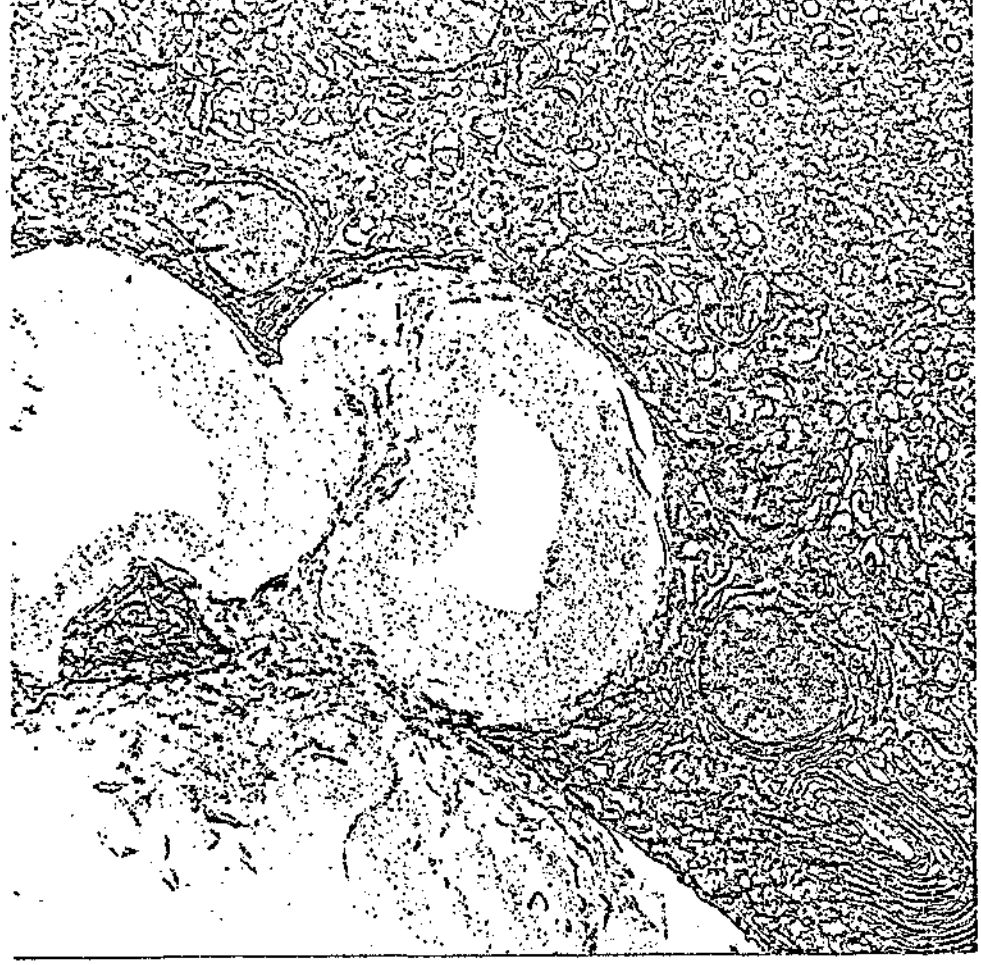

Fig 10

Fig 11

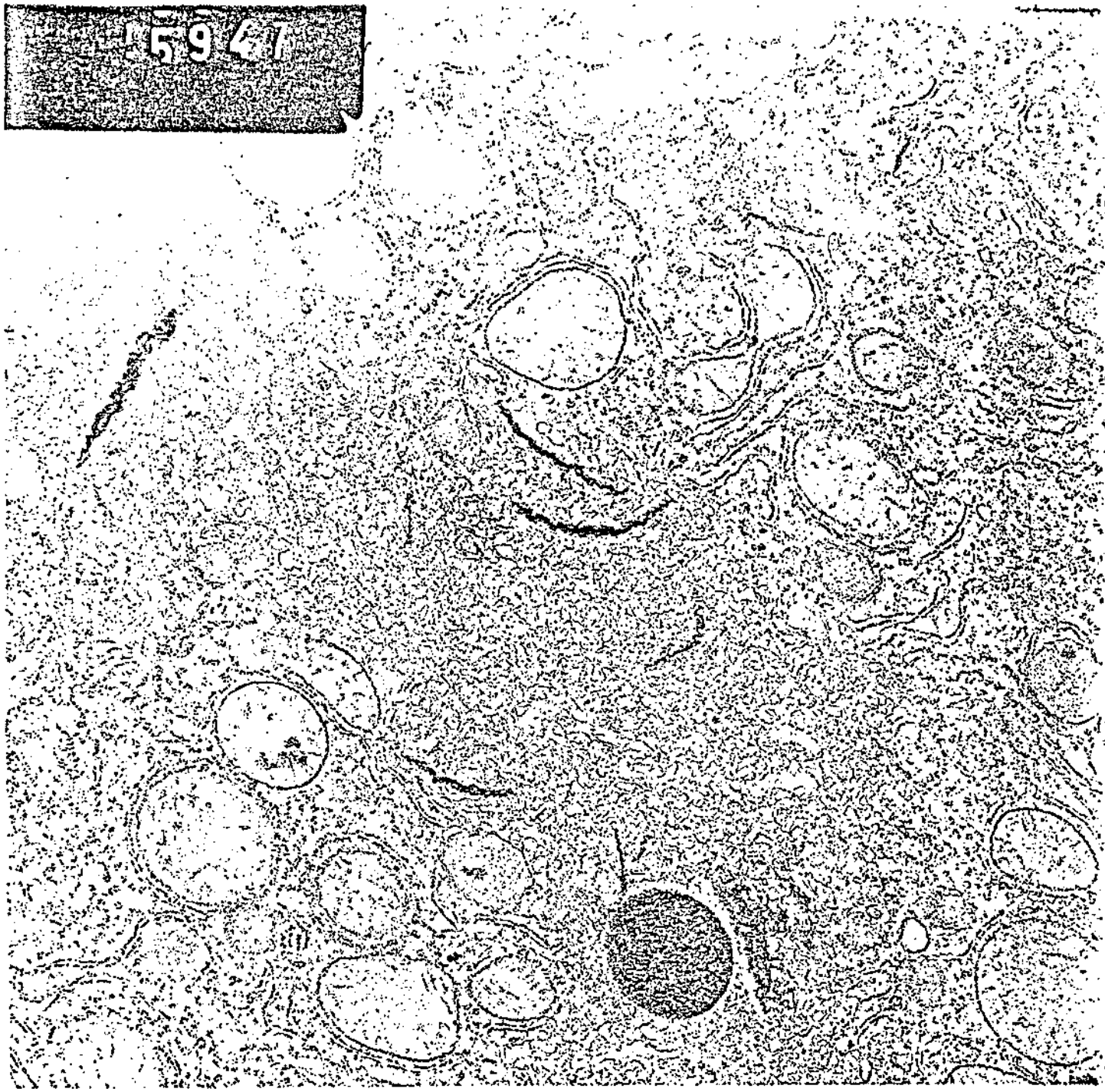

Fig 12

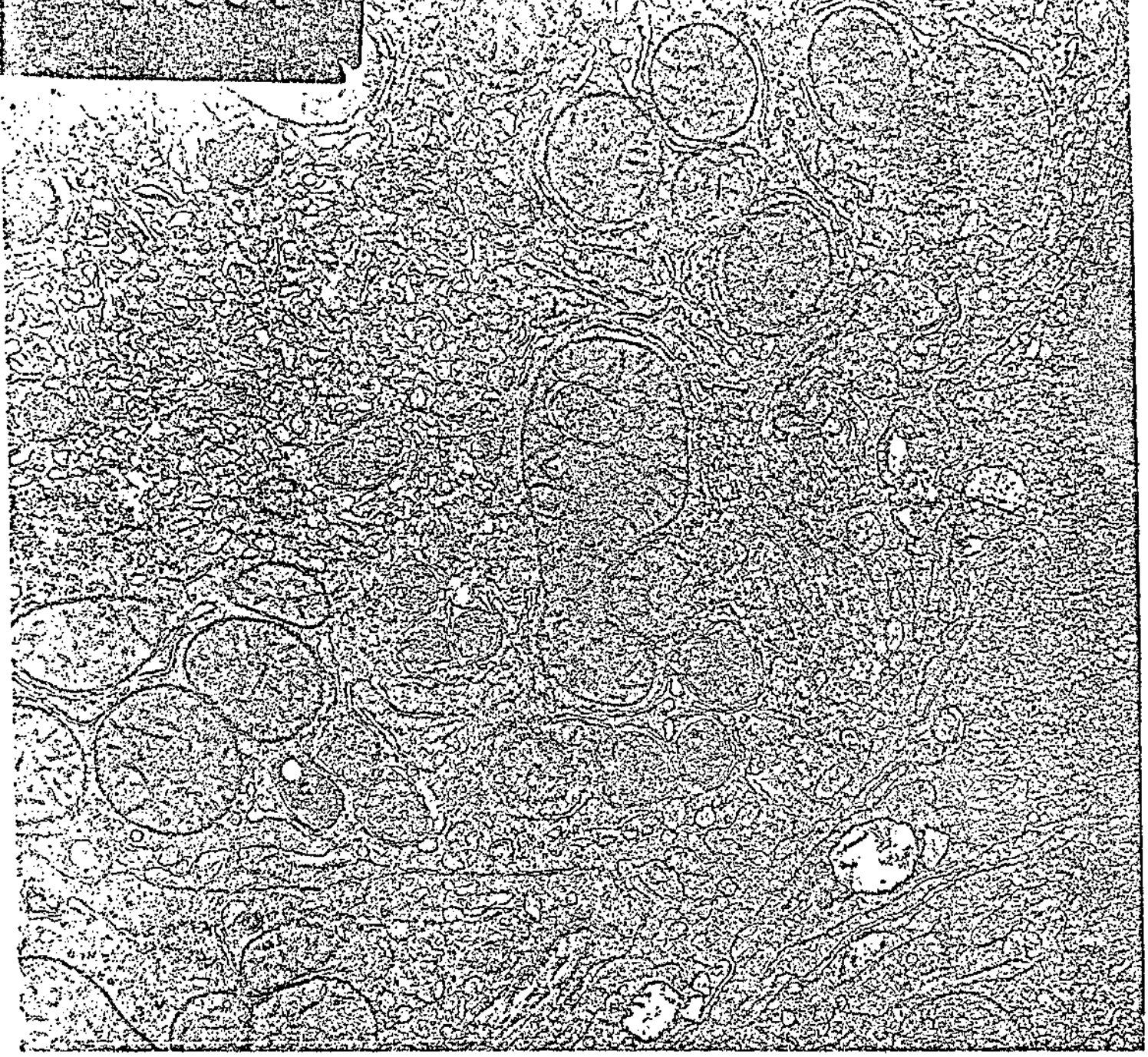

Fig 13

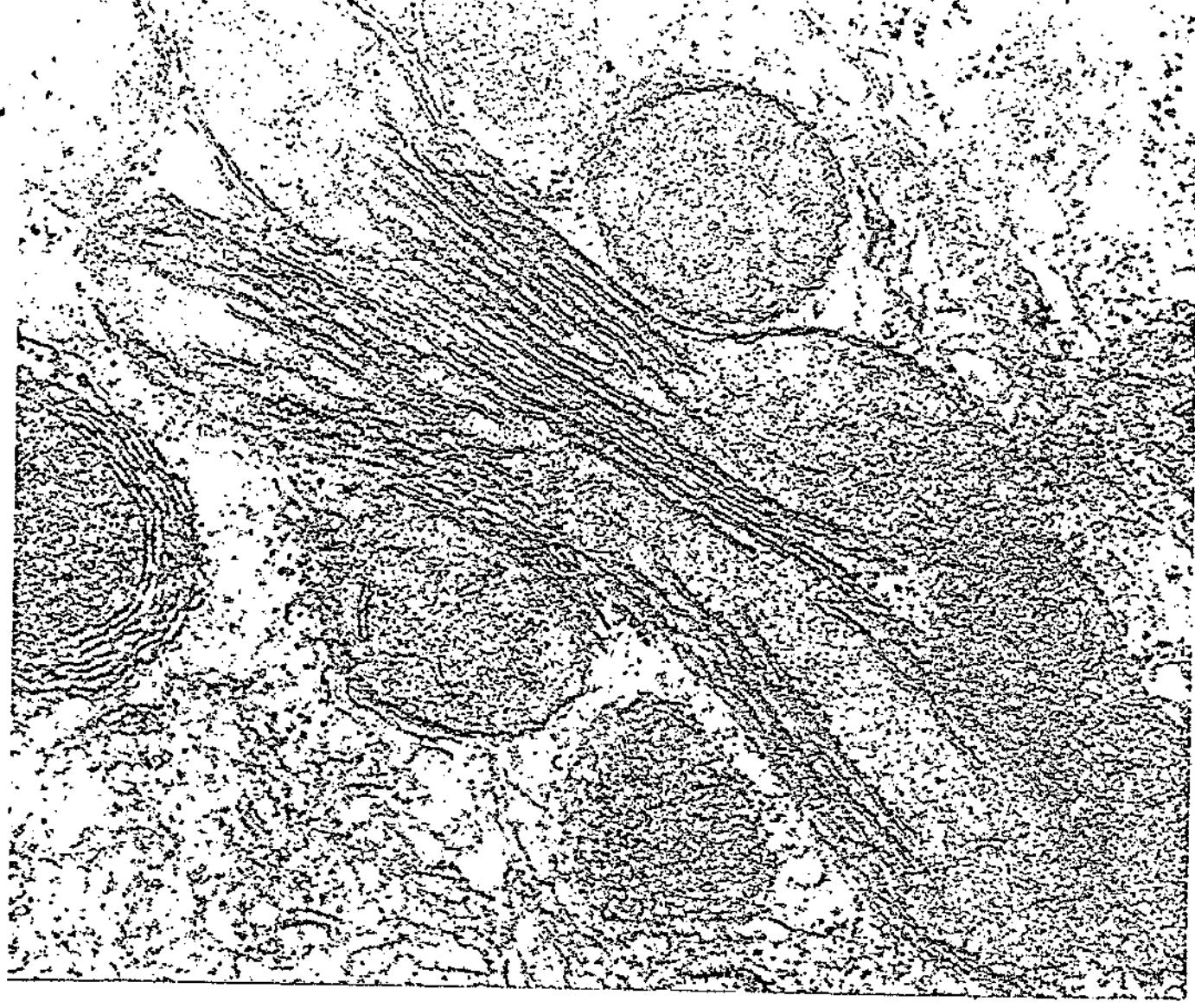

Fig 14