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(54) Titre : TRAITEMENT DE PLAIES ET COMPOSITIONS UTILISEES
(54) Title: TREATMENT OF WOUNDS AND COMPOSITIONS EMPLOYED

(57) **Abrégé/Abstract:**

A synthesized composition containing zinc ions, calcium ions, rubidium ions and/or potassium ions in a pharmaceutically acceptable carrier, which, when applied to an open wound, effectively modulates the activity of at least MMP-2 and/or MMP-9 in the wound. A method for treatment of wounds is disclosed.



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(54) Title: TREATMENT OF WOUNDS AND COMPOSITIONS EMPLOYED

(57) Abstract: A synthesized composition containing zinc ions, calcium ions, rubidium ions and/or potassium ions in a pharmaceutically acceptable carrier, which, when applied to an open wound, effectively modulates the activity of at least MMP-2 and/or MMP-9 in the wound. A method for treatment of wounds is disclosed.

TITLE OF THE INVENTION

TREATMENT OF WOUNDS AND COMPOSITIONS EMPLOYED

5 RELATED APPLICATIONS

[0001] This application is a non-provisional application claiming priority based on Provisional application Serial No. 60/334,337, filed November 29, 2001, said Provisional application, in its entirety, being incorporated herein by
10 reference.

FIELD OF INVENTION

[0002] This invention relates to the treatment of wounds, particularly open wounds which resist healing, such
15 as decubitus ulcers and diabetic ulcers. It further relates to the use of inorganics as an aid in the establishment and/or control over the chemical environment associated with extra cellular matrices.

[0003] More particularly, this application relates to
20 synthetic compositions for the modulation of matrix metalloproteinases (MMPs), especially in the treatment of open chronic wounds and other skin disorders.

[0004] In the prior art it is known that there exist within the human body a plurality of metal
25 metalloproteinases. It has been suggested that at least certain of these MMPs lie relatively dormant ("Pre-MMP") until activated, whereupon various of the MMPs affect cellular growth or lack of growth, the MMPs acting at least in part through the extracellular matrix (ECM) of the cells

[0005] MMP-2 has been particularly indicated in the healing of wounds. In its inactive state, Pro-MMP-2 includes a ribbon of protein which covers its active site. Removal (cleavage) of this protein must occur before this
5 MMP can become activated. This has been termed a "Cysteine switch". Zinc ions at the active site have been noted to activate MMP-2. Also, calcium ions at a secondary site are believed to provide the MMP with the proper geometry in its active state. Inhibitors of metalloproteinase (TIMP) have
10 been identified.

SUMMARY OF THE INVENTION

[0006] The present inventors have identified MMP-2 and MMP-9 in increased quantities both in the peripheral region
15 and particularly within the deep recesses of a chronic wound. It has also been a noted increase in these MMPs in "difficult to heal" open wounds. Further the present inventors have discovered a synthesized composition containing zinc ions, calcium ions, rubidium ions and/or
20 potassium ions in a pharmaceutically acceptable carrier, which, when applied to an open wound, after two weeks of treatment, effectively shuts down the activity of MMP-2 and/or MMP-9 in the wound as evidenced by analysis of wound cultures for the presence of MMPs 2 and 9, and resulting
25 visually observable improvement in the healing of the wound. The visually observable improvement in the healing process of the wound is dramatic and takes place within an unexpectedly short time frame.

[0007] Moreover, continued application of the
30 composition of the present invention to a chronic wound

site has been found effective in bringing about complete healing of chronic wounds, often within a matter of weeks. Especially, the composition containing the effective ingredients of the present invention has been determined effective to modulate the presence, hence the activity of, MMPs within the deeper inner recesses of the wound, as opposed to the outer peripheral regions of the wound. The present composition further appears to act as an oxygen scavenger and thereby eliminating or materially reducing the ill effects of oxygen radicals within the inner recesses of the wound.

[0008] Wounds such as decubitus ulcers, and deep burns have been effectively treated employing the concepts of the present invention.

15

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a photograph of depicting a wound having applied thereto a composition embodying the present invention;

20 Figures 2-5 are photographs of typical non-responding wounds;

Figures 6 and 7 are photographs of the leg wound of Example I, depicting the wound of Example I before and after treatment, respectively, in accordance with the present invention;

25

Figure 8 is a photograph of the leg wound of Example I before treatment in accordance with the present invention;

Figure 9 is a microphotograph of a biopsy of the wound depicted in Figure 8;

Figure 10 is a microphotograph depicting the levels of MMP-2 in the upper layers of Zones A and B of
5 Figure 9;

Figure 11 is a microphotograph depicting the levels of MMP-2 in the deeper layers of Zone C of Figure 9;

Figure 12 depicts the appearance of Zones A, B and C of Figure 9 after 14 days of treatment in accordance
10 with the present invention;

Figure 13 is a photograph depicting an external view of the wound depicted in Figure 8 after 14 days of treatment;

Figure 14 is a microphotograph of Zone B of Figure 9
15 after 14 days of treatment;

Figure 15 is a photograph of the wound of Example I after 6 weeks of treatment;

Figure 16 is a microphotograph of a biopsy of the wound depicted in Figure 15;

Figure 17 is a photograph of the wound of Example II prior to commencement of treatment in accordance with
20 the present invention;

Figure 18 is a microphotograph of the wound depicted in Figure 17 after complete healing of the wound
25 following 4½ weeks of treatment;

Figure 19 is a photograph of the wound of Example III prior to the start of treatment in accordance with the present invention;

Figure 20 is a photograph depicting the wound of Example III as being fully healed after 7 weeks of treatment in accordance with the present invention;

Figure 21 is a photograph of the wound of Example
5 IV prior to the commencement of treatment in accordance with the present invention;

Figure 22 is a photograph of the wound of Example IV as being fully healed at week 7 following treatment in accordance with the present invention;

10 Figure 23 is a microphotograph of the wound of Example IV and depicted in Figure 21;

Figure 24 is a microphotograph of the wound of Example IV taken in the superficial region of the wound prior to treatment in accordance with the present
15 invention;

Figure 25 is a microphotograph of the wound of Example IV taken in the deep regions of the wound prior to treatment in accordance with the present invention;

Figure 26 is photograph depicting the wound of
20 Example IV after 3 weeks of treatment in accordance with the present invention;

Figure 27 is a microphotograph of the wound depicted in Figure 26;

Figures 28 and 29 are microphotographs depicting
25 the progress of healing of the wound of Example IV;

Figure 30 is a photograph of the wound of Example IV after 5 weeks of treatment in accordance with the present invention;

Figure 31 is a microphotograph of the wound depicted in Figure 30;

Figures 32 and 33 are microphotographs of the wound of Example IV after 5 weeks of treatment in accordance with the present invention and depicting the decrease in MMP expression;

Figure 34 is a photograph of a right let wound of Example V prior to commencement of treatment in accordance with the present invention;

Figure 35 is a photograph showing full healing of the right leg wound of Example V after 8½ months of treatment in accordance with the present invention;

Figure 36 is a photograph of a left leg wound of Example V prior to commencement of treatment in accordance with the present invention;

Figure 37 is a photograph of the left leg wound of Example V after nine months of treatment in accordance with the present invention;

Figure 38 is a pictorial representation of the wound healing process;

Figure 39 is a pictorial representation of the balancing of MMPs within a wound;

Figure 40 is a pictorial representation of ECM generation and degradation in a wound; and,

Figure 41 is a pictorial representation of collagen formation in a wound.

DETAILED DESCRIPTION OF THE INVENTION

[0009] In initial experimentation conducted with rats (partial thickness excision wounds) and Yorkshire pigs (contact burn wounds), the present inventors found that
5 compositions containing the ingredients of the present invention promoted epithelialization,, resulting in a more "normal" epidermis. The wound bed contained less activated macrophages, cells staining positive for acid phosphatase.

[0010] Infliction of deep dermal contact wounds in
10 domestic pig models induce defects which are not fully epithelialized, depending on the treatment applied. Tissue biopsy wounds are deep full thickness skin defects measuring 9 by 2 cm. Such biopsy wounds have a slow tendency to epithelialize. When excision biopsy wounds are
15 filled up with granulation tissue there is a clear visible healing of the wound by contraction. These wounds are ideal test models to get a clear macroscopic impression of the efficacy of test substances applied. Compositions containing the ingredients of the present invention have
20 been found to convert such wounds, which mainly healed by epithelialization starting a couple of days after the first application. Also, such biopsy wounds showed clear epithelialization instead of contraction in comparison with wounds treated with the present compositions.

25 [0011] Employing the domestic pig model, compositions containing the ingredients of the present invention were compounded and tested. These tests showed clear expression of MMP-2 in untreated wounds. Only minimal expression of MMP-2 was observed in comparative wounds treated with a
30 composition containing the ingredients of the present invention.

[0012] The foregoing tests were followed by *in vitro* human studies employing a composition containing the ingredients of the present invention. In these tests, the composition was impregnated onto an ethylene vinylacetate carrier for form an impregnated dressing for the wound site.

[0013] In the present studies, 31 patients were initially involved in the study. Five patients dropped out of the study and eight patients are receiving continuing treatment. Of these patients, the wound(s) of 18 patients were completely healed with an average healing time of 10 weeks. All of the patients in the study responded positively.

[0014] The following specific examples are provided as exemplary of the results observed in the human studies. In each instance, a composition in accordance with the present invention, on an EVOH carrier defining a bandage was applied to the wound site. The bandage was removed at various intervals and replaced with a fresh bandage. A sufficient quantity of the composition of the present invention was placed on the carrier to substantially fully fill the wound cavity.

Example I

Female 74 years of age

History:

Rheumatoid Arthritis.

Medication:

High doses of steroids.

Type wound:

Post traumatic ulcer on lateral lower leg
after infected hematoma.

Duration of Wound

Wound had existed for more than one year prior to
5 commencement of present treatment.

Earlier Treatments

DUODERM

HYDROGEL

Vacuum system

10 Honey and SSD,

[0015] Figure 6 depicts this wound at the time of
commencement of treatment. Prior to entry into the present
study. Figure 7 depicts the healed wound after 30 weeks of
15 treatment. It is noted that after 12 weeks of treatment
with the composition, this patient was treated with
steroids. This action was noted to delay the healing
process and was discontinued. Thus, without the
intervention of the steroid treatment, the healing time for
20 this patient would have been shorter.

[0016] Referring to Figures 8 and 9, at Day One, the
wound of this patient was about 6 cm long and about 2 cm
wide. The wound extended deeply into the leg. A biopsy of
the wound is depicted in Figure 9 wherein a cross-section
25 of the wound is depicted as including Zones A, B and C.
Zone A consists of a broad fibrin layer with necrotic
cellular debris. Zone B is a rather broad zone with
breakdown of matured collagen and inflammation. Zone C is
adjacent the bottom of the wound and depicts a decline of

inflammation at this location. Examination of the Day One biopsy for MMP-2 prior to the treatment showed fibroblasts in the upper layers of the wound to be expressing high levels of MMP-2 (Figure 10). This same biopsy depicted no
5 more than a single fibroblast staining positive for MMP-2 in the deeper layers of the wound. As depicted in Figures 12 and 13, after 14 days of treatment with the composition, all zones are readily identifiable, with the fibrin cap depicting large accumulations of neutrophils. Zone B at
10 this time of treatment is identifiable directly beneath the fibrin cap and shows less old collagen and the appearing of neo-dermis. Figure 13 shows the overall appearance of the wound after 14 days treatment and clearly indicates both a "cleaner" wound and reduction in the overall size of the
15 original wound. Biopsies of the wound after 14 days of treatment showed no clear change in the expression of MMP-2 in Zone B (Figure 14). As shown in Figures 15 and 16, after 6 weeks of treatment, the wound was further decreased in size and healing was progressing. A biopsy of the wound
20 at this time showed that the necrotic cap had vanished and the neo-dermis was healthy. Further, the biopsy the expression of MMP-2 within the wound had declined to near zero, coinciding with the healthy appearance of the neo-dermis.

25 [0017] Between the 6th and 12th weeks of treatment of the present patient, steroid treatment was conducted. At week 12, a biopsy of the wound clearly showed that the fibroblasts began again to express MMP-2. Treatment of the wound using steroids was ceased and the wound fully healed
30 within a total treatment time of 30 weeks as shown in Figure 7.

Example II

Male 75 years of age

History

Decompensation cordis

5 Vascular insufficiency

Diabetes Mellitus

Wound type

Post traumatic

Lacerations

10 Duration of Wound

Wound had existed for weeks

Earlier Treatments

ADAPTIC

SSD (FLAMMAZINE)

15

[0018] Figure 17 depicts the wound of Example II at Day One, prior to the commencement of treatment with the composition. Figure 18 depicts that portion of the arm treated with the composition as being completely healed
20 after 4 ½ weeks of treatment.

Example III

Male 81 years of age

Type of wound

2nd and 3rd degree burns by electricity

25 Duration of wound

Wound had existed 16 days

Earlier Treatments

SSD (FLAMMAZINE)

ELASTO-GEL

- 5 [0019] Figure 19 depicts this wound at Day One of the commencement of treatment of the wound with the composition. Figure 20 depicts the completely healed wound after 7 weeks of treatment.

Example IV

- 10 Male 57 years of age

History

Diabetes Mellitus

Pilonfracture

Osteosynthesis

- 15 Type of wound

Post traumatic ulcer lateral malleolus

Duration of wound

Wound had existed for more than one year

Earlier Treatment

- 20 KALTOSTAT

[0020] Figure 21 depicts the present wound at Day One and prior to commencement of treatment. Figure 22 depicts the completely healed wound at week 7.

- 25 [0021] A biopsy of a cross-section of the wound depicted in Figure 21 is shown in Figure 23. Of note is the fibrous

cap consisting of fibrin and dead cells on top of the wound. Figures 24 and 25 show the expression of MMP-2 being high in the superficial and deep regions of the wound, at Day One.

5 [0022] At week 3 of treatment, the wound showed clear progress in epithelial outgrowth (Figure 26) and reduction in the size of the fibrinous cap (Figure 27). Examination of biopsies of the wound at week 3 further showed an increase in fibroblast and blood vessels (Figure 28) and
10 diminished MMP-2 expression in the fibroblast (see also Figure 29).

[0023] At week 5, the wound was almost fully closed and the fibrinous cap had further diminished (Figures 30 and 31). Biopsies of the wound at week 5 showed slightly more
15 active stellate fibroblasts, an increase in inflammation and a decrease of MMP-2 expression. (Figures 32 and 33).

[0024] As noted, complete healing of the wound occurred after only 7 weeks of treatment.

Example V

20 Female 76 years of age

History

Rheumatoid arthritis

Morbus Reynaud

Lumbal sympatechtomy

25 Amputation of first digit

Venous insufficiency

Type of Wound

Leg ulcer right medial ulcer

Leg ulcer left medial ulcus

Duration of wound

Wounds had existed for more than 4 years
(open/healed)

5 Earlier Treatment

SSD (FLAMMAZINE)

BIATIN foam

Compression bandage

[0025] Figures 35 and 36 depict the two wounds involved
10 in Example V. Figures 35 and 37 depict the same two wounds
after fully healed. Full healing of the wound of Figure 34
was effected after 8 ½ months of treatment, and full
healing of the wound of Figure 36 was effected after 9
months of treatment.

15 [0026] In one embodiment, the composition of the present
invention includes zinc ions, rubidium ions, potassium
ions, and calcium ions.

[0027] Solutions including various of the above-listed
ingredients were prepared as follows:

20 Composition I

potassium citrate	0.895 moles/l
rubidium chloride	3.1 millimoles/l
zinc chloride	64 micromoles/l
citric acid	(sufficient to adjust 25 the pH of the solution to 5.5)

Composition II

	potassium citrate	0.895 moles/l
	rubidium chloride	3.1 millimoles/l
	zinc chloride	64 micromoles/l
5	calcium chloride	0.2 millimoles/l
	citric acid	(sufficient to adjust the pH of the solution to 5.5)

10 Composition III

	potassium hydroxide	0.895 moles/l
	rubidium chloride	3.1 millimoles/l
	zinc chloride	64 micromoles/l
15	citric acid	(sufficient to adjust the pH of the solution to 5.5)

Composition IV

	potassium hydroxide	0.895 moles/l
	rubidium chloride	3.1 millimoles/l
20	zinc chloride	64 micromoles/l
	calcium chloride	0.2 millimoles/l
	citric acid	(sufficient to adjust the pH of the solution to 5.5)

25 [0028] Preferably, pharmaceutical grade ingredients are employed in each composition of the present invention.

[0029] Compositions I and III were subjected to chemiluminescence assay (indicative of inhibition of production of reactive oxygen species, complement assay (classical pathway, indicative of complement activity).

5 These compositions of the present invention exhibited IC-50 values as follows:

TABLE A

		Chemiluminescence	Complement
		Assay	Assay
10	Example I	10 μ l/ml	9 μ l/ml
	Example II	36 μ l/ml	28 μ l/ml

[0030] Composition II which included potassium hydroxide required a greater amount of citric acid to produce a pH of 5.0, indicating that the potassium citrate employed in

15 Example I was more active, hence the lower IC-50 values exhibited by Composition I. In any event the complement assay results clearly show the effectiveness of the present composition in the modulation of MMPs found in chronic wounds such as diabetic ulcers, decubitus ulcers, and other

20 wounds.

[0031] In one embodiment, the composition of the present invention may be incorporated into a pharmaceutically acceptable carrier such as WHITFIELD'S ointment or other suitable cr  me.

25 [0032] A composition of the present invention, preferably in a cr  me-type carrier, may be applied directly to an open wound or the like or through the use of a gauze bandage to which the composition is applied.

[0033] A preferred composition for use in the treatment of various open wounds comprises 0.895 moles/l potassium citrate, 3.1 millimoles rubidium chloride, 0.2 millimoles/l calcium chloride and 64 micromoles zinc chloride in a solution employing distilled water. The solution is acidified to pH 5.0 employing citric acid.

[0034] Whereas the compositions of the present invention function to scavenge superoxide anions, addition of other pharmaceutically acceptable scavengers of superoxide anions may be employed. Naturally occurring polyether or caffeic acid may be beneficial in the treatment of wounds, particularly burn wounds. Such additives may reduce the chemiluminescence and/or DPPH assay (anti-oxidant activity by donating electrons or hydrogen) values of the composition into the microgram range.

[0035] The preferred composition of the present invention may be modified by eliminating calcium ions, but with some reduction in the efficacy of the composition in treating at least certain wounds. As noted, substitution of potassium hydroxide for potassium citrate in the present composition is permissible, but not preferred, due to the increased need for acid to adjust the pH of the solution to 5.0. Though present in a relatively small amount, the presence of zinc ions in the solution appear to be important to the desired level of effectiveness of the present composition. This same factor appears true for rubidium ions. Whereas the sources of the inorganic ions of the present composition are given herein, it is to be recognized that other sources of these ions may be acceptable for given applications of the composition. Initial tests have indicated that the quantity of the

several inorganic ions in the composition may be varied from the preferred composition without destruction of, but with possible reduction of, the wound healing efficacy of the composition. In all instances, preferably, the pH of the solution is adjusted to substantially 5.0 thereby imparting desirable buffering properties to the composition.

[0036] In any event, the active ingredients of the present composition have been found to include zinc, potassium, rubidium and/or calcium. Calcium does not appear to be critical to the desired healing process, it does not appear to be detrimental when included in the present composition, and in certain instances is considered desirable. On the other hand, zinc appears to be essential to the healing qualities of the present composition, and rubidium is also strongly indicated for those compositions employed in cancer, ulcer and others of those maladies for which the present compositions have been found useful as healing agents.

[0037] Citric acid, preferably, when included in the present composition for pH control purposes has been found effective in such role. Other acids for normalizing the pH of present solution, for example hydrochloric acid, may be employed.

[0038] Polyethylene glycol has been found particularly effective as a component of the present solution, in part due to its oxygen scavenging properties.

[0039] In one embodiment of the present invention, a channeling agent, such as monoxidil, has been found to be effective in lieu of the potassium ions.

[0040] Whereas the compositions of the present invention may include other inactive ingredients which are biologically relatively inert or inactive relative to the healing process of a wound, the present inventors have
5 found that the absence of ions of zinc, potassium, rubidium and calcium (in certain compositions) are essential to obtaining the aforementioned dramatic results of wound healing.

[0041] During wound repair, different MMPs are produced by multiple cell types. MMP-2 is produced only by
10 inflammatory cells. MMP-9 is produced by keratinocytes as well as inflammatory cells. MMP-2 and MMP-9 act on cleaved collagen better than other MMPs. MMPs are not actively expressed in uninjured skin either in the epidermis or dermis. The idea exists that MMPs are stored in the matrix
15 awaiting activation by migrating cells. Inflamed tissues in chronic wounds exhibit excessively high MMP levels in comparison to normal healing wounds, the excess being in the range of 30% greater MMP levels in chronic wounds.

[0042] In accordance with one aspect of the present
20 invention, the compositions of the present invention exhibit those properties which are known to increase tissue regeneration of chronic open wounds, providing full wound closure of demonstrated non-responding or slow-healing wounds.

25 [0043] At a first level, compositions of the present invention clearly modulate the expression of one or more MMPs, particularly MMP-2 and MMP-9, thereby reducing the levels of these MMPs in chronic wounds to normalize wound healing. At second and further levels, compositions of the
30 present invention function to scavenge oxygen radicals from wound sites, normalizing the pH levels within a wound and

thereby developing an environment within the wound which is favorable to healing. Still further, the compositions also can reduce inflammation, scavenge free oxygen radicals, reduce scar tissue, and act as a powerful antimicrobial.

5 [0044] Dermal wound healing is recognized as a complex, but orderly process which takes place in injured tissue. Subsequently the injured tissue respond with inflammation, granulation tissue formation, extracellular matrix (ECM) deposition, contraction and remodeling of the deposited
10 collagen. This process is depicted in Figure 37. The present inventors have found that remodeling results when there is a balance between ECM-synthesis and ECM-degradation. Many different circumstances can influence these processes thus shifting the balance toward a state of
15 excess or shortage of ECM, thereby inhibiting the remodeling process (See Figure 38). As seen in Figure 39, fibroblast synthesis of collagen, the major constituent of the dermal tissue, is stimulated by growth factors and cytokines. Soluble pro-collagen peptides are released in
20 the environment of the fibroblasts. Pro-collagen peptidase cleaves of the terminal peptide chains allow true collagen fibrils to form. Lysyl-oxidase promotes the cross-linking of these fibrils rendering structural stability to the matrix. In the ECM, several types of collagen can be
25 recognized, along with other substances which contribute to the ECM.

[0045] The production of MMPs, enzymes that serve to degrade collagen, are also under the influence of growth factors. Stimulating and inhibition factors result I the
30 release of pro-metalloproteinases. These pro-forms are activated by plasmin. Activated metalloproteinases are

quickly deactivated by Tissue Inhibitors of metalloproteinases (TIMPs) so that the spatial action of the proteolytic enzyme is limited. The main action of the MMPs is to degrade the collagen. It has to be borne in mind that this scheme is likely to be an oversimplification of what is happening *in vivo*. For example, (a) plasmin release from plasminogen is regulated by the action of plasminogen activator (PA) and plasminogen Activator Inhibitor (PAI) both of which are also produced by fibroblasts under the influence of growth factors and cytokines; (b) Metalloproteinases can also be activated by other substances as HOCL- from the oxidative burst of granulocytes ($H_2O_2 + MPO + Cl^- \rightarrow HOCl-$ which is strongly anti-bacterial); (c) metalloproteinases can also be activated by other than TIMP, for instance alpha2-Macroglobulin (anti-protease in serum); and/or (d) metalloproteinases can cleave other molecules than collagen for instance other ECM molecules by cleavage capacity can perhaps also lead to activation of the complement system (C5a and C3A).

[0046] Very little appears to be known about the distribution of MMPs in time. It is known that normal skin shows basic levels of MMP-2, but shows no MMP-9 expression. The present inventors have shown elevated levels of MMPs in chronic wounds.

[0047] Irrespective of the complexity of the wound healing mechanism, the present inventors have discovered a combination of metal ions which in solution, preferably substantially at a pH of 5.0, when applied over time to a chronic or other dermal wound, dramatically enhances the healing of the wound. The composition of the present

invention is further indicated in the treatment of cancers, psoriasis, and a variety of skin infections, burns, and/or lesions.

WHAT IS CLAIMED:

Claim 1. A composition for enhancing the healing of chronic open wounds comprising a mixture of pharmaceutically effective amounts of each of ions of zinc and rubidium in a physiologically inert carrier.

Claim 2. The composition of Claim 1 and including a pharmaceutically effective amount of ions of calcium.

Claim 3. The composition of Claim 1 and including a pharmaceutically effective amount of ions of potassium.

Claim 4. The composition of Claim 2 and including a pharmaceutically effective amount of ions of potassium.

Claim 5. The composition of Claim 1 and including an acid suitable for adjusting the pH of the composition.

Claim 6. The composition of Claim 5 wherein said acid is citric acid.

Claim 7. The composition of Claim 1 wherein said composition includes polyethylene glycol.

Claim 8. The composition of Claim 1 and including a pharmaceutically effective amount of a channeling agent.

Claim 9. A composition for enhancing the healing of chronic open wounds comprising a mixture of pharmaceutically effective of each of ions of zinc and rubidium, and in a physiologically inert carrier, said mixture have a substantially neutral pH.

Claim 10. The composition of Claim 9 wherein said carrier comprises polyethylene glycol.

Claim 11. The composition of Claim 9 and including a pharmaceutically effective amount of ions of calcium.

Claim 12. The composition of Claim 9 and including a pharmaceutically effective amount of a channeling agent.

Claim 13. A composition for demodulating matrix metalloproteinases 2 and/or 9 associated with a wound comprising a pharmaceutically effective amount of a solution containing ions of zinc and rubidium.

Claim 14. The composition of Claim 12 and including a pharmaceutically effective amount of a channeling agent.

Claim 15. The composition of Claim 12 and including a pharmaceutically effective amount of ions of potassium.

Claim 16. The composition of Claim 12 and including a pharmaceutically effective amount of ions of calcium.

Claim 17. The composition of Claim 12 and including a pharmaceutically effective amount of each of ions of potassium and calcium.

Claim 18. The composition of Claim 12 and including polyethylene glycol.

Claim 19. The composition of Claim 12 wherein said composition exhibits a pH of substantially 5.0.

Claim 20. A method of treatment of an open chronic wound comprising introducing into the wound a pharmaceutically effective quantity of a solution containing therapeutically effective quantities of ions of zinc and rubidium and having a substantially neutral pH.

Claim 21. The method of Claim 20 wherein said mixture includes a pharmaceutically acceptable carrier.

Claim 22. The method of Claim 20 wherein said solution includes a pharmaceutically effective amount of an oxygen scavenging agent.

Claim 23. The method of Claim 20 and including a pharmaceutically effective amount of a channeling agent.

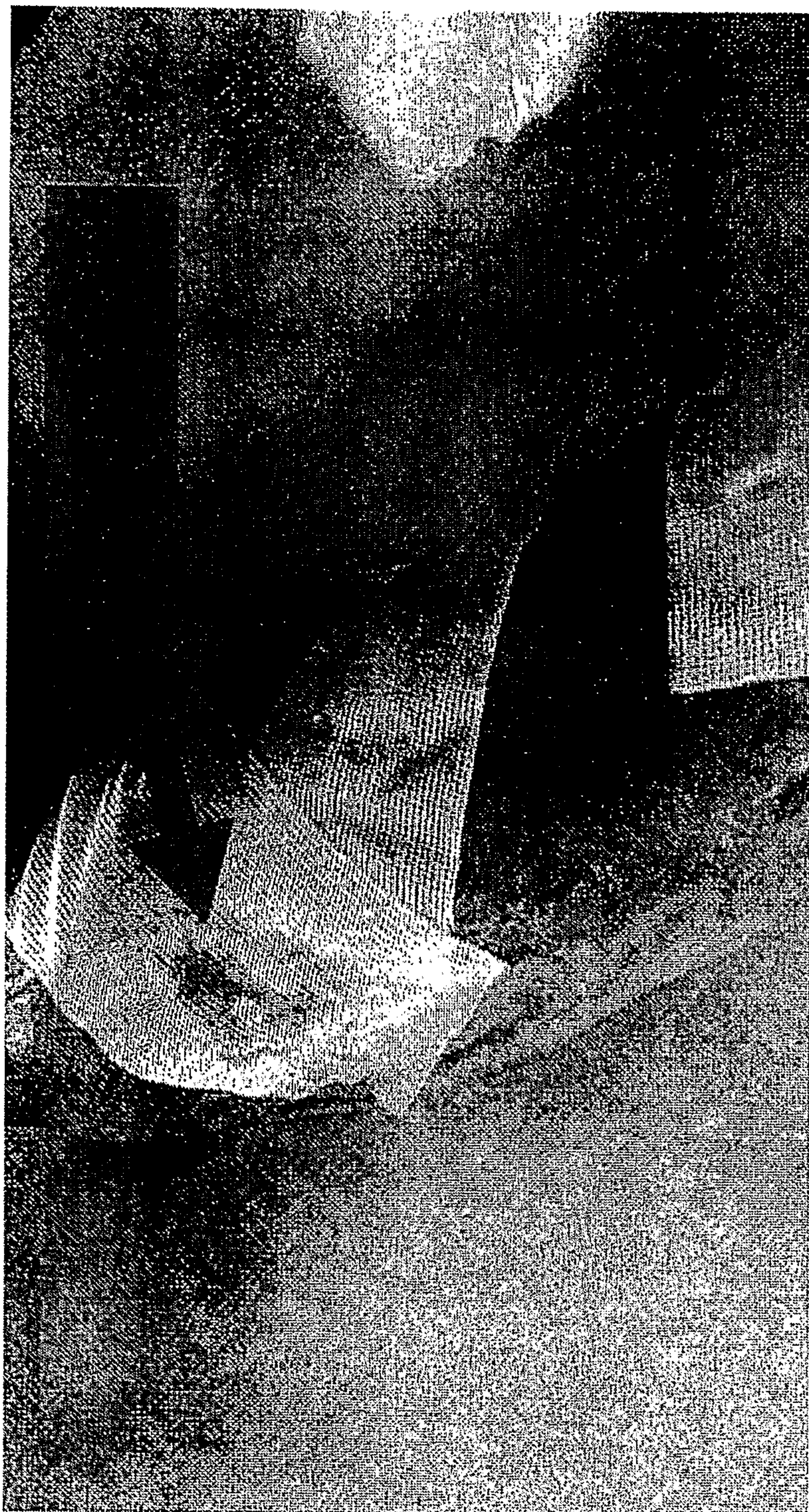


Fig 1

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Non-responding wounds



FIG 3



FIG 5



FIG 2



FIG 4

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Fig 7



Fig 6

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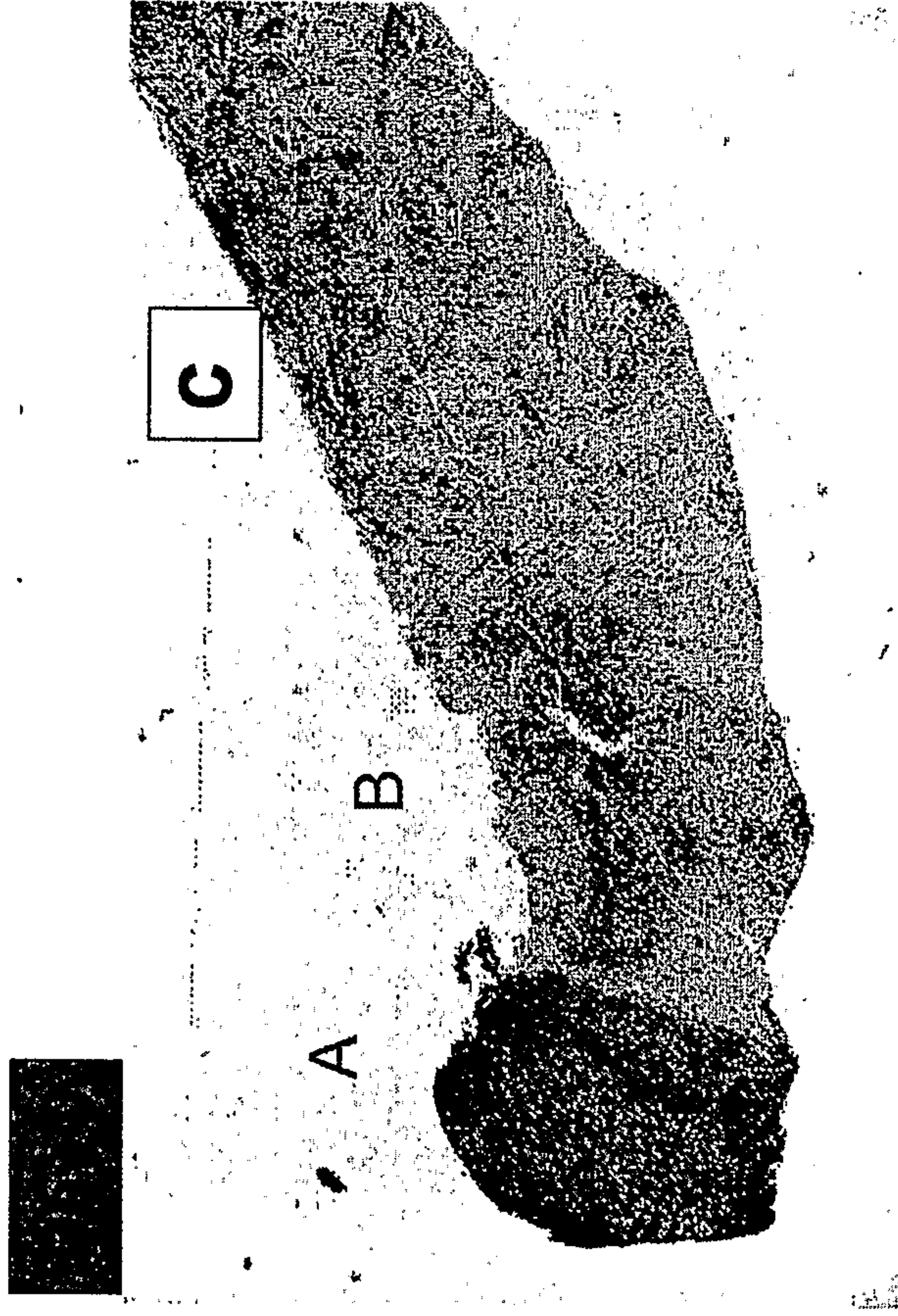


FIG 9

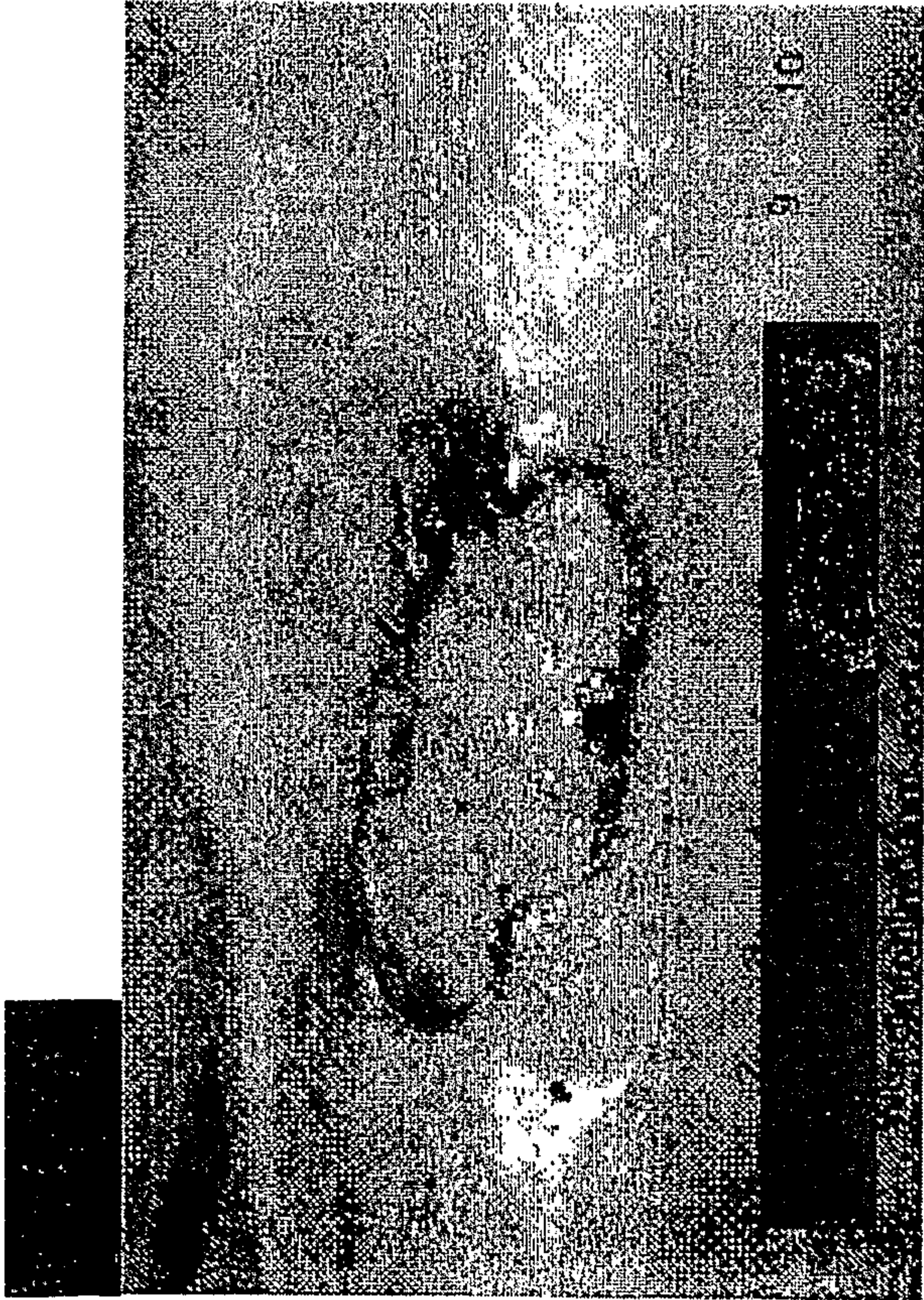


FIG 8

Top end consists of a broad fibrin layer with necrotic
cellular debris (A)

Adjacent there is a rather broad zone with breakdown of
matured collagen and inflammation (B)

Toward the bottom the inflammation declines (C)

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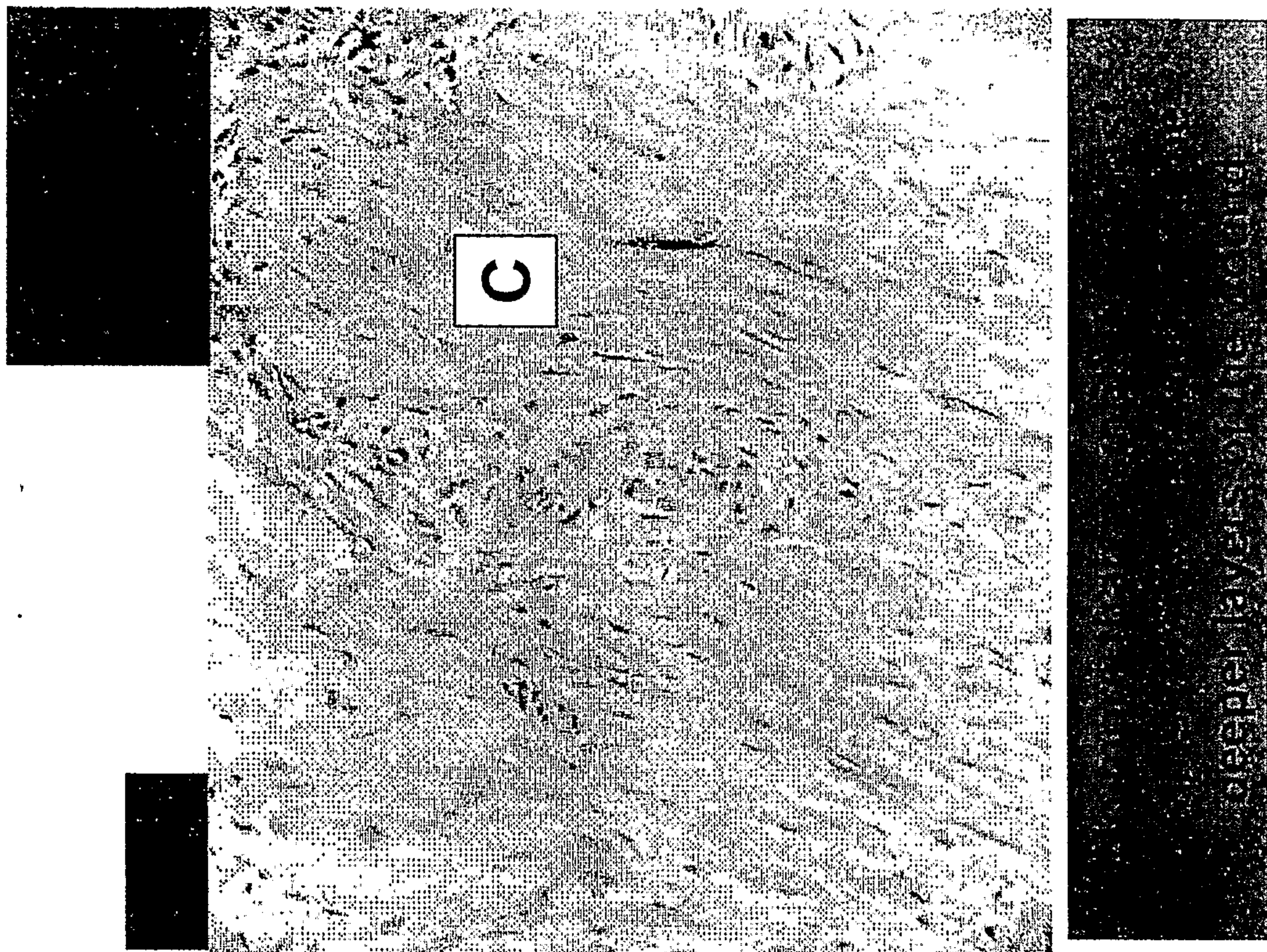


Fig 11

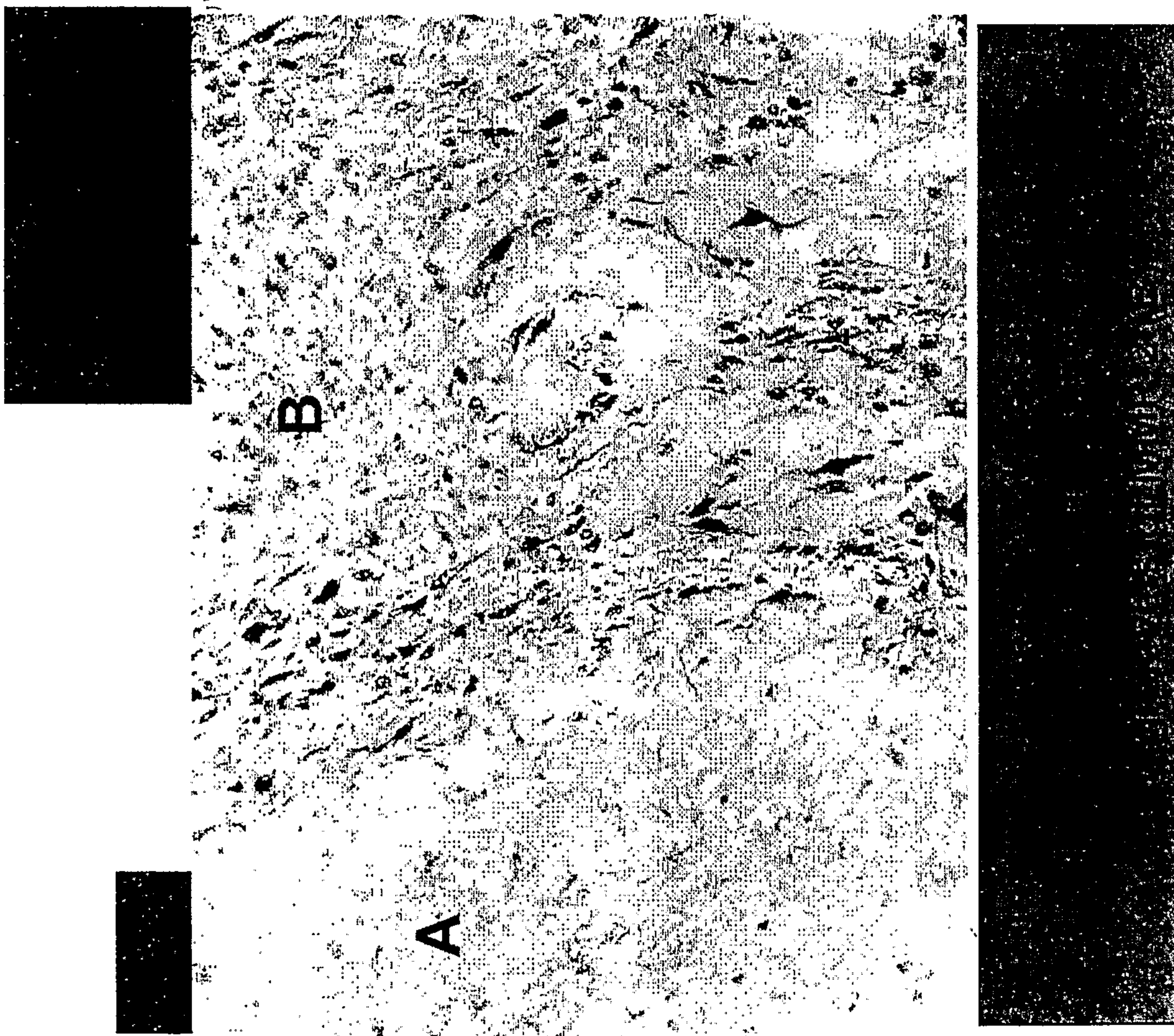


Fig 10

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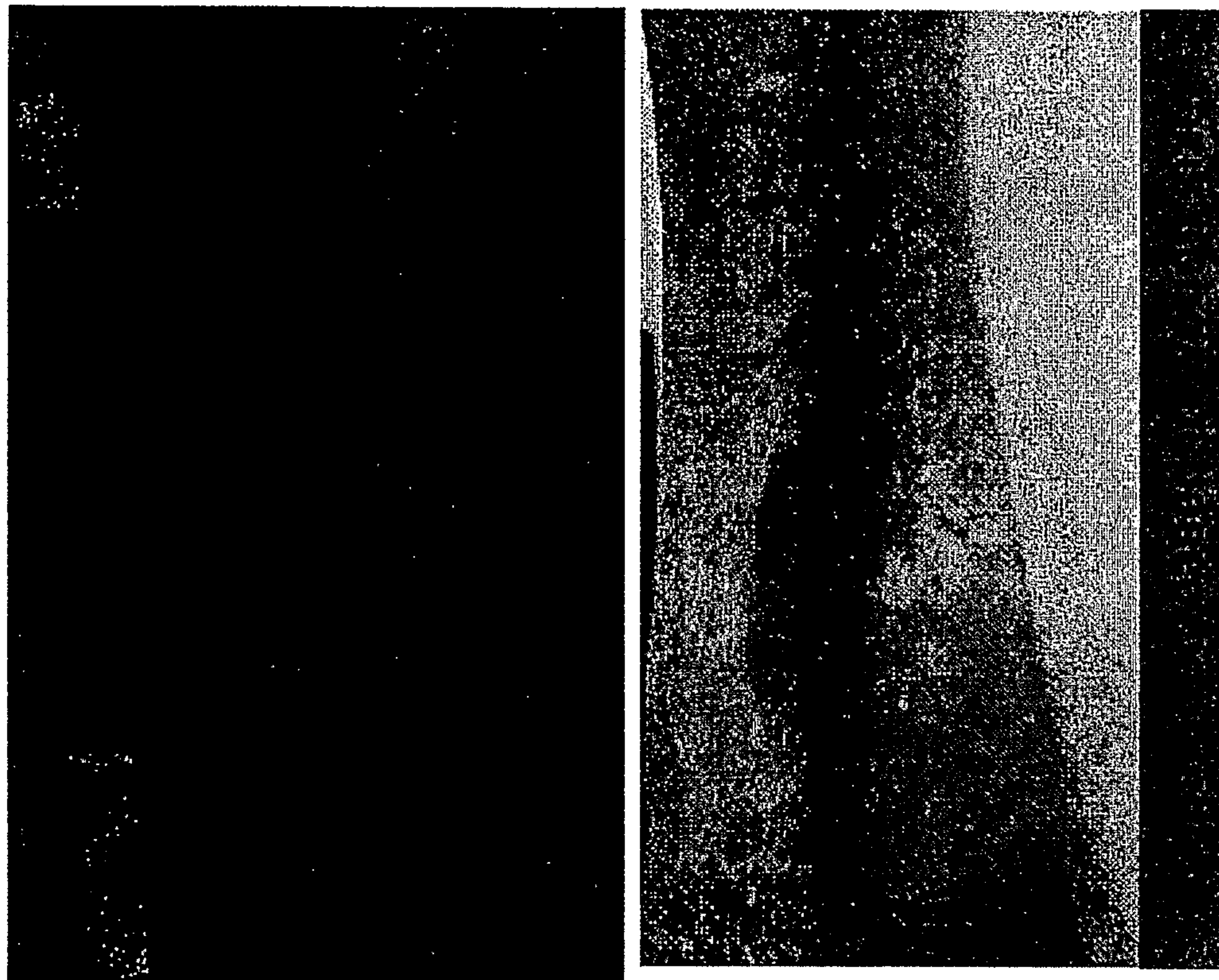
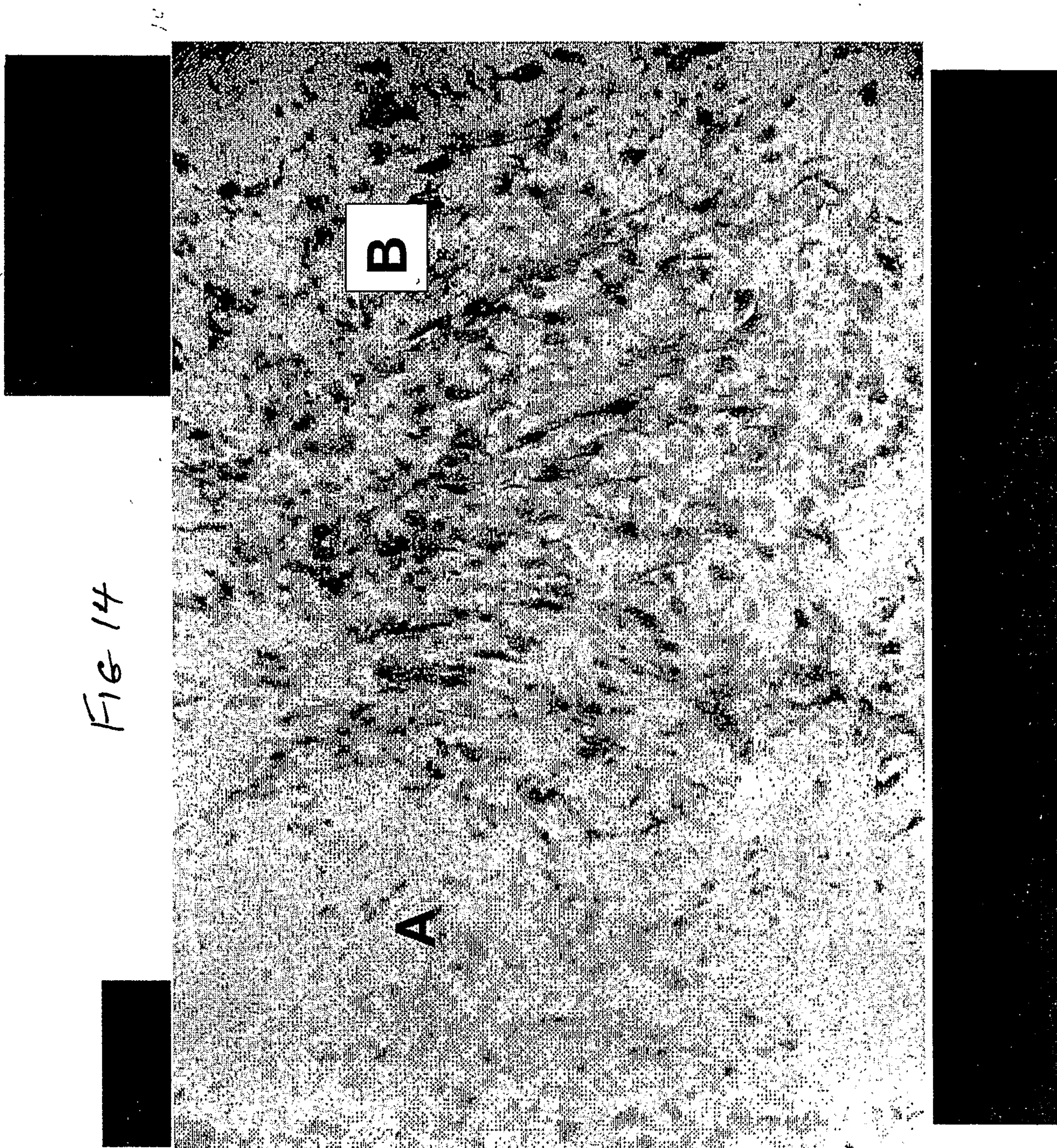


FIG 13



FIG 12

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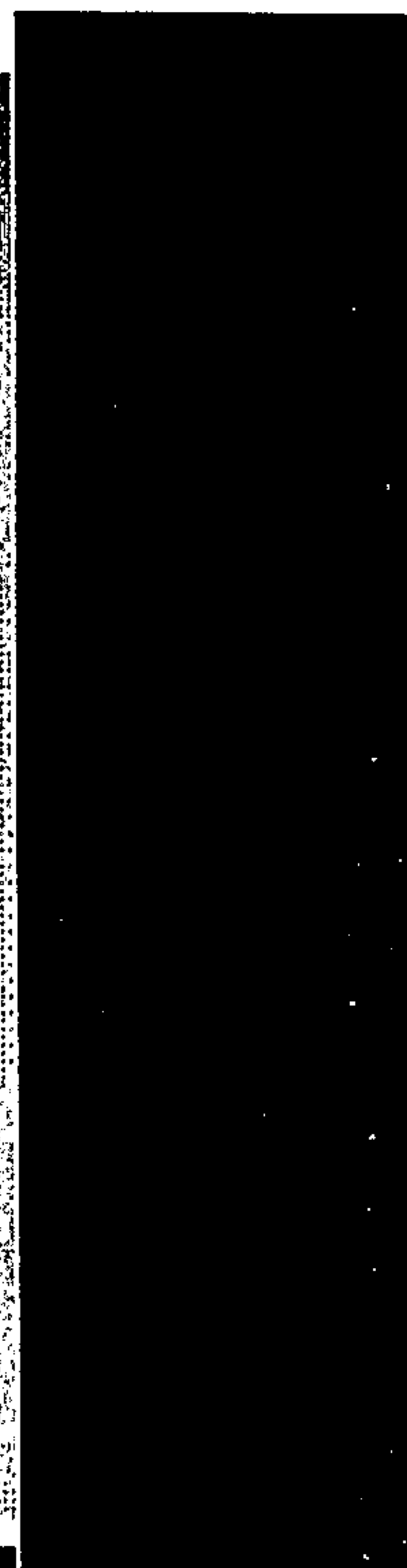
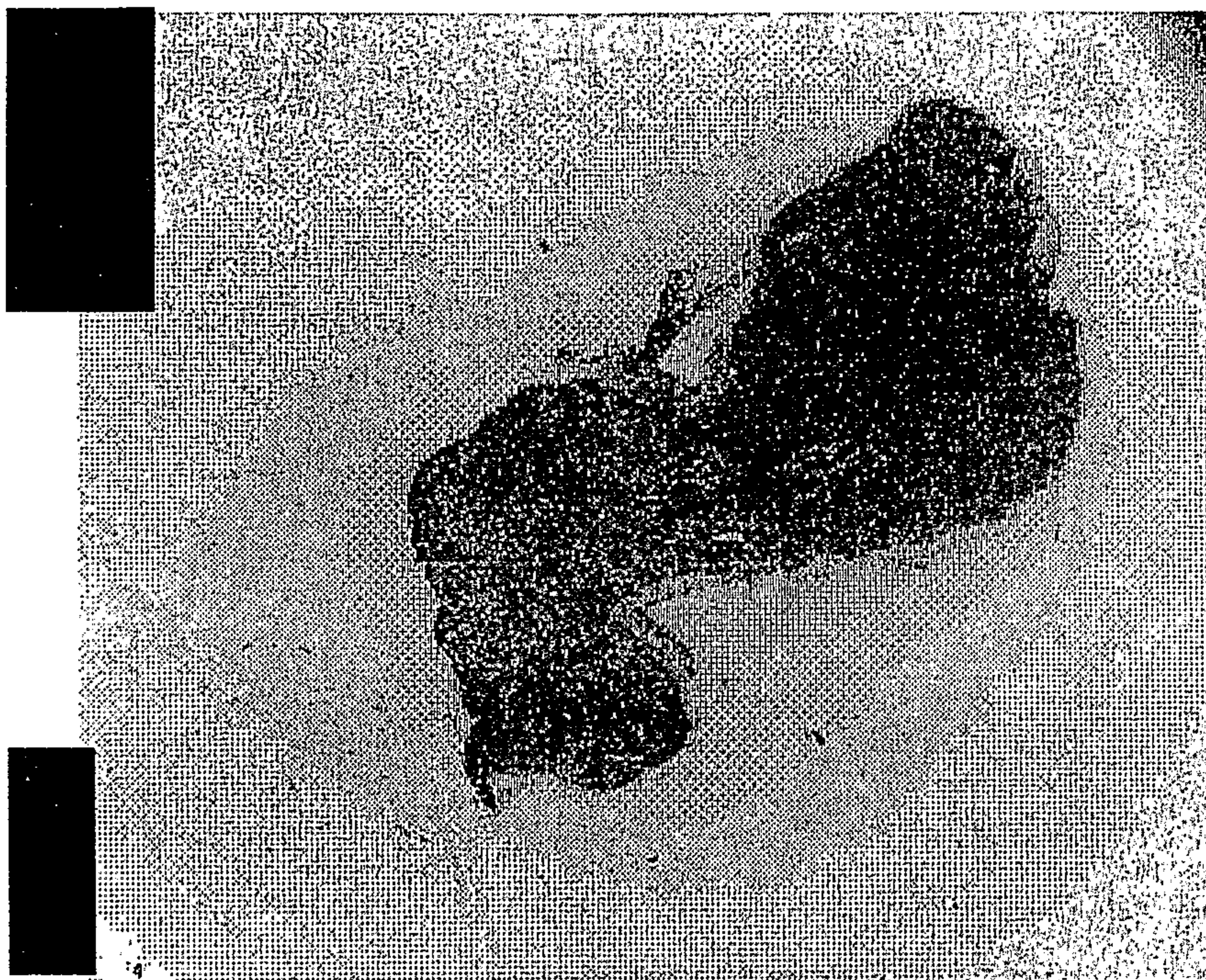


Fig 16

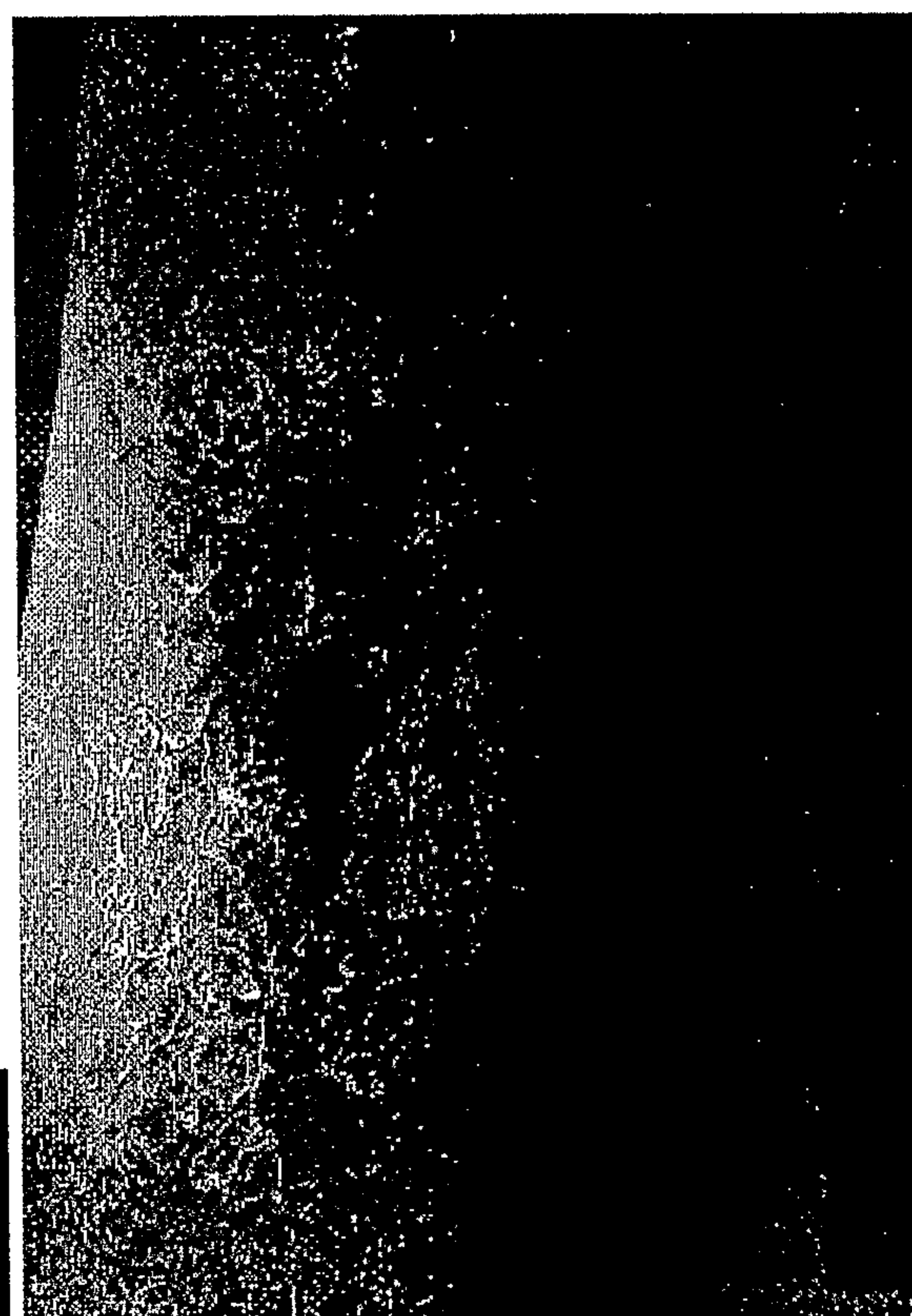


Fig 15

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Fig 17

Male, 75 year

History:

- Vascular insufficiency
- Decompensation cordis
- Diabetes mellitus

Medication:

- Cortisone usage

Type wound:

- Post traumatic
- Lacerations

Duration ulcer:

- 2 weeks

Earlier treatments:

- SSD (Flammazine)
- Adaptic



Fig 18

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Male, 81 year

FIG 19

Type wound:

- 2nd / 3rd Degree burns by electricity

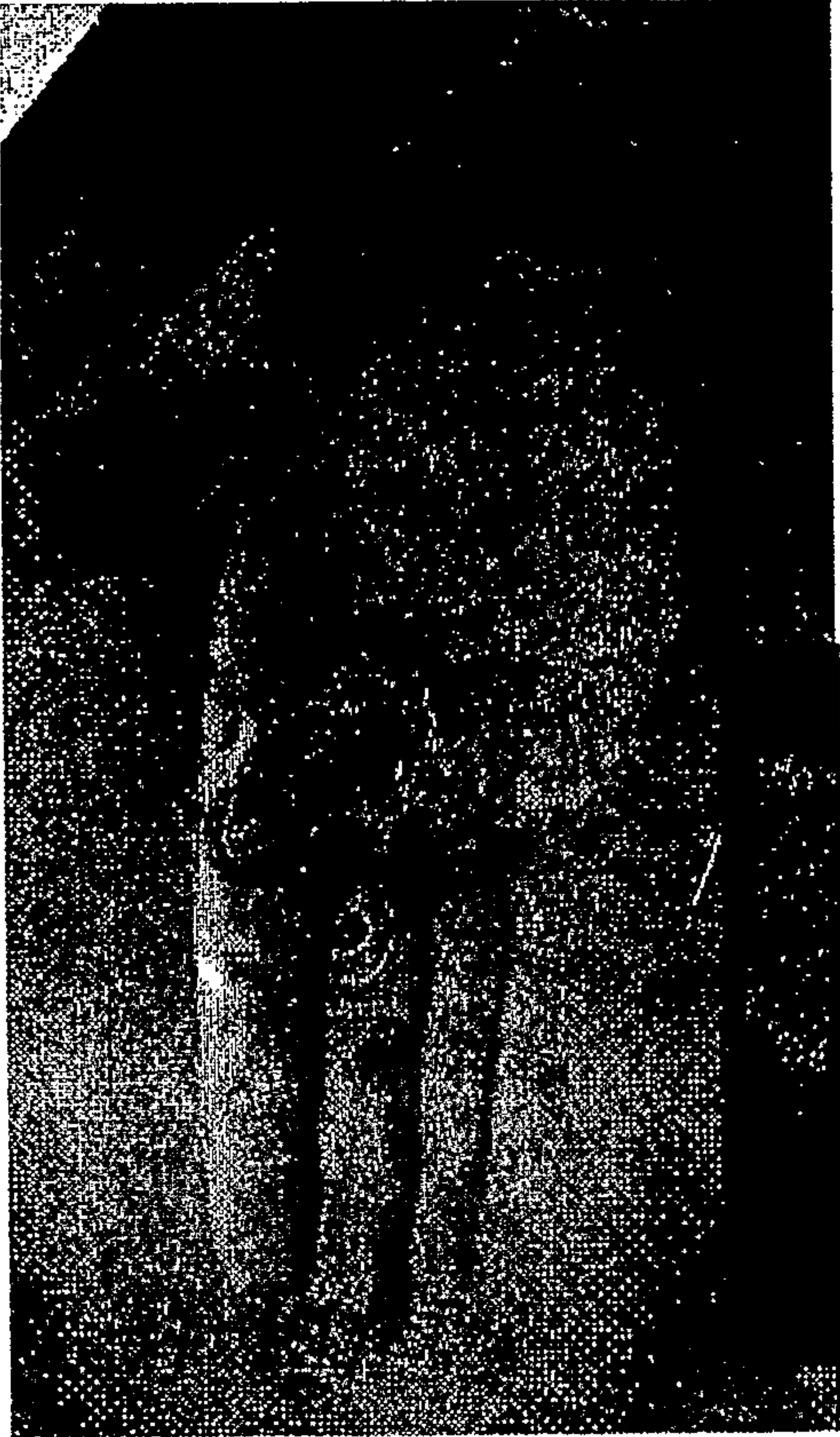
Duration burns:

- 16 days

Earlier treatments:

- SSD (Flammazine)
- Elasto-Gel

FIG 20



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Fig 22

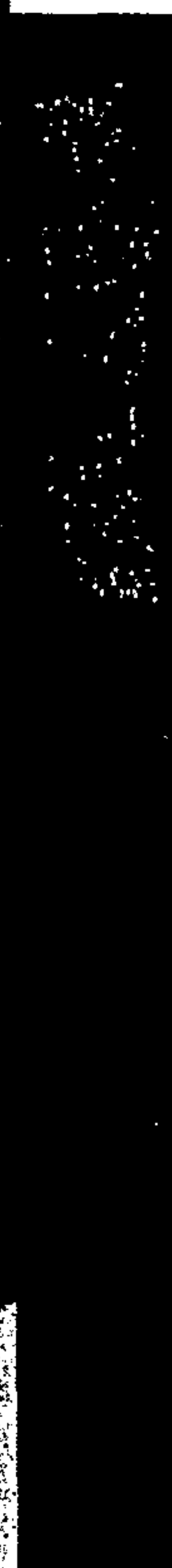
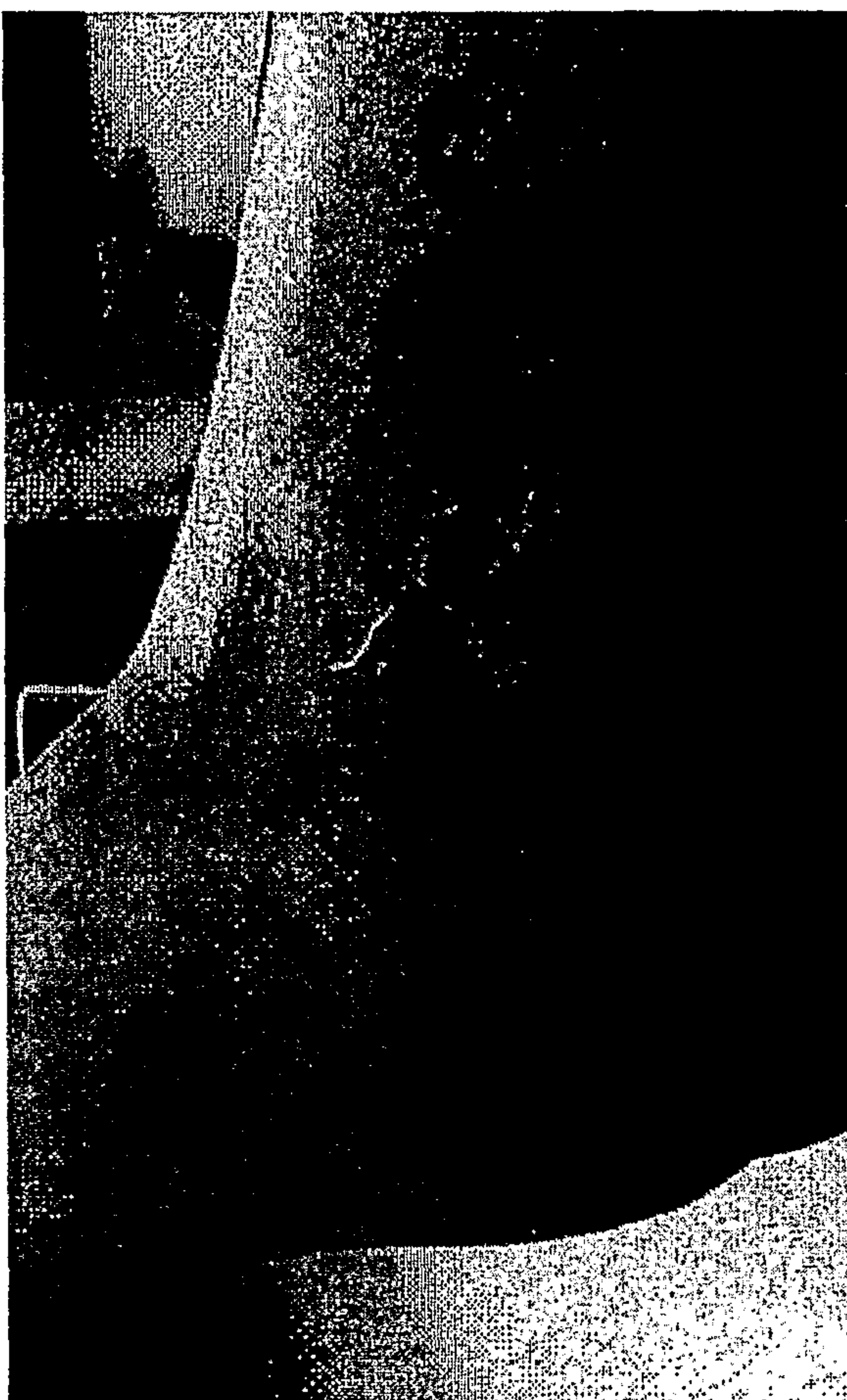


Fig 21

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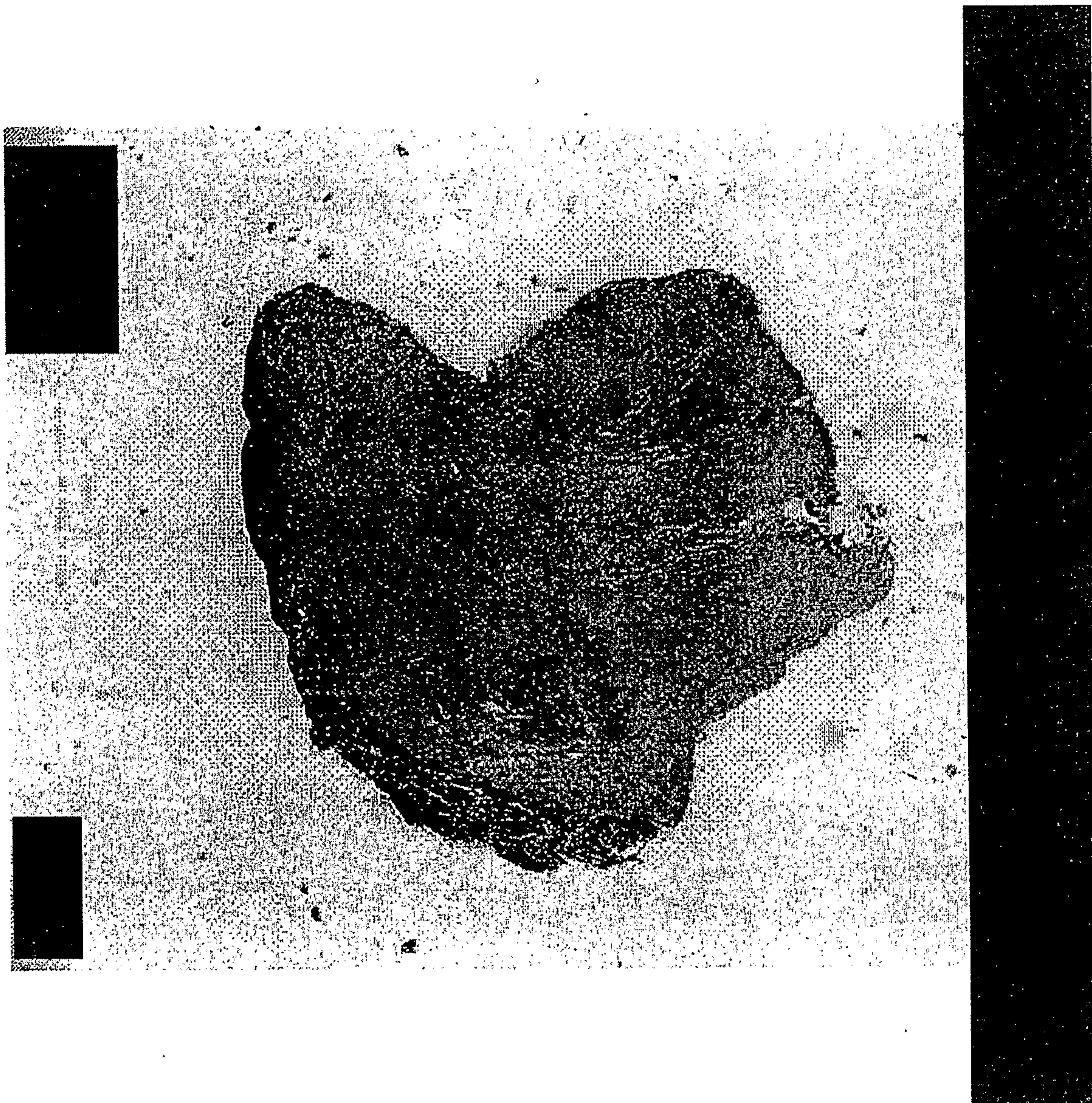


Fig 23

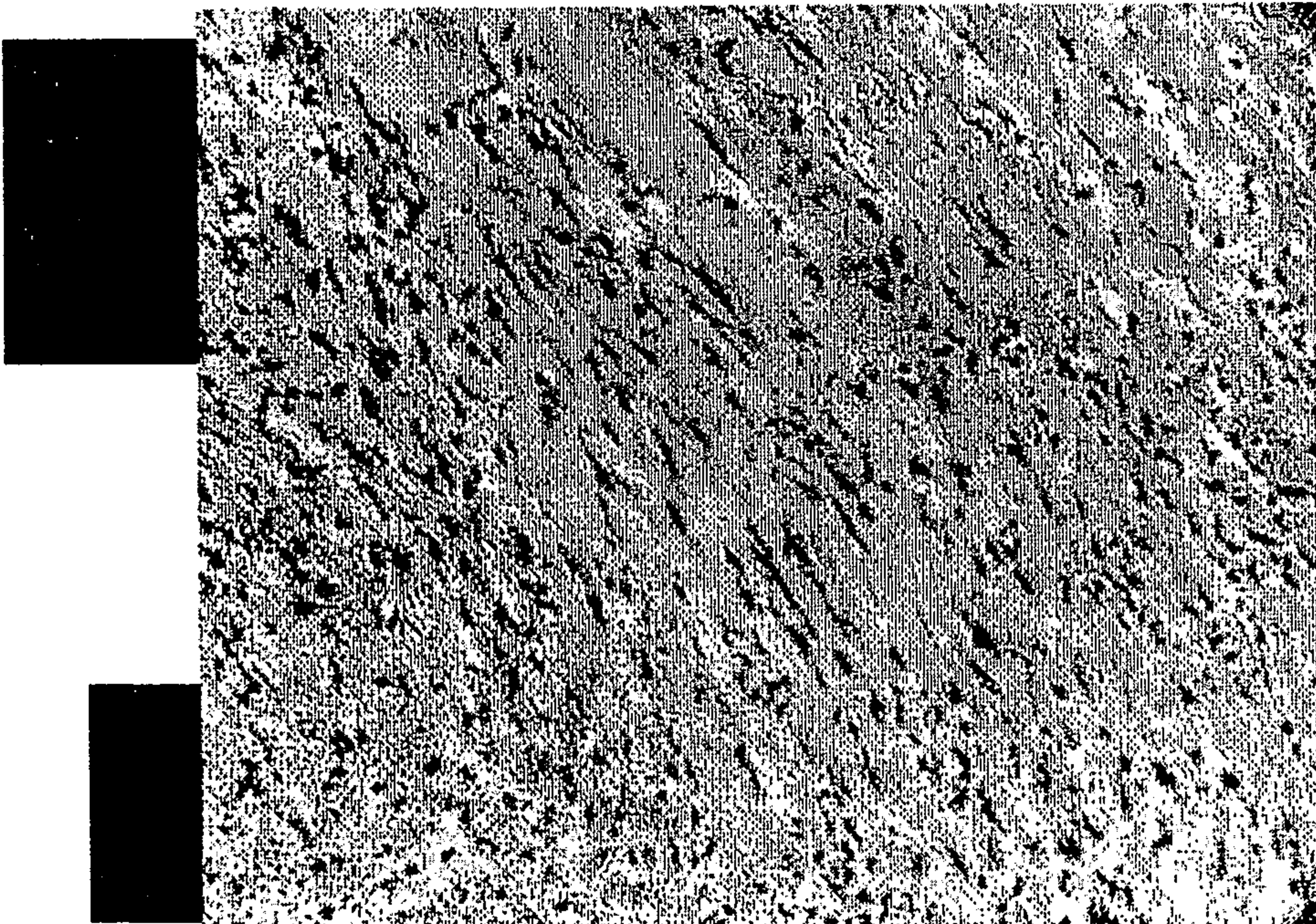
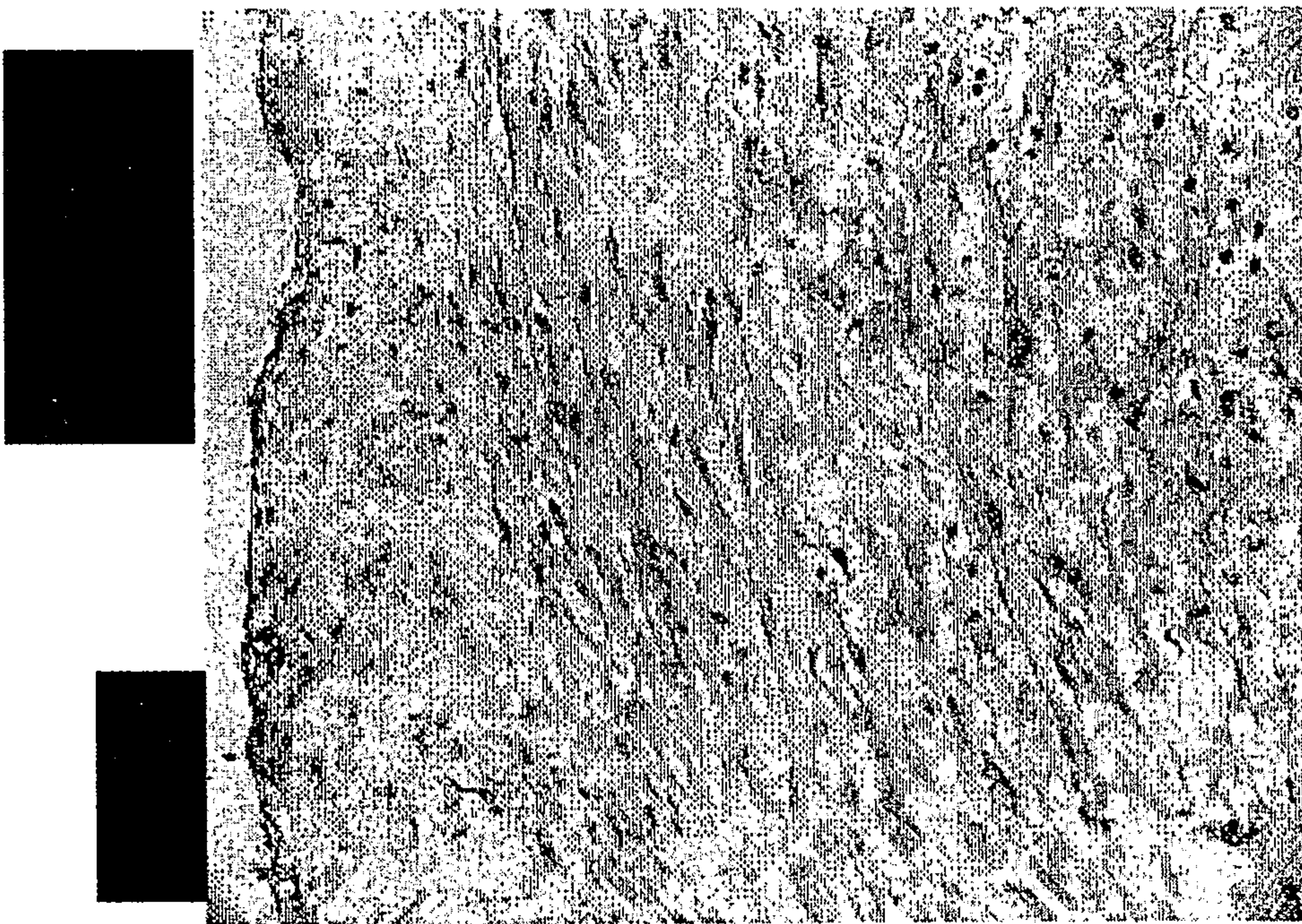


Fig 23-

Fig 24

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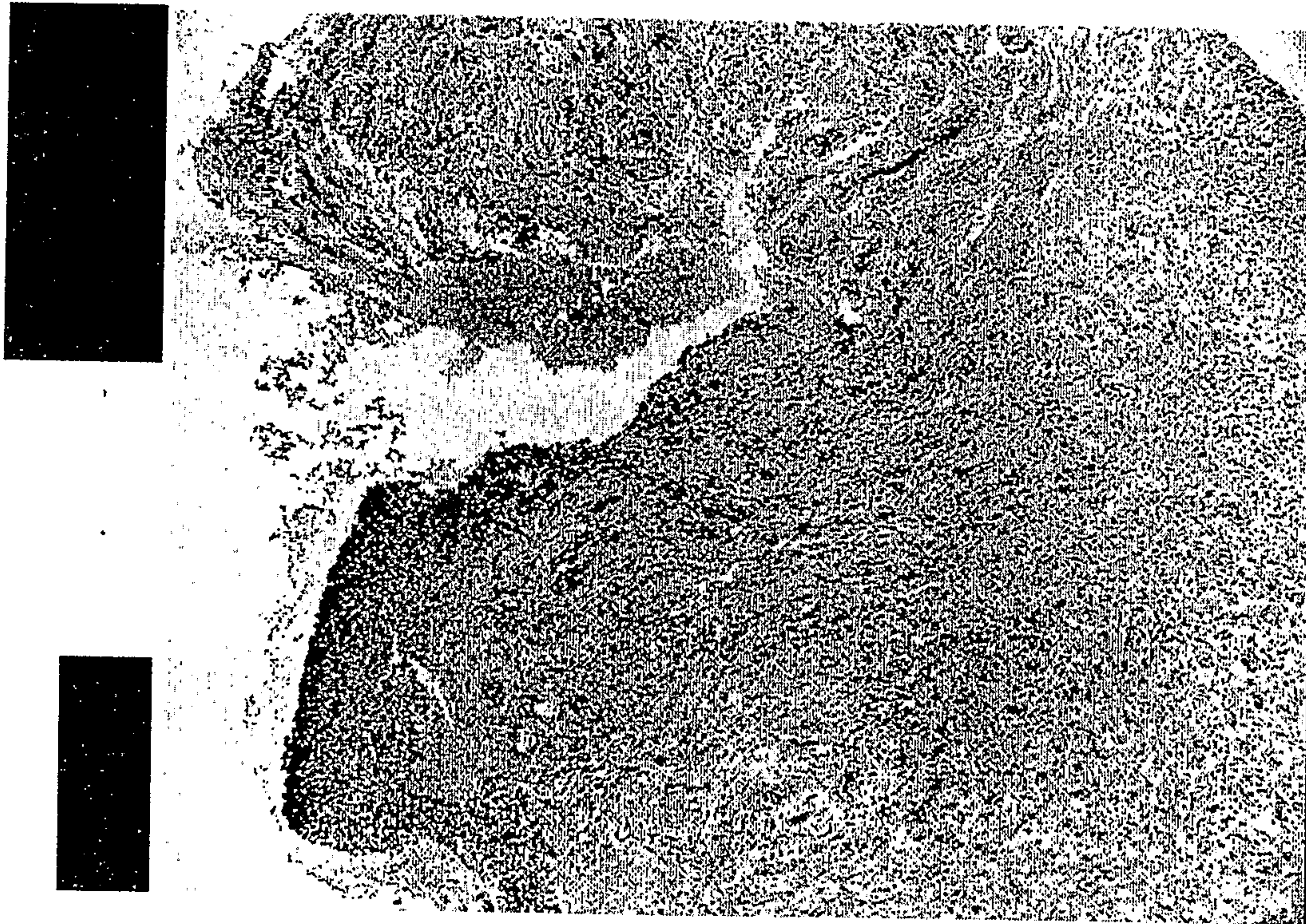


Fig 27



Fig 26

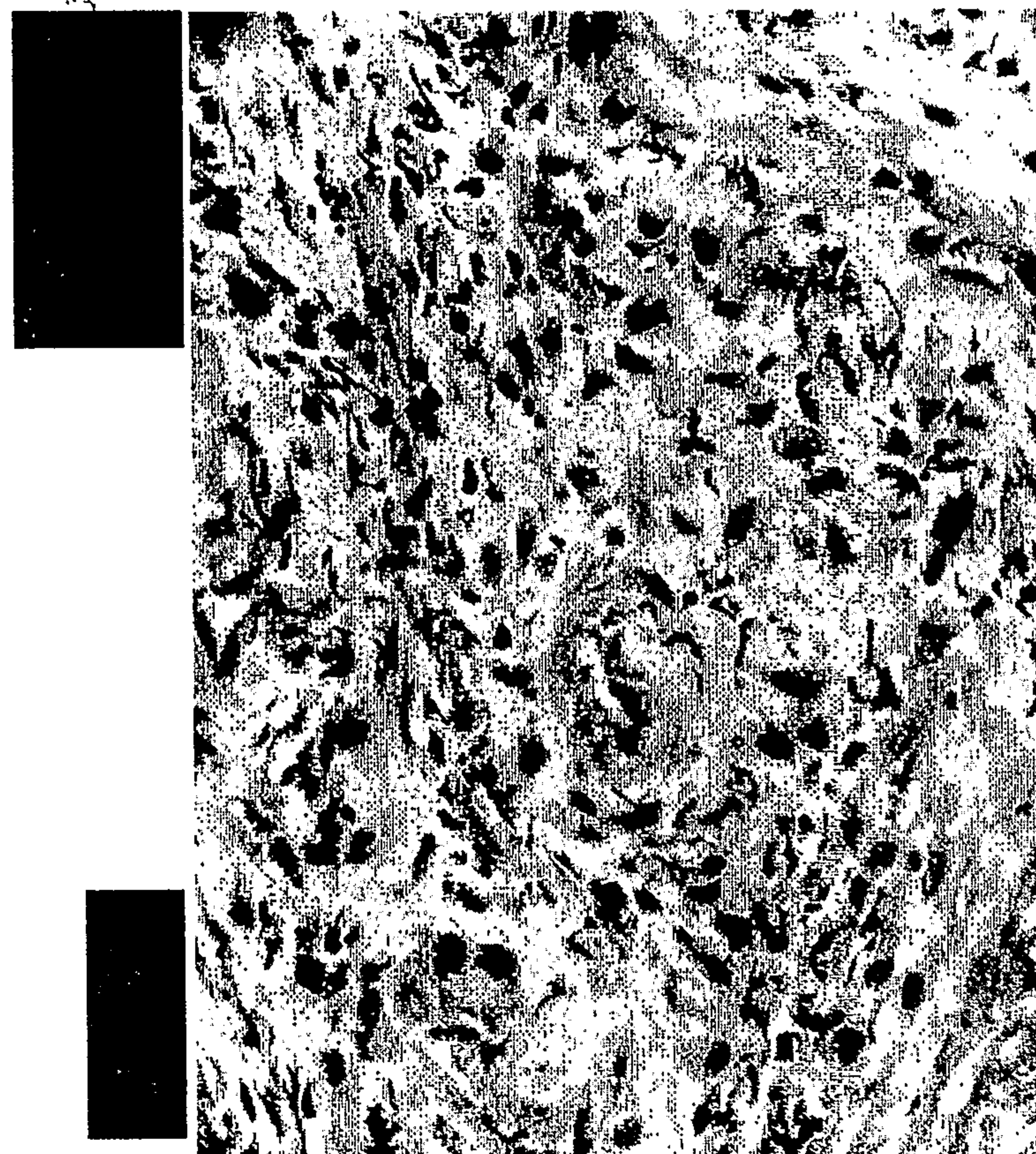
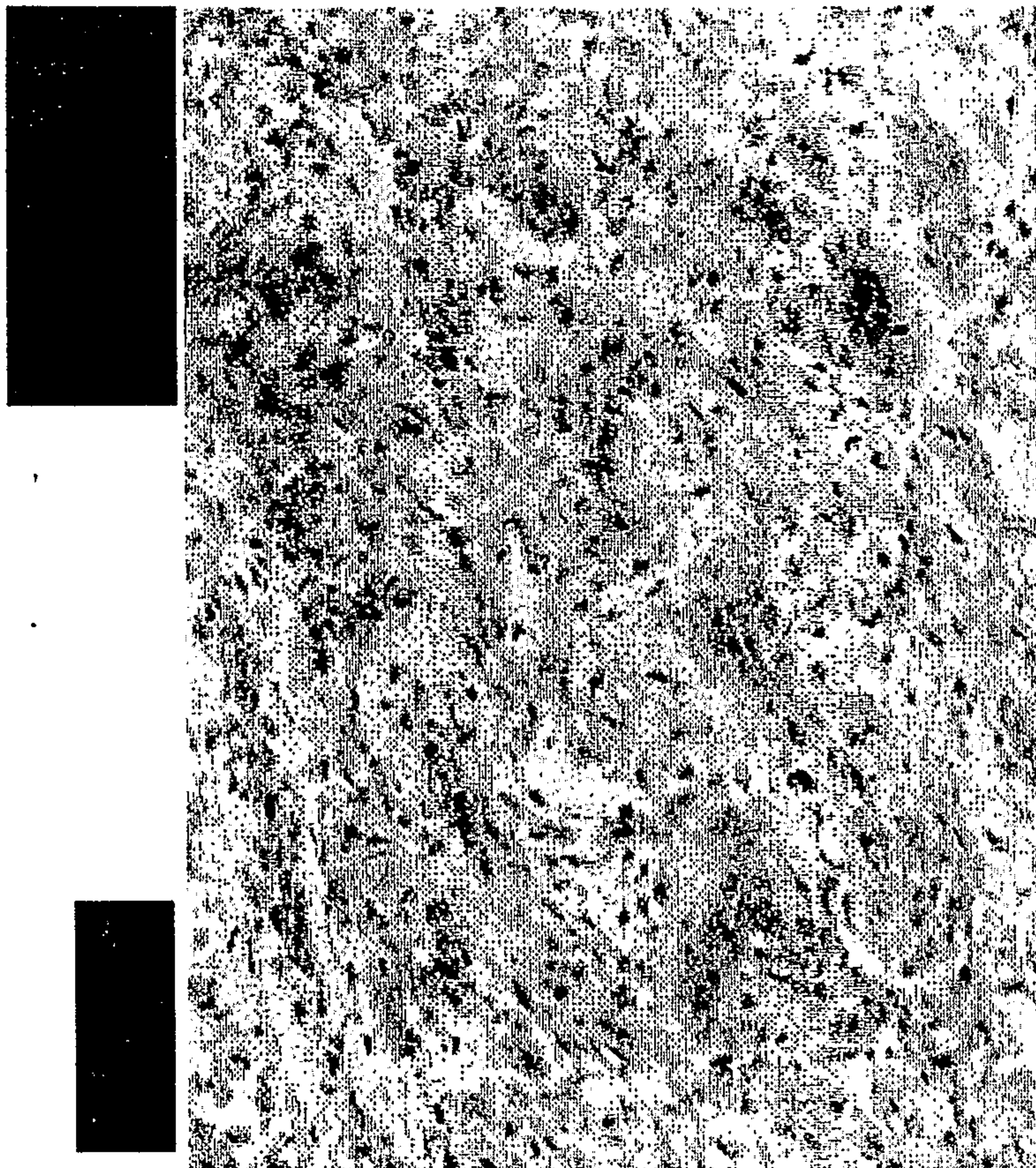


FIG 29

FIG 28

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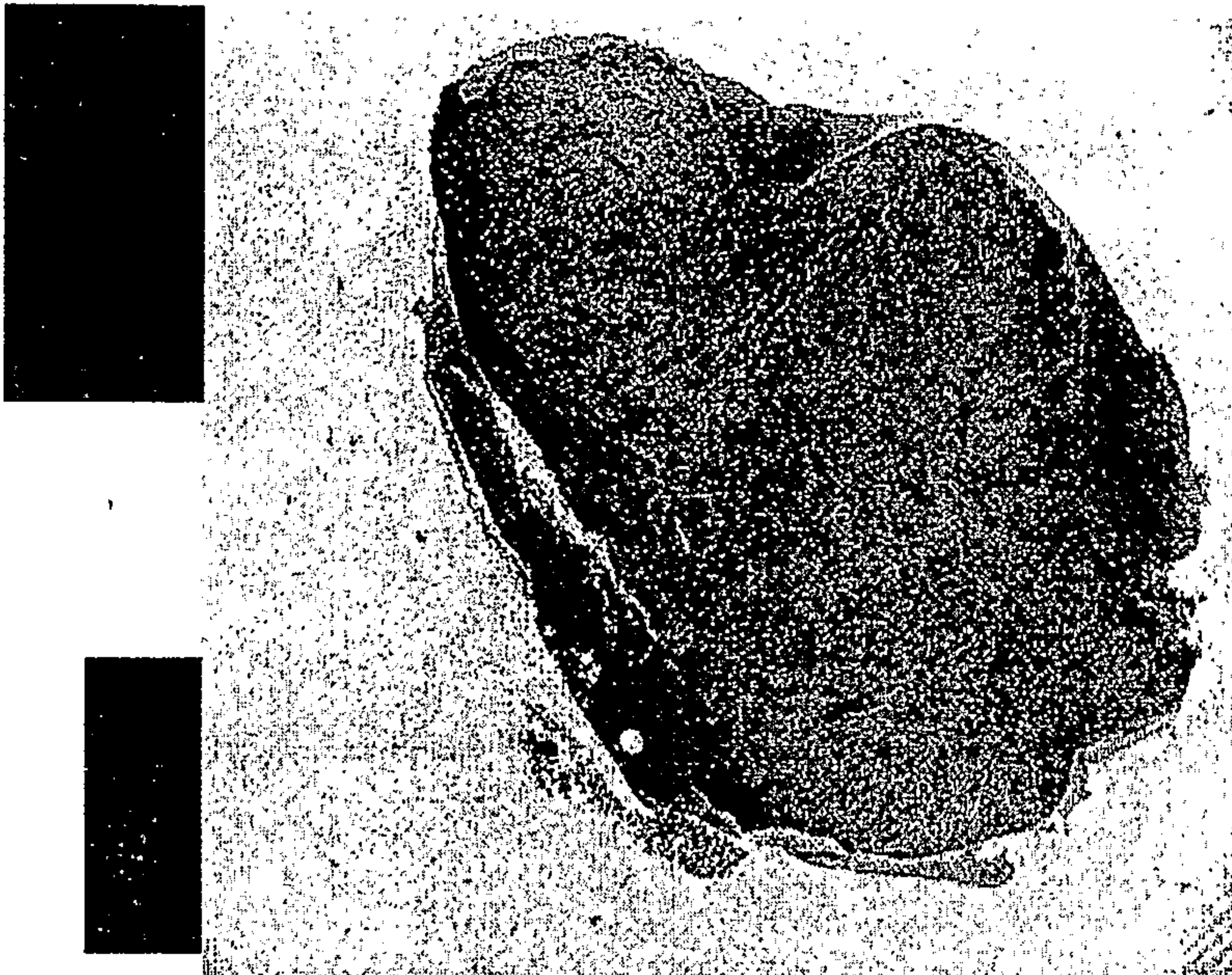


FIG 31



FIG 30

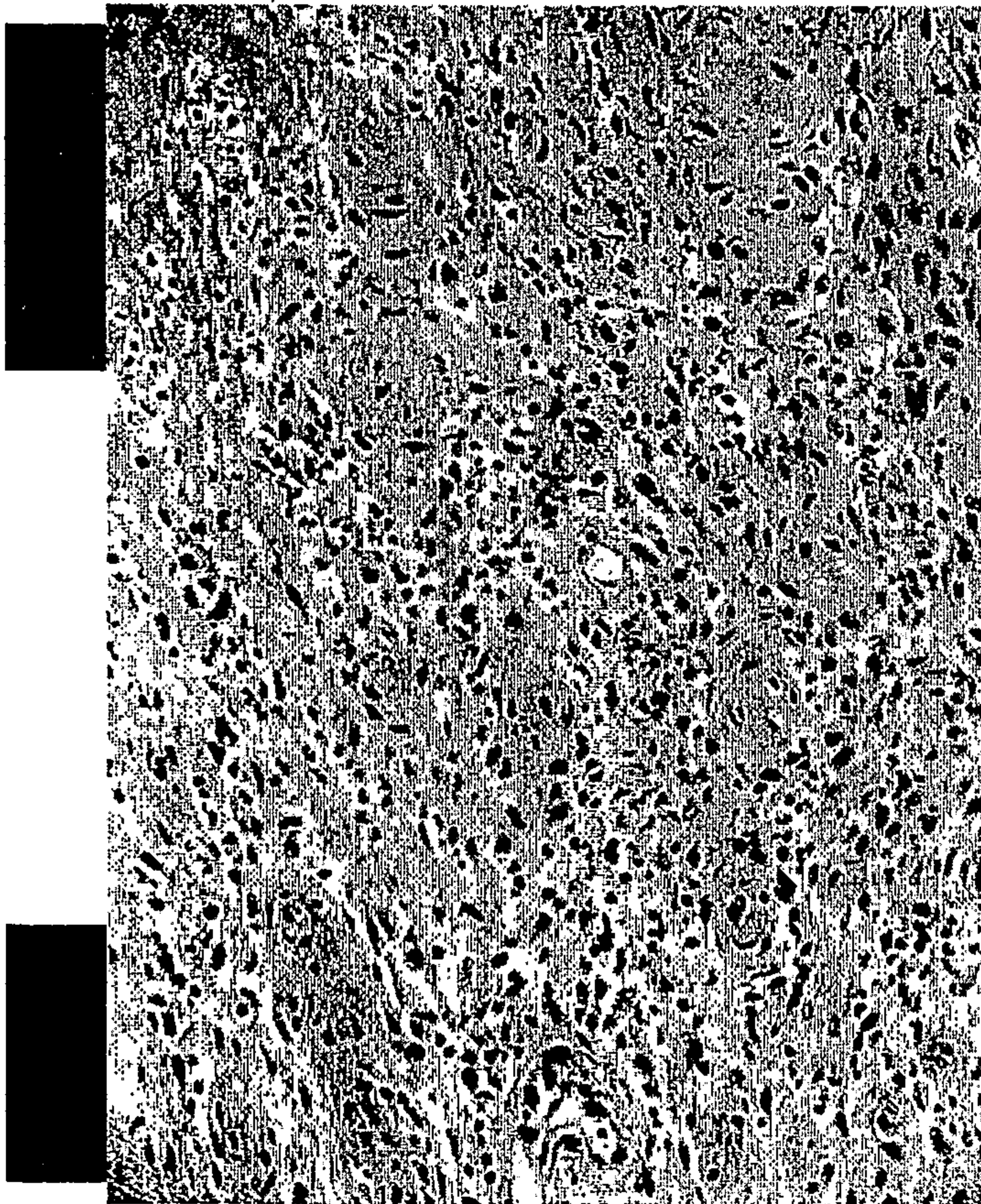
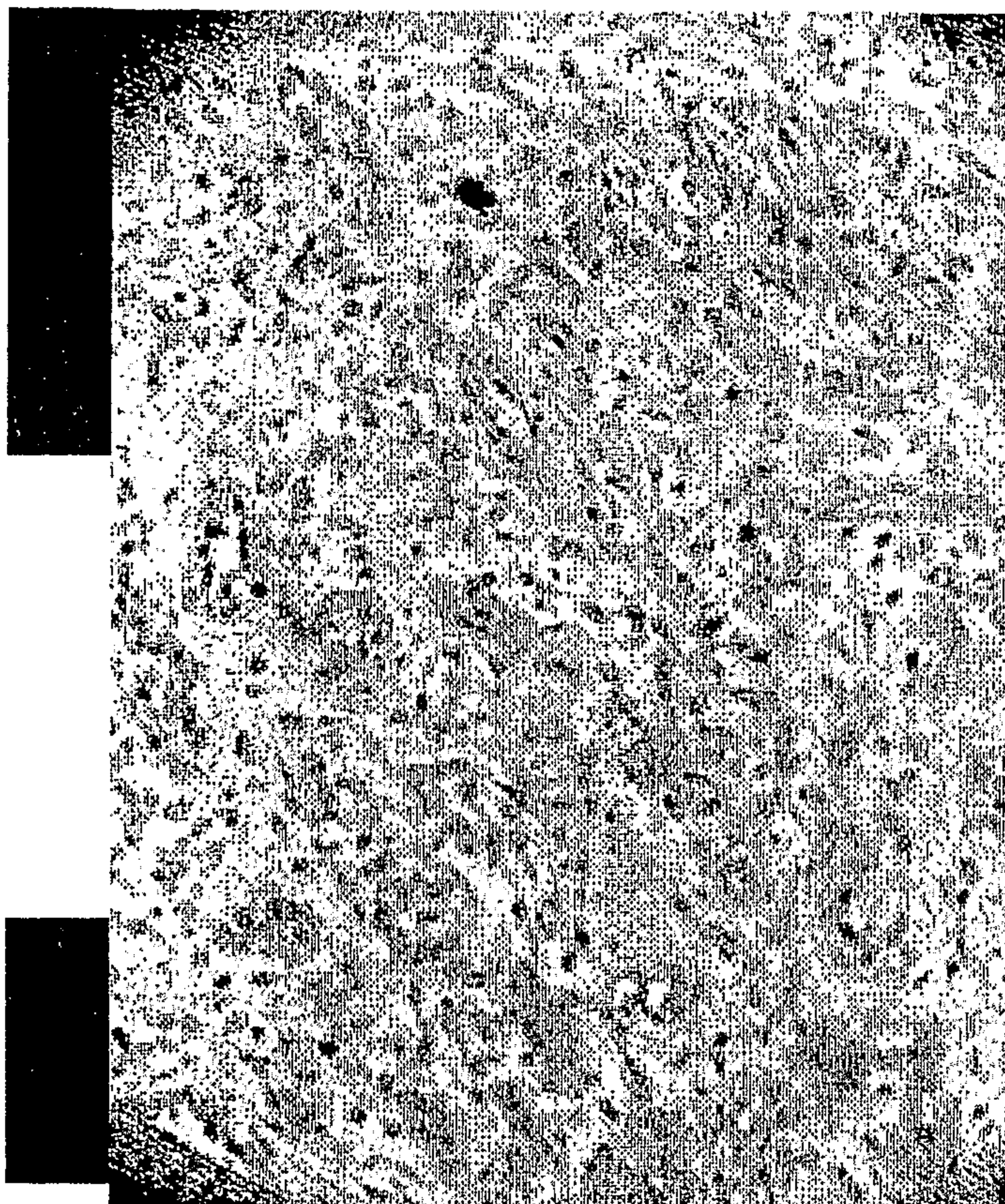


FIG 33

FIG 32

FIG 34



FIG 35



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FIG 36

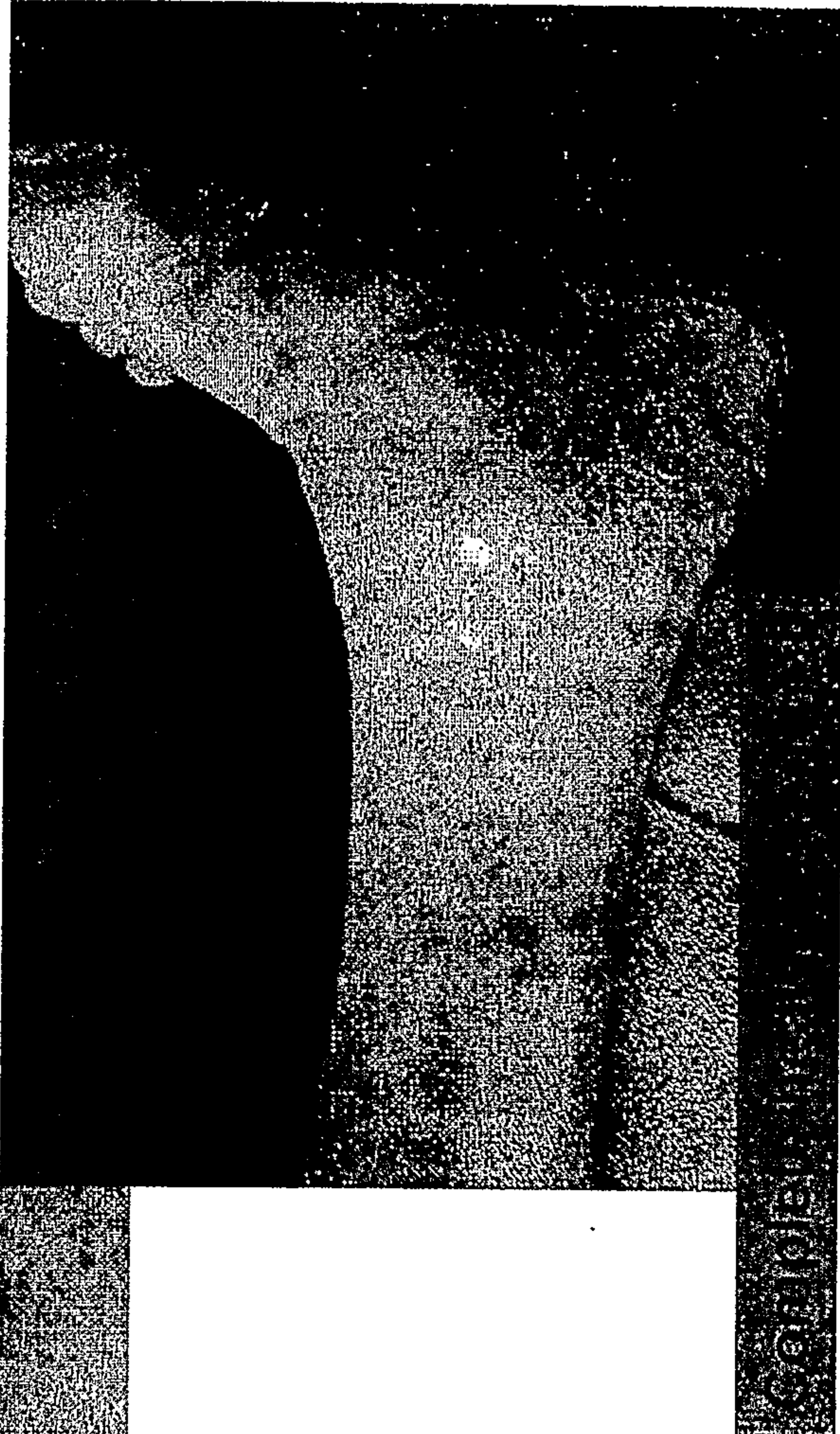


FIG 37

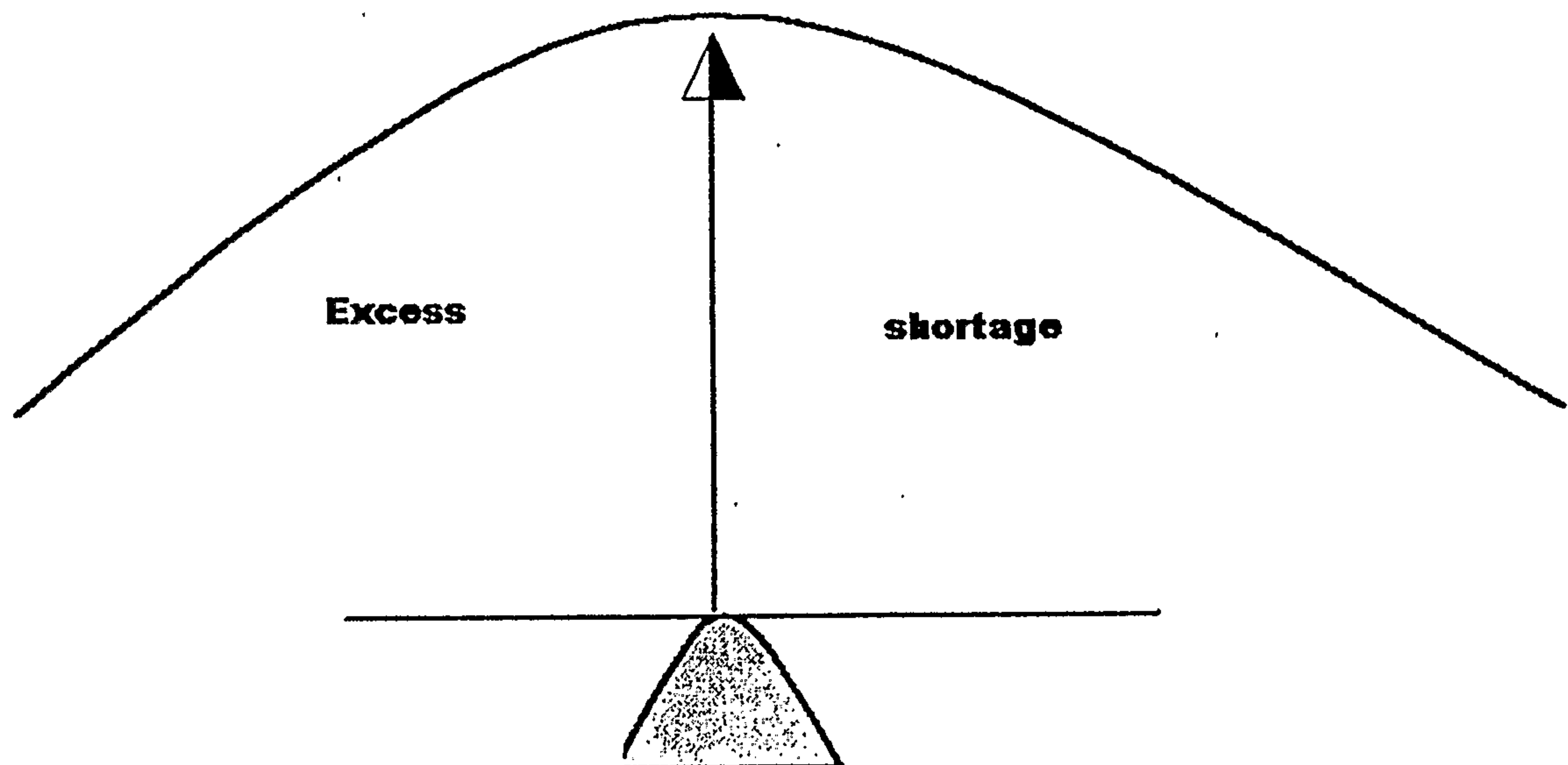
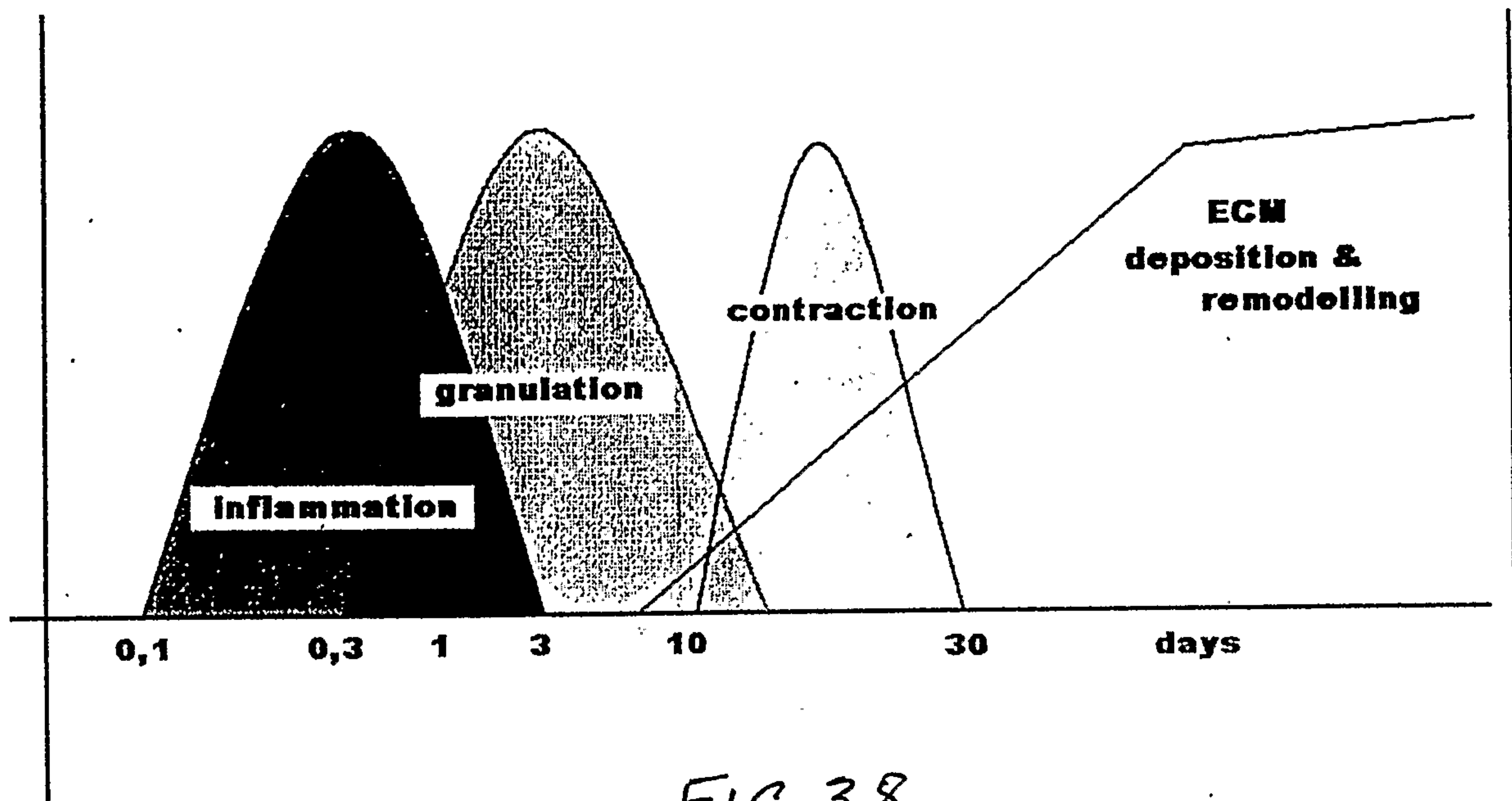


FIG 39

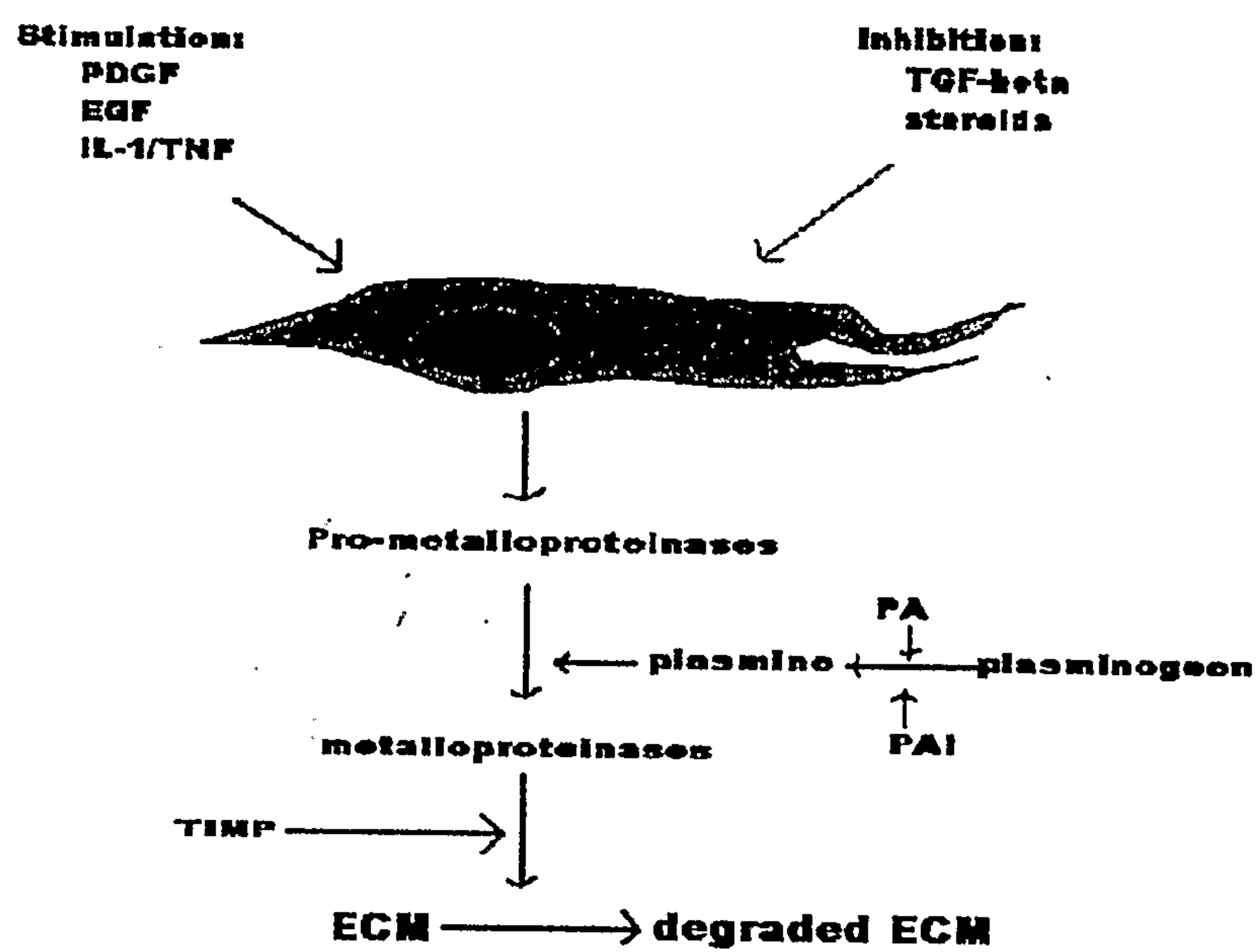


FIG 40

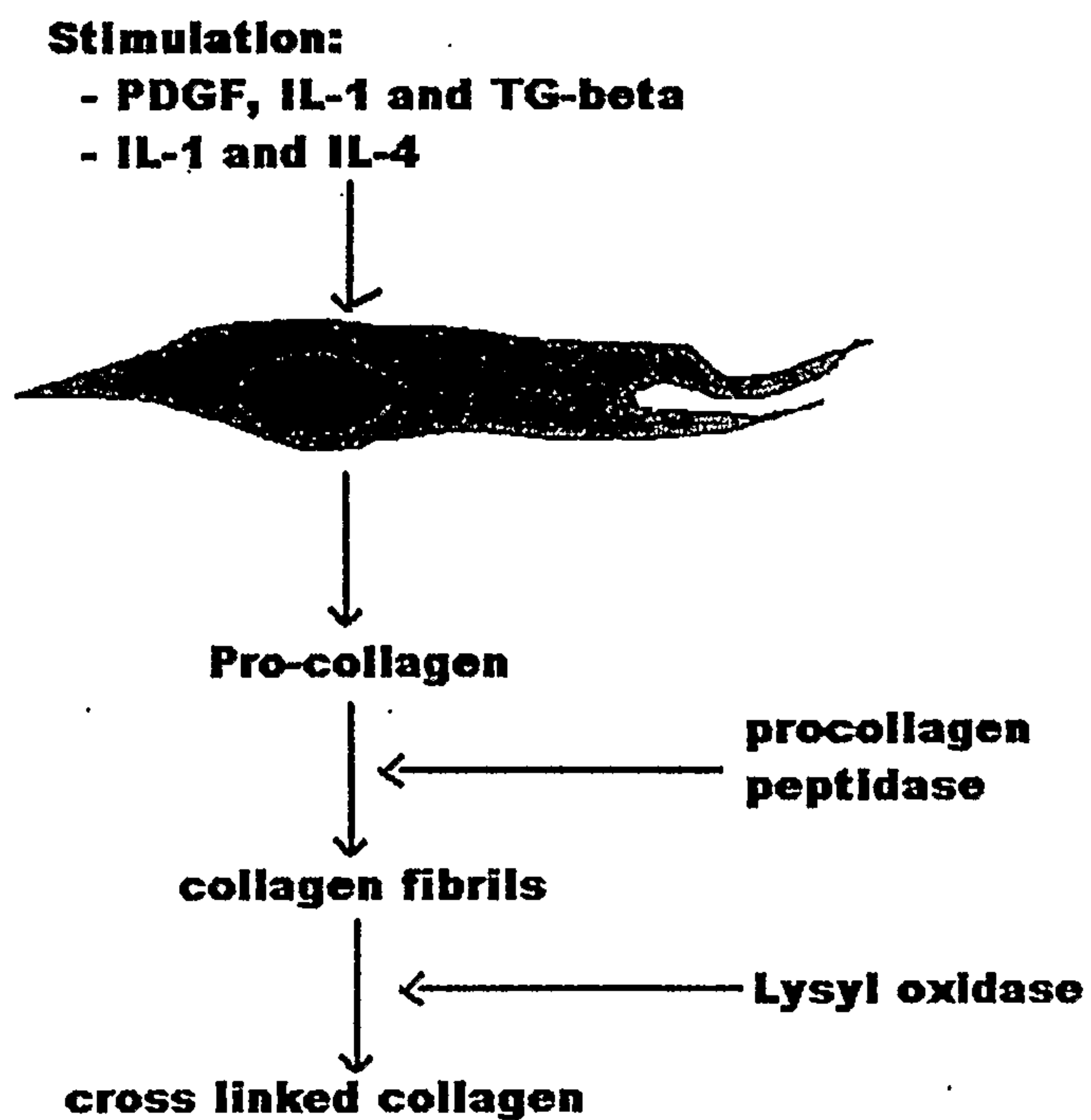


FIG 41