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(54) Titre : PROCEDES POUR LA GENERATION DE NOUVEAUX FOLLICULES CAPILLAIRES, DE TRAITEMENT DE
LA CALVITIE, ET L'ELIMINATION DE POILS

(54) Title: METHODS FOR GENERATING NEW HAIR FOLICLES, TREATING BALDNESS, AND HAIR REMOVAL

(57) **Abrégé/Abstract:**

The present invention provides methods of treating baldness in a subject and generating new hair follicles, comprising epidermal disruption and administration of a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell. The present invention also provides methods for hair removal and inducing hair pigmentation.

ABSTRACT OF THE INVENTION

The present invention provides methods of treating baldness in a subject and generating new hair follicles, comprising epidermal disruption and administration of a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell. The present invention also provides methods for hair removal and inducing hair pigmentation.

WHAT IS CLAIMED IS:

1. A method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of:
 - 5 (a) disrupting an epidermis of said scalp, eyebrow, or scarred region; and
 - (b) contacting said scalp, eyebrow, or scarred region with a compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell, thereby generating a hair follicle in a scalp, eyebrow, or scarred region of a subject.
- 10 2. A method for treating an androgenetic alopecia (AGA) in a scalp, the method comprising the steps of:
 - (a) disrupting an epidermis of said scalp; and
 - (b) contacting said scalp with a compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell, thereby treating AGA in a scalp.
- 15 3. A method for increasing a size of a hair follicle in a scalp, eyebrow, or scarred region of a subject, the method comprising the steps of:
 - (a) disrupting an epidermis of said scalp, eyebrow, or scarred region; and
 - (b) contacting said scalp, eyebrow, or scarred region with a compound or factor that

promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell,
thereby increasing a size of a hair follicle in a scalp, eyebrow, or scarred region of a subject.

4. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from an inhibitor of an Epidermal Growth Factor (EGF) or an inhibitor of an EGF receptor.
5. The method of claim 4, wherein said inhibitor of an EGF or an EGF receptor is selected from AG1478, panitumumab, nimotuzumab, HuMax EGFR, cetuximab, IMC 11F8, matuzumab, SC 100, ALT 110, PX 1032, BMS 599626, MDX 214, and PX 1041.
6. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is an inhibitor of a tyrosine kinase activity of an Epidermal Growth Factor (EGF) receptor.
7. The method of claim 6, wherein said inhibitor of a tyrosine kinase activity of an EGF receptor is selected from gefitinib, erlotinib, canertinib, pelitinib, ZD 1839, CL 387785, EKI 785, and vandetanib.
8. The method of claim 6, wherein said inhibitor of a tyrosine kinase activity of an EGF receptor is leflunomide.
9. The method of claim 6, wherein said inhibitor of a tyrosine kinase activity of an EGF receptor is A77 1726.

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10. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from a β -catenin protein, a nucleotide encoding a β -catenin protein, an activator of a β -catenin protein, or an inhibitor of a protein that suppresses an activity of a β -catenin protein.
- 5 11. The method of claim 10, wherein said activator of a β -catenin protein is selected from a Wnt7 protein, a nucleotide encoding a Wnt7 protein, or an activator of a Wnt7 protein.
12. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from a fibroblast growth factor (FGF) protein, an FGF receptor, a nucleotide encoding an FGF
10 protein or FGF receptor, an activator of an FGF protein or FGF receptor, or an inhibitor of a protein that suppresses an activity of an FGF protein or FGF receptor.
13. The method of claim 12, wherein said protein that suppresses an activity of said FGF protein or FGF receptor is selected from an FGF binding protein or a nucleotide encoding an FGF binding protein.
- 15 14. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from an ectodysplasin protein, an ectodysplasin receptor, a nucleotide encoding an ectodysplasin protein or ectodysplasin receptor, an activator of an ectodysplasin protein or ectodysplasin
20 receptor, or an inhibitor of a protein that suppresses an activity of an ectodysplasin protein or ectodysplasin receptor.

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15. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is a minoxidil.
16. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from a
5 Noggin protein, a nucleotide encoding a Noggin protein, or an activator of a Noggin protein.
17. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from a Hedgehog protein, a nucleotide encoding a Hedgehog protein, or an activator of a Hedgehog protein.
- 10 18. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from a Transforming Growth Factor (TGF)-beta1 protein, a nucleotide encoding a TGF-beta1 protein, an activator of a TGF-beta1 protein, a TGF-beta3 protein, a nucleotide encoding a TGF-beta3 protein, and an activator of a TGF-beta3 protein.
- 15 19. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from an antagonist of a Transforming Growth Factor (TGF)-beta1 protein and an antagonist of a TGF-beta3 protein.
20. The method of any of claims 1-3, wherein said compound or factor that promotes a
20 differentiation of an uncommitted epidermal cell into a hair follicle cell acts directly on said

uncommitted epidermal cell.

21. The method of any of claims 1-3, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell acts on said uncommitted epidermal cell via a mesenchymal cell.

5 22. A method for generating a hair follicle in a scalp, eyebrow, or scarred region of a subject, comprising the steps of:

(a) disrupting an epidermis of said scalp, eyebrow, or scarred region; and

(b) contacting said scalp, eyebrow, or scarred region with a cell selected from (a) a precursor cell that is capable of differentiation into a hair follicle cell; (b) an inductive
10 cell that is capable of inducing differentiation of an uncommitted epidermal cell into a hair follicle cell; or (c) a hair follicle or portion thereof,

wherein step (b) is performed 3-12 days after step (a), thereby generating a hair follicle in a scalp, eyebrow, or scarred region of a subject.

23. A method for treating an androgenetic alopecia (AGA) in a scalp, comprising the steps of:

15 (a) disrupting an epidermis of said scalp; and

(b) contacting said scalp, eyebrow, or scarred region with a cell selected from (a) a precursor cell that is capable of differentiation into a hair follicle cell; (b) an inductive cell that is capable of inducing differentiation of an uncommitted epidermal cell into a

hair follicle cell; or (c) a hair follicle or portion thereof,

thereby treating AGA in a scalp.

24. The method of any of claims 22-23, wherein said precursor is selected from a hair follicle stem cell, an epidermal cell, a dermal papilla cell, or a connective tissue sheath cell.

5 25. The method of any of claims 1-24, further comprising the step of depilating said scalp, eyebrow, or scarred region.

26. The method of any of claims 1-25, further comprising the step of administering a topical retinoid to said scalp, eyebrow, or scarred region.

10 27. The method of any of claims 1-26, further comprising contacting said scalp, eyebrow, or scarred region with a compound or factor that suppresses an expression of a Wnt protein therein.

28. The method of any of claims 1-27, further comprising contacting said scalp, eyebrow, or scarred region with an antagonist of an androgen or an antagonist of an androgen receptor.

15 29. A method for removing a hair follicle from a skin or scalp, comprising the steps of: (a) disrupting an epidermis of said skin or scalp; and (b) contacting said skin or scalp with either: (i) an Epidermal Growth Factor (EGF) protein; (ii) an EGF receptor; (iii) a nucleotide encoding an EGF protein or EGF receptor; or (iv) a compound or factor that activates a EGF protein or EGF receptor, thereby removing hair from a skin or scalp.

30. The method of claim 29, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from a Transforming Growth Factor (TGF)-beta1 protein, a nucleotide encoding a TGF-beta1 protein, an activator of a TGF-beta1 protein, a TGF-beta3 protein, a nucleotide encoding a TGF-beta3 protein, and an activator of a TGF-beta3 protein.
31. The method of claim 29, wherein said compound or factor that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell is selected from an antagonist of a Transforming Growth Factor (TGF)-beta1 protein and an antagonist of a TGF-beta3 protein.
32. The method of any of claims 1-31, wherein the step of disrupting said scalp, eyebrow, or scarred region is performed by mechanical means.
33. The method of any of claims 1-31, wherein the step of disrupting is performed by exposing said scalp, eyebrow, or scarred region to a chemical.
34. The method of any of claims 1-31, wherein the step of disrupting is performed by irradiating said scalp, eyebrow, or scarred region.
35. The method of any of claims 1-34, wherein the step of disrupting an epidermis comprises a disruption of a follicle of said epidermis and a disruption of an interfollicular region of said epidermis.
36. The method of any of claims 1-34, wherein the step of disrupting an epidermis comprises a disruption of a follicle of said epidermis and does not comprise a disruption of an

interfollicular region of said epidermis.

37. The method of any of claims 1-36, wherein said subject is a human.

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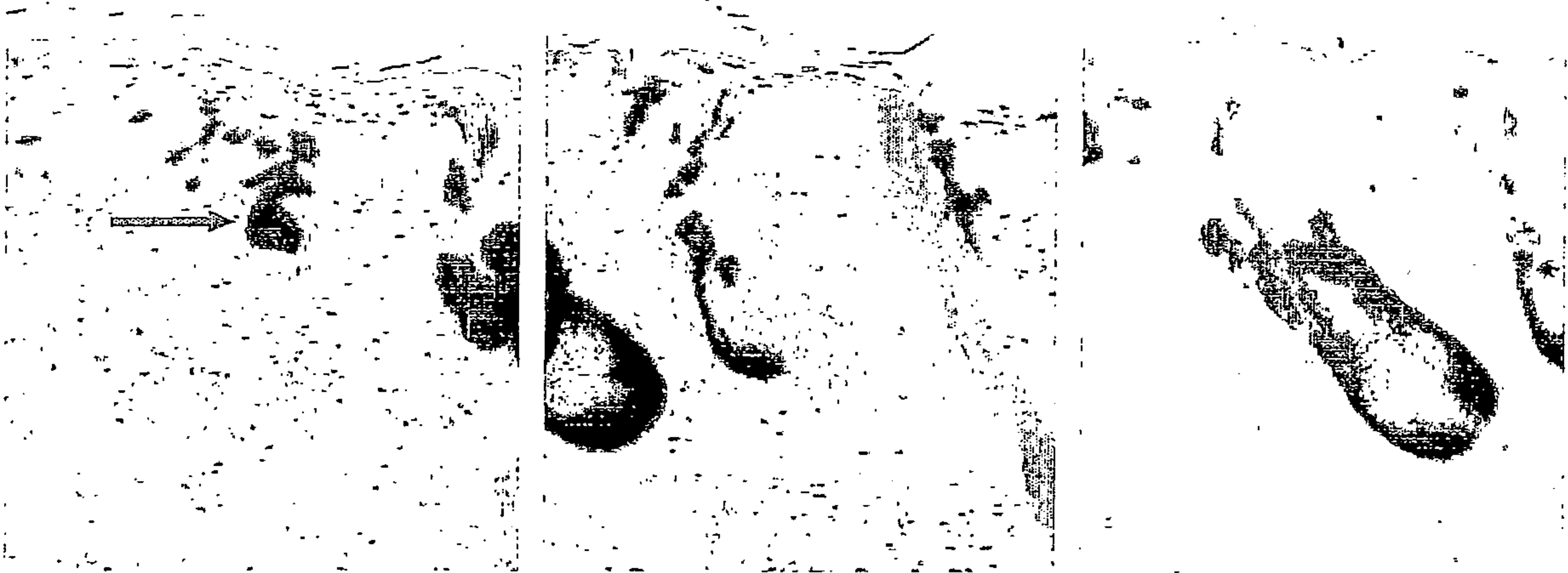


Figure 1

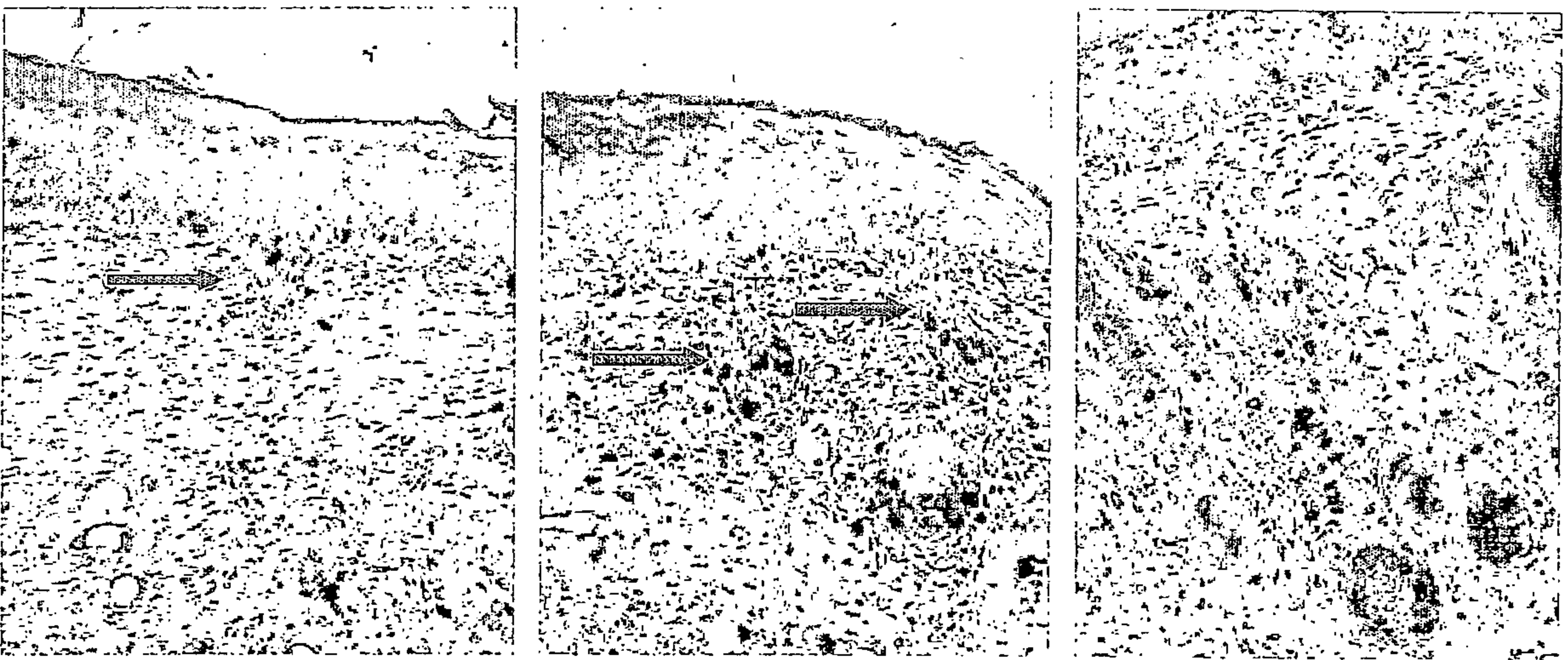


Figure 2

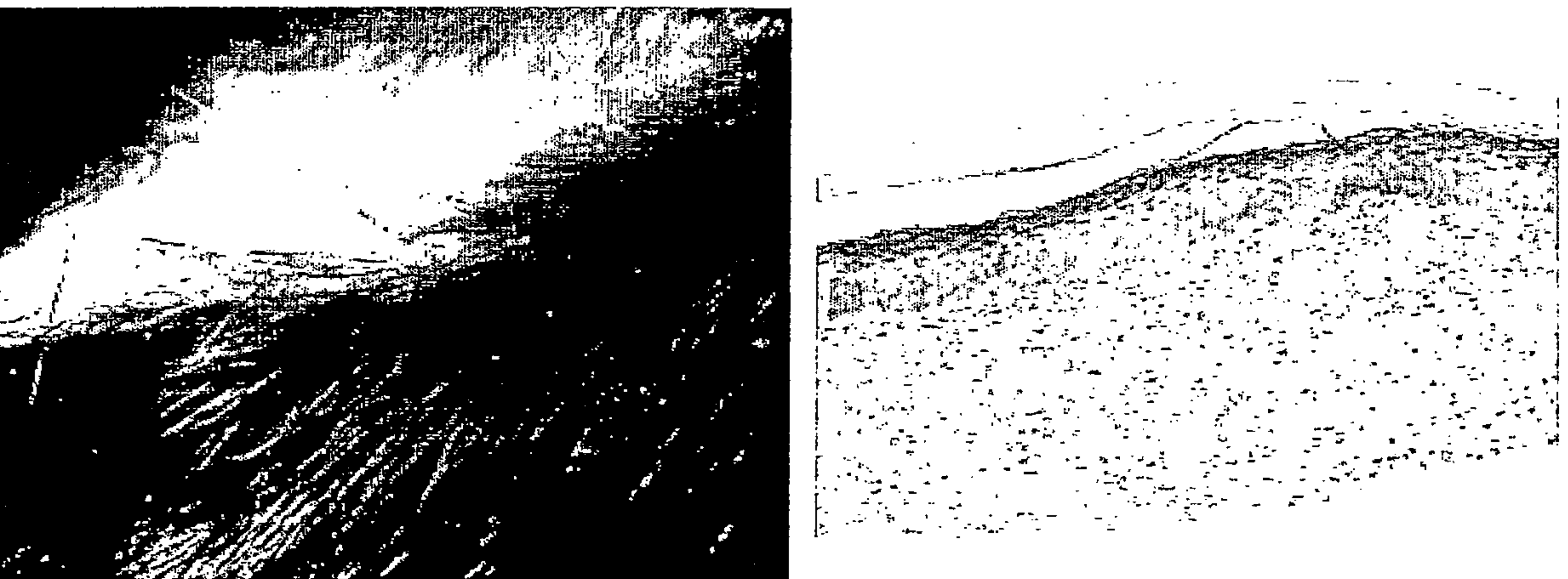


Figure 3

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Figure 4

K 17 immuno-stain

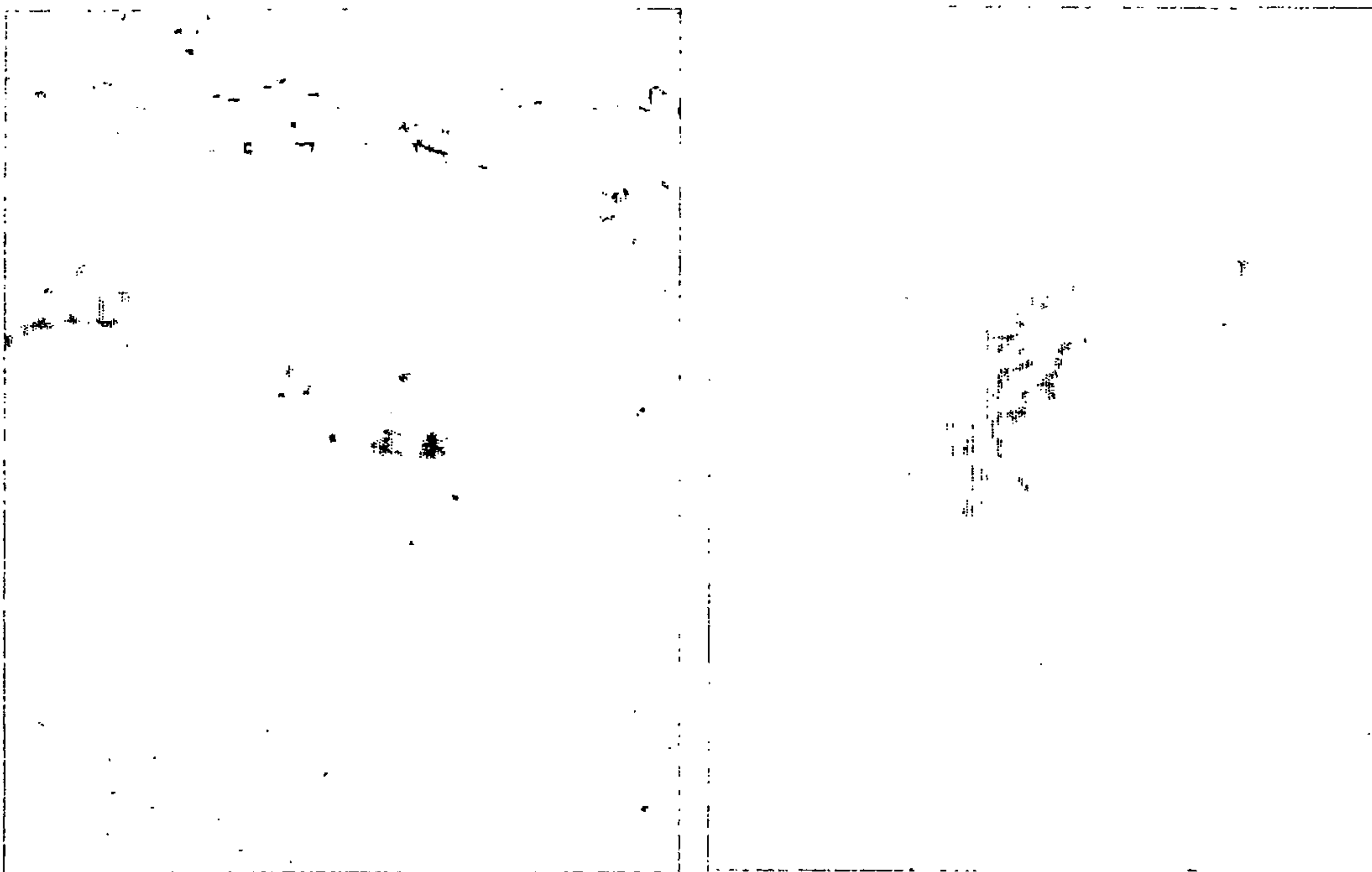


Figure 5

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Alkaline Phosphatase

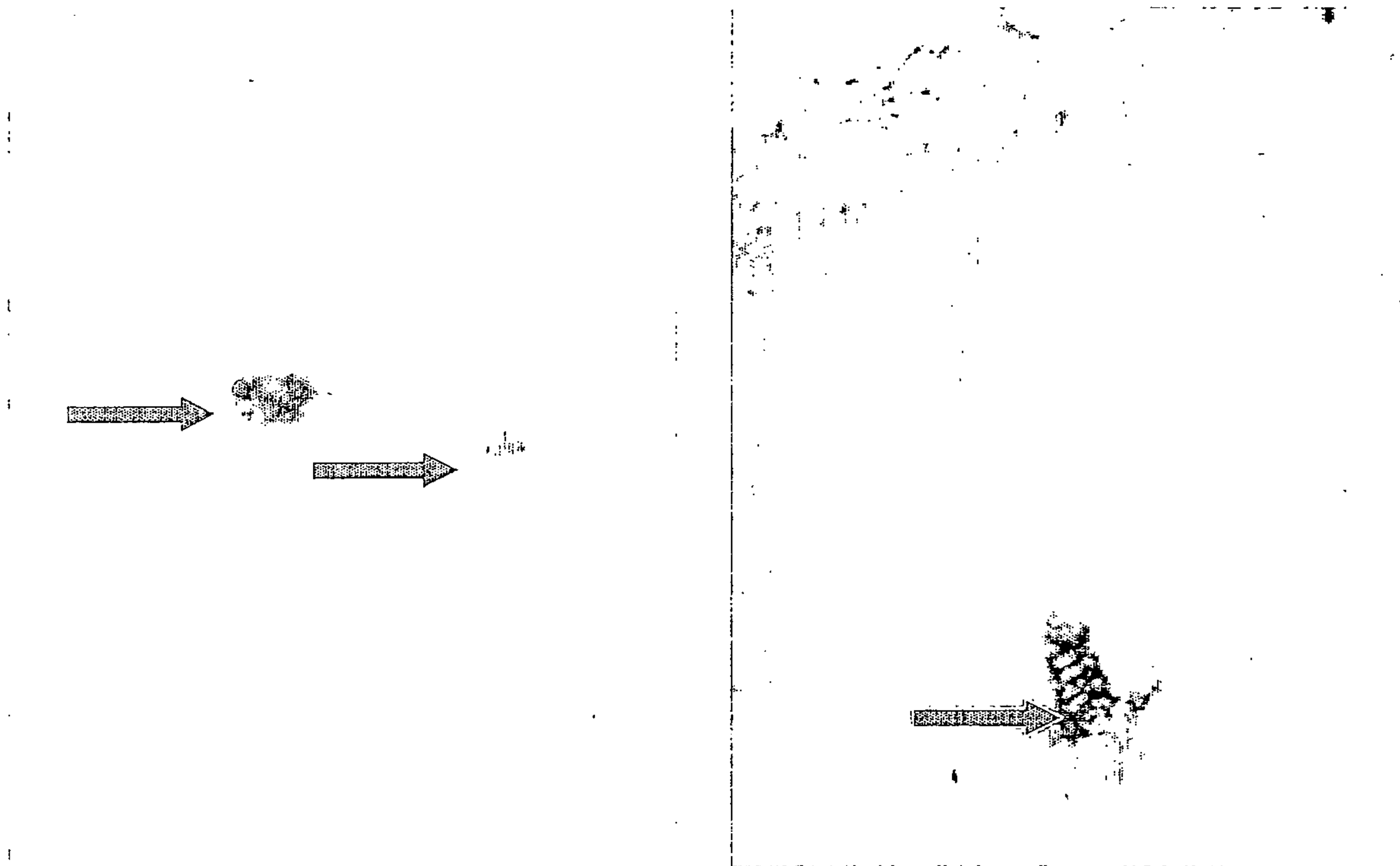


Figure 6

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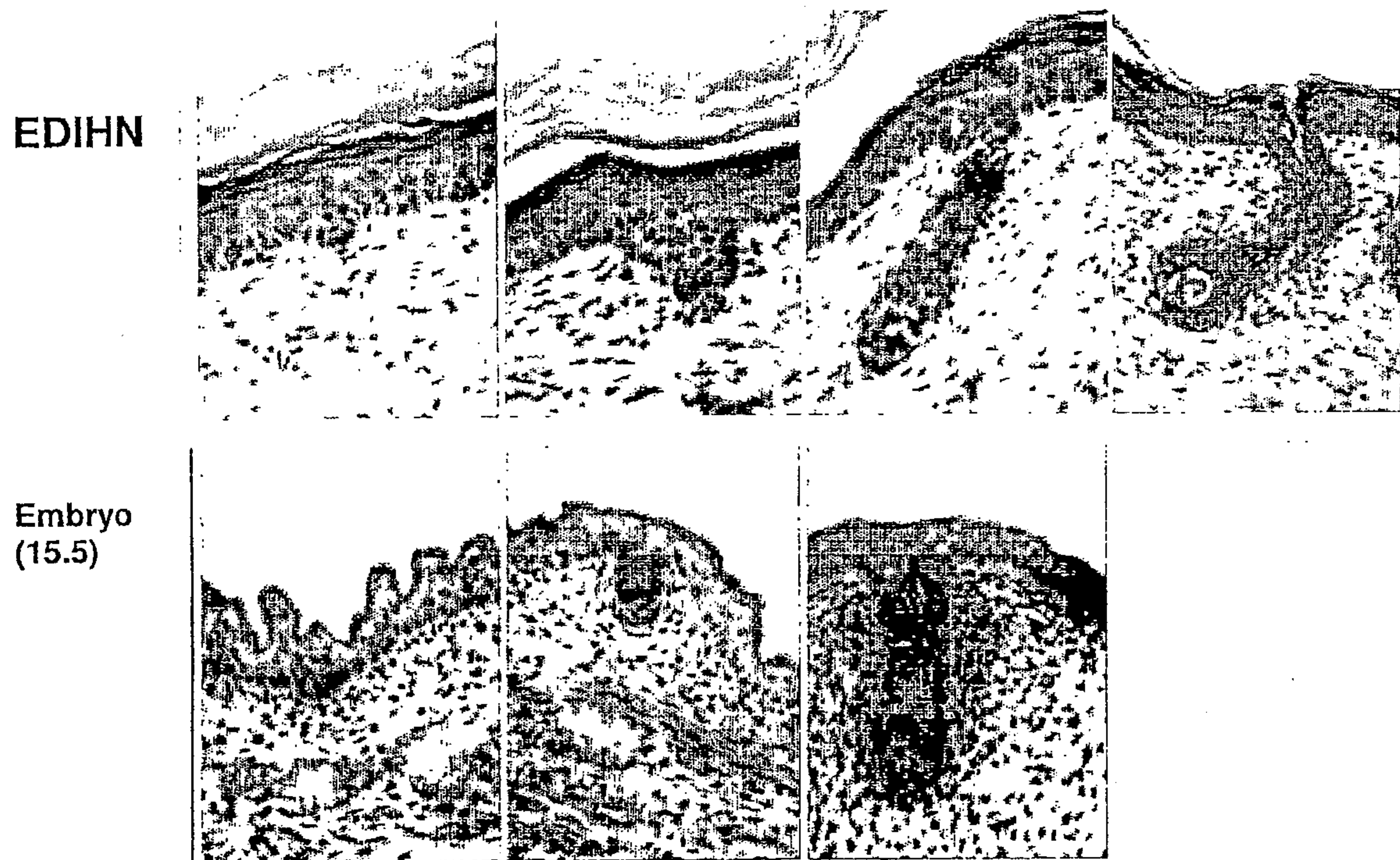


Figure 7

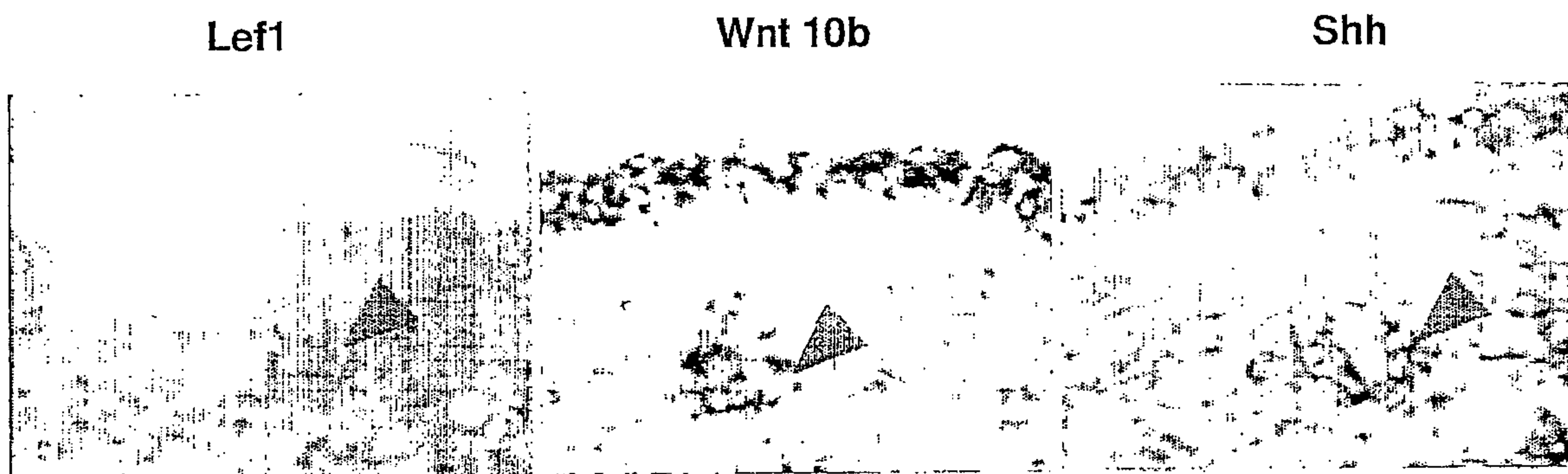


Figure 8

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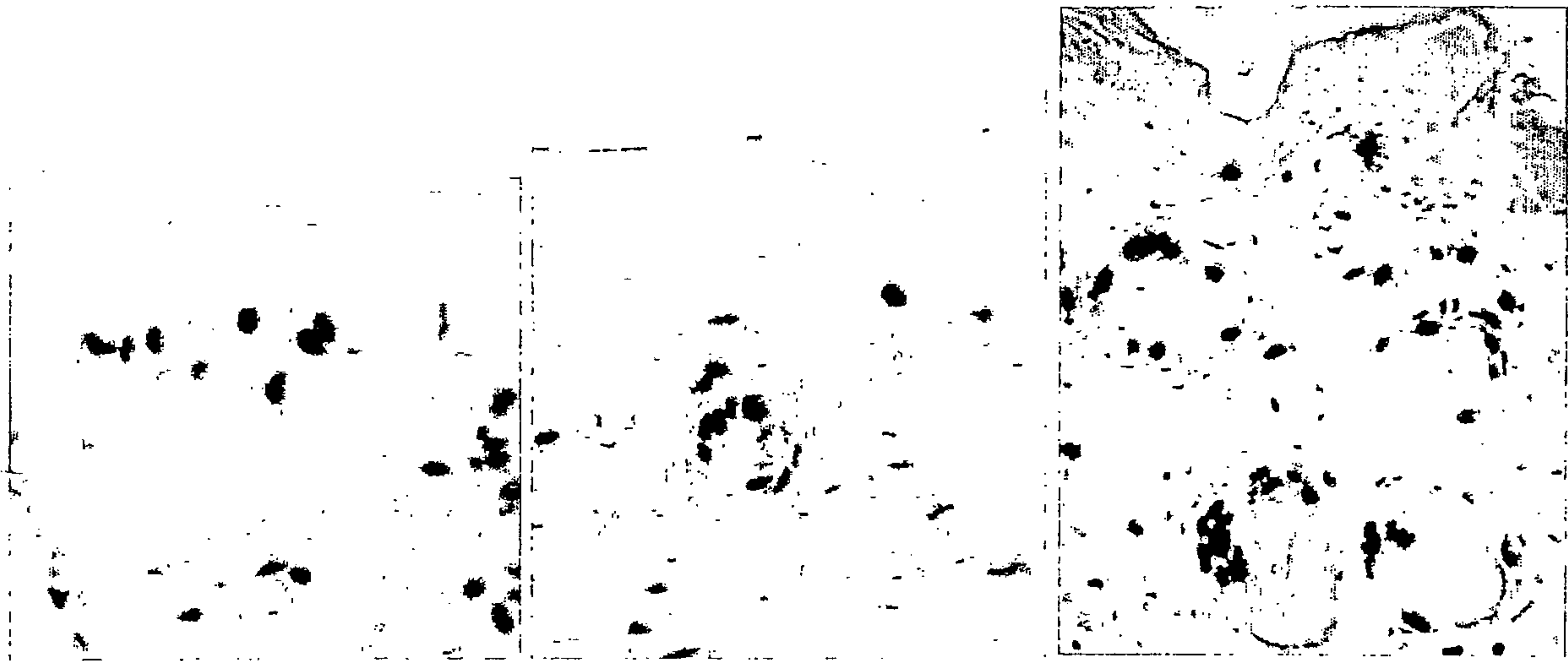


Figure 9

Cuticle , cortex : S100A3



IRS, medulla: S100A6

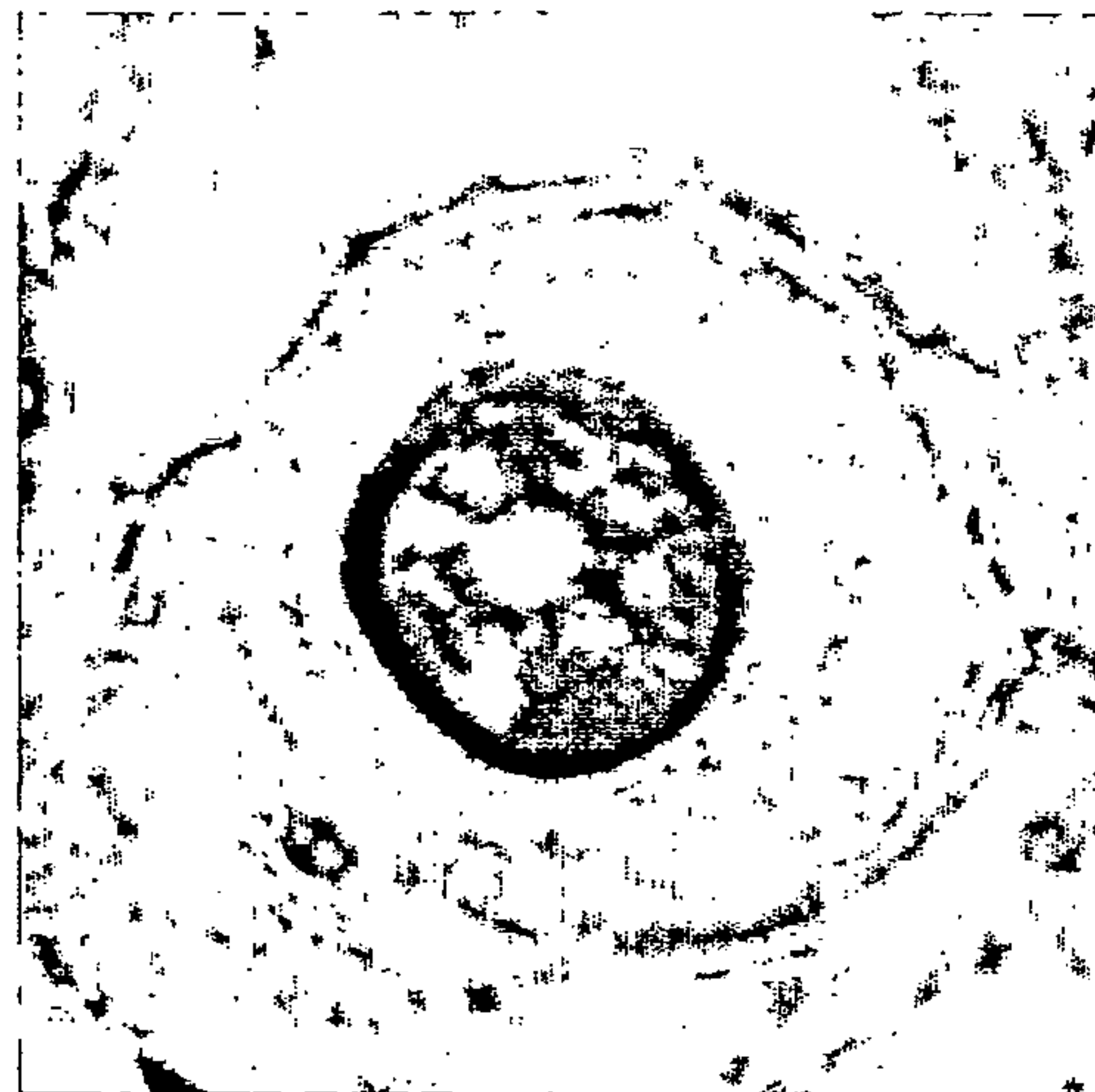


Figure 10

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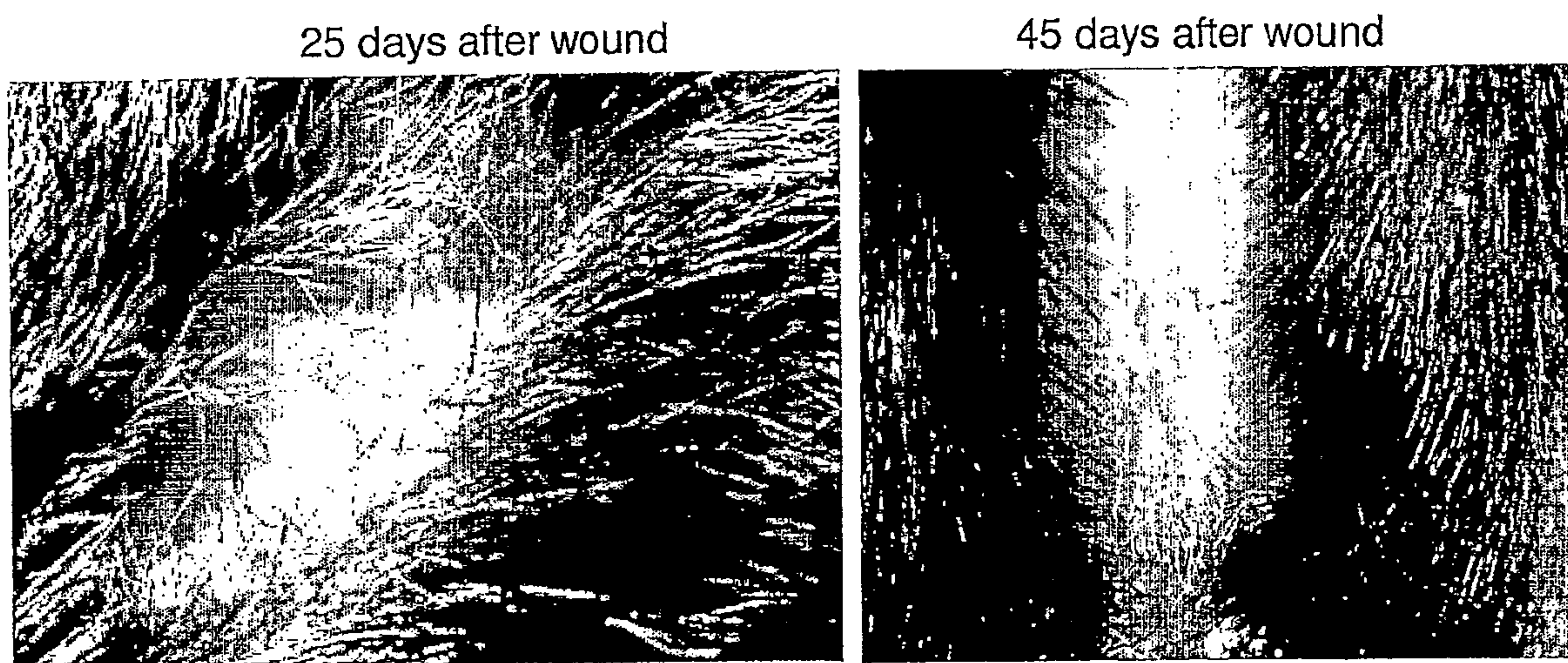


Figure 11

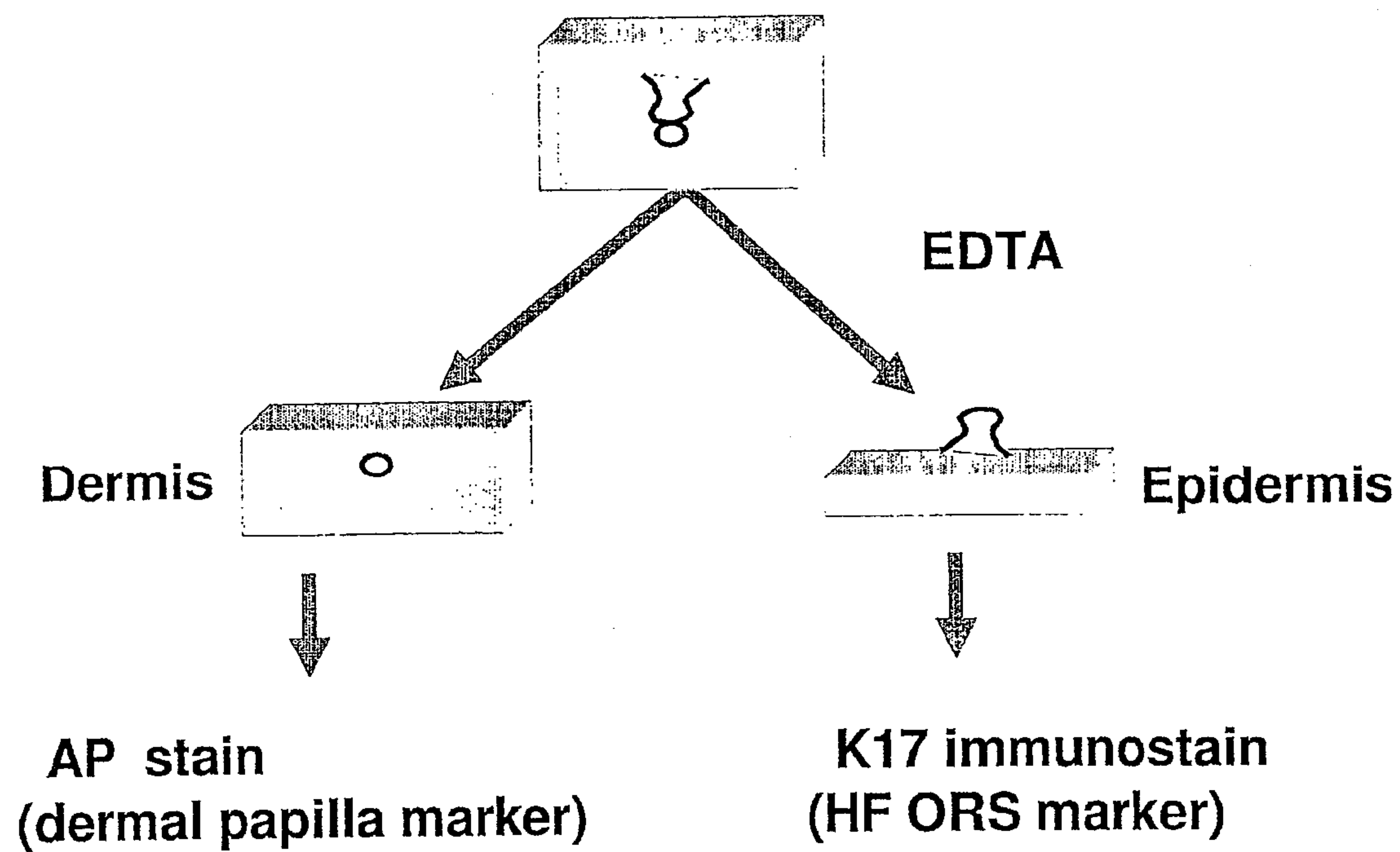


Figure 12

Label retaining cells

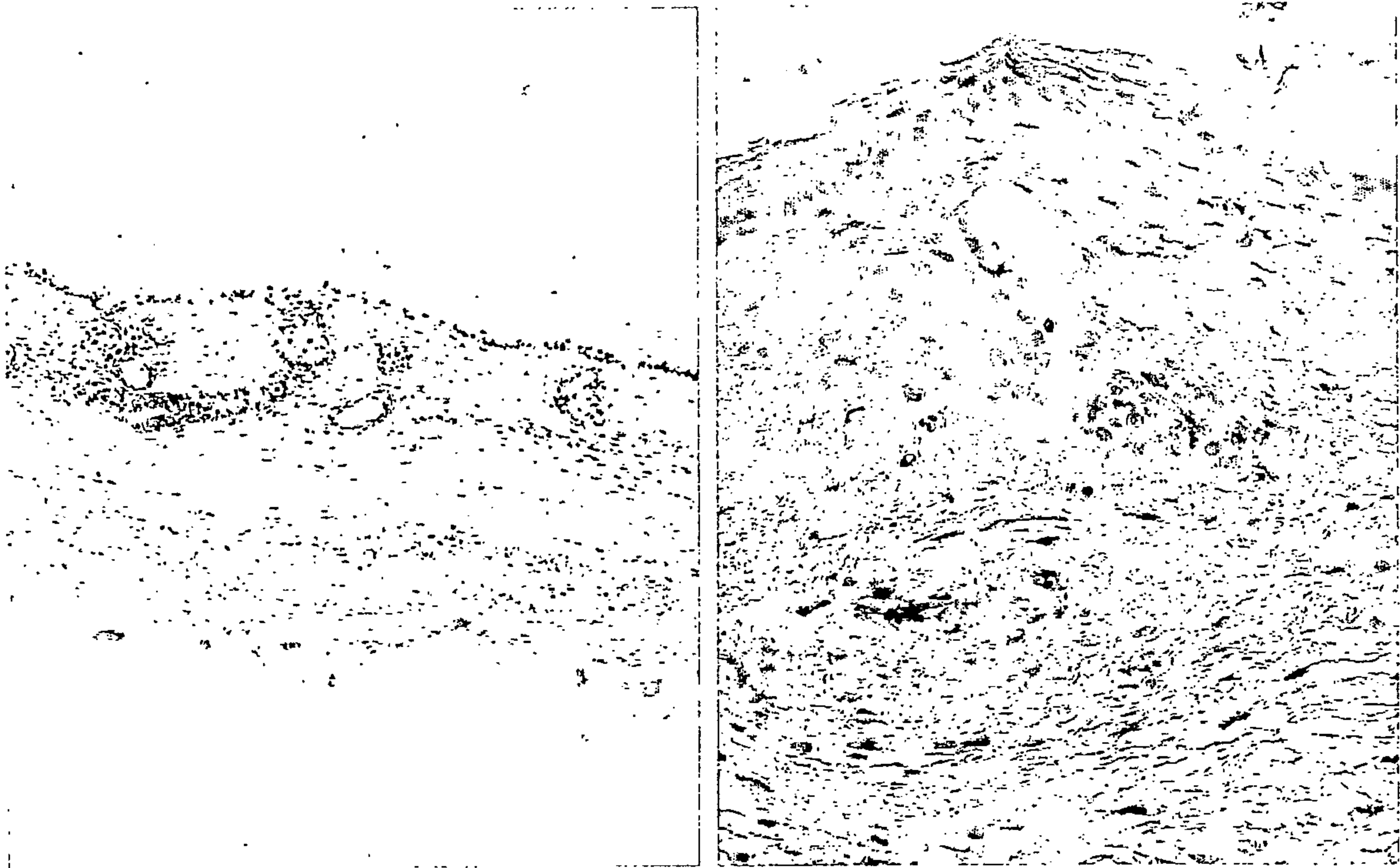
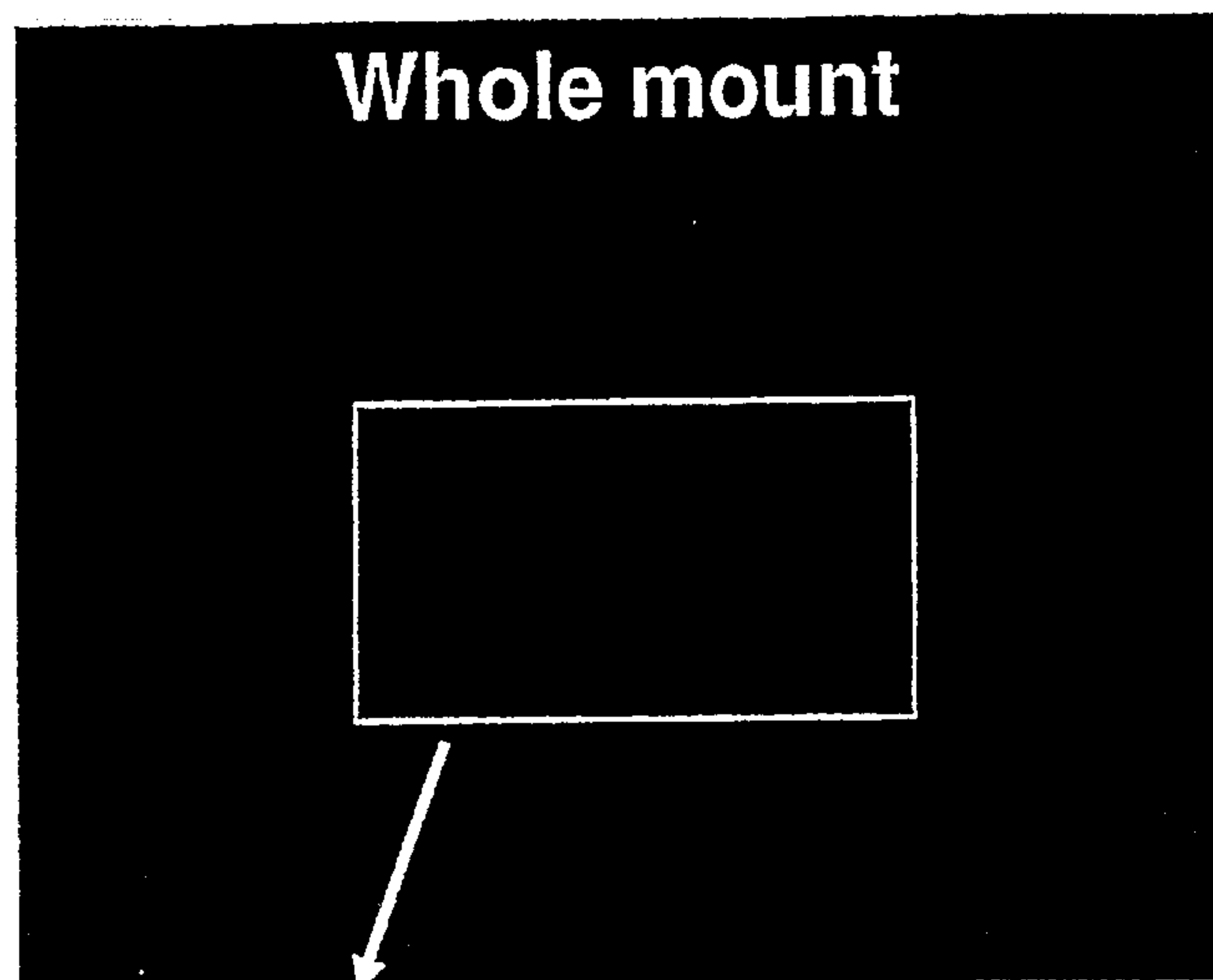
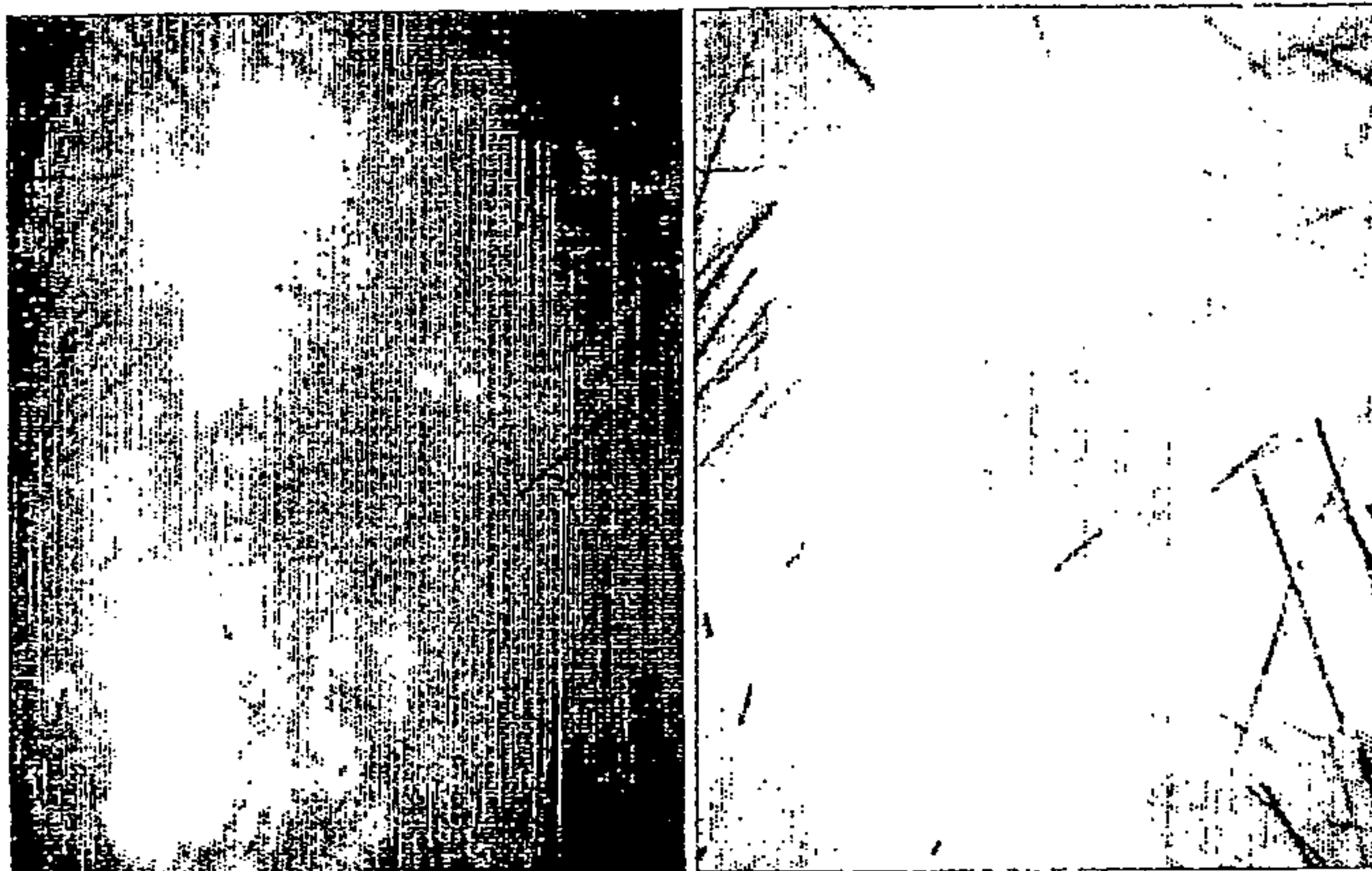
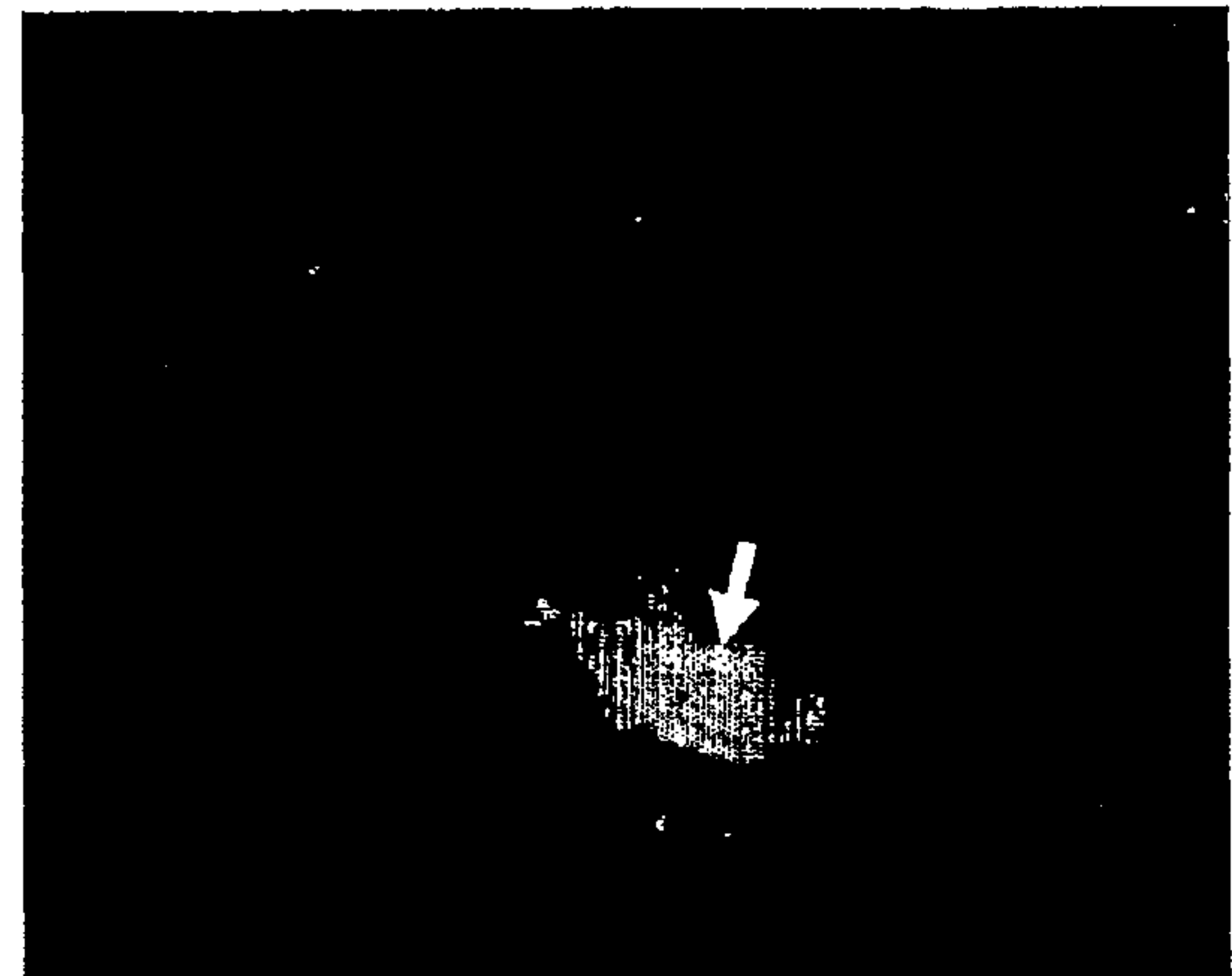


Figure 13

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Tissue section



35d after wound

Figure 14A

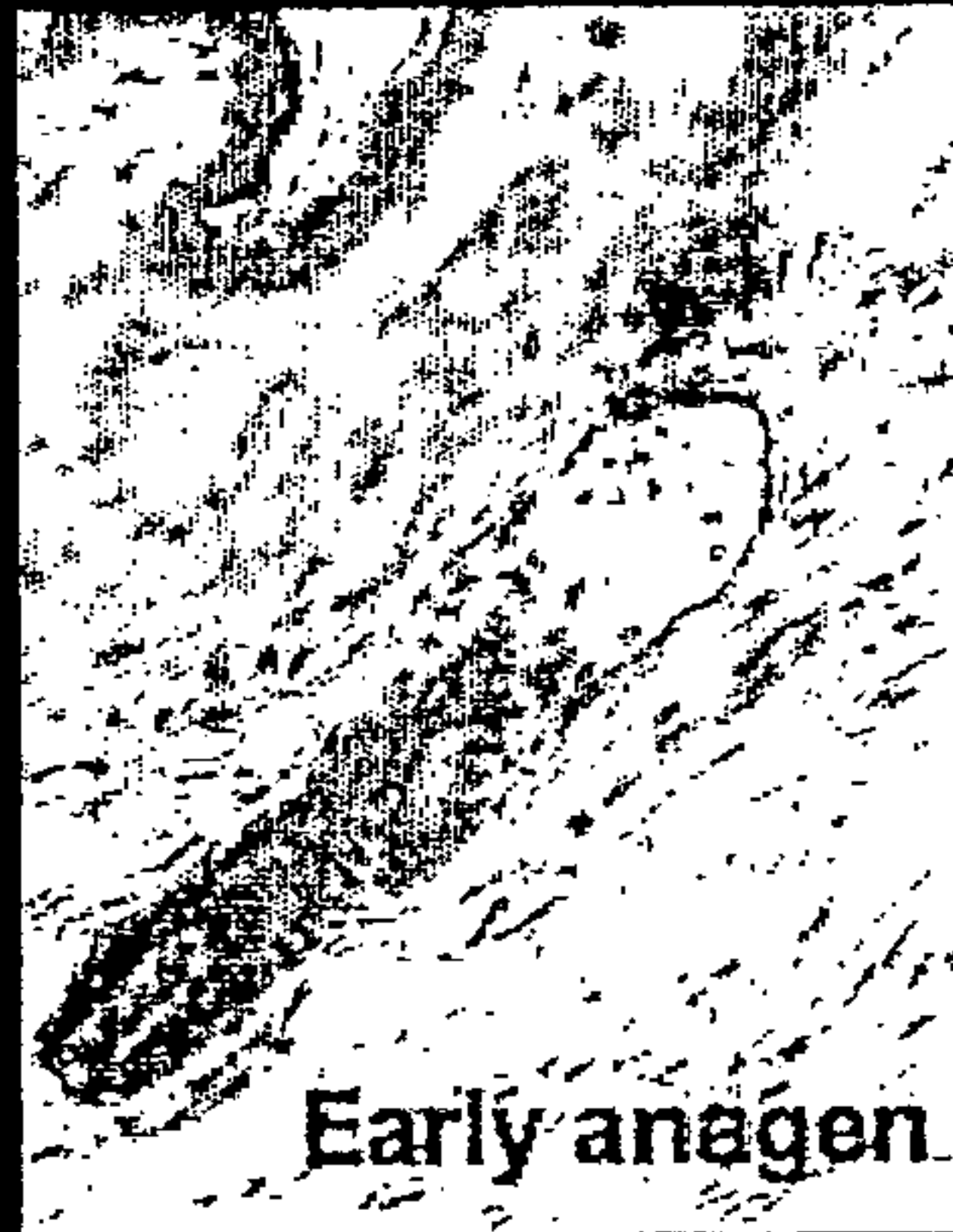
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Neogenesis hair follicles go to next hair cycle

35 d after wound



38 d after wound



45 d after wound



Figure 14B

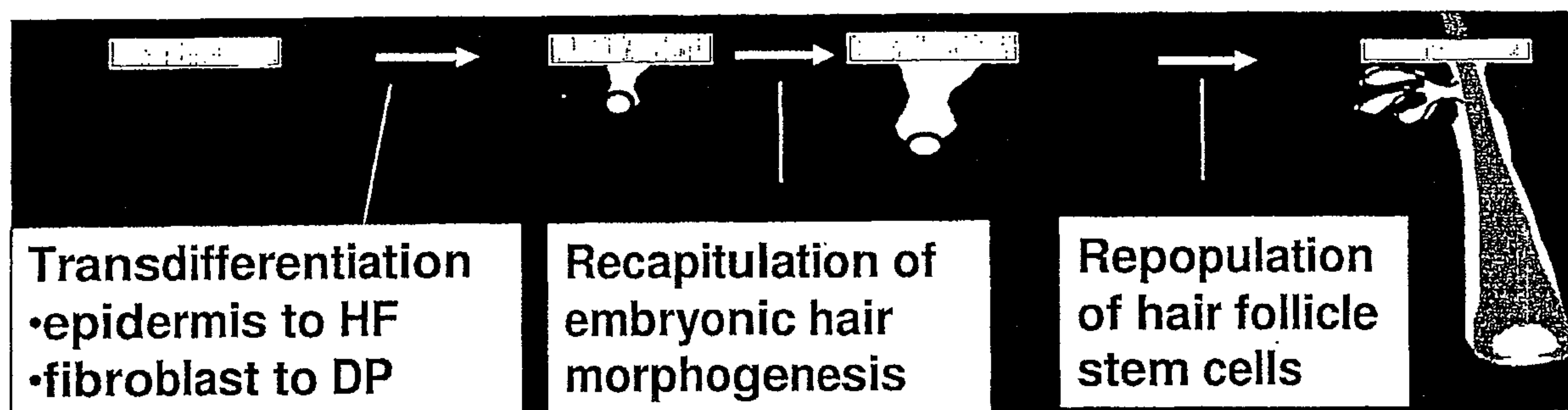
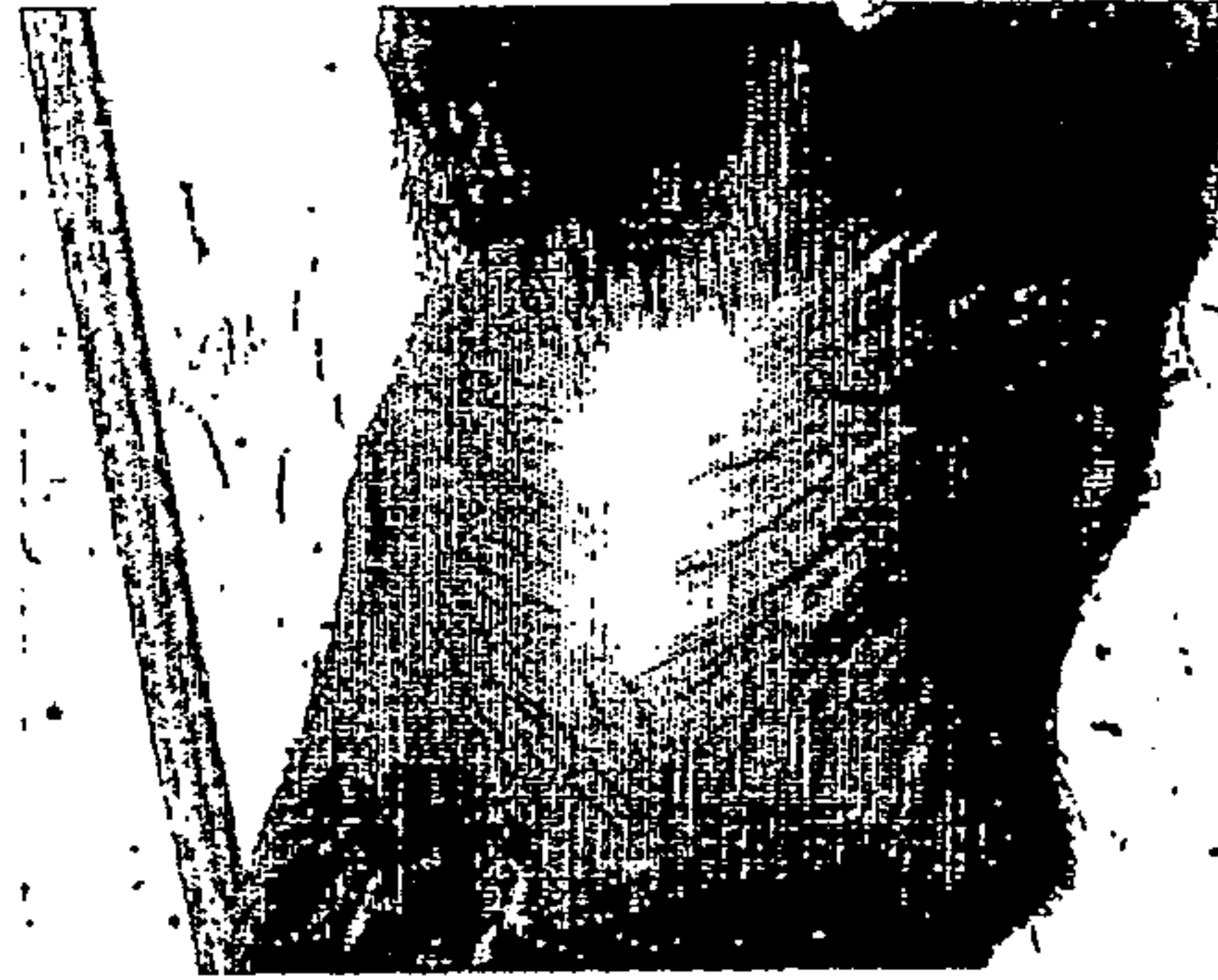


Figure 15

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11 days after wound



AP stain



K17 immunostain

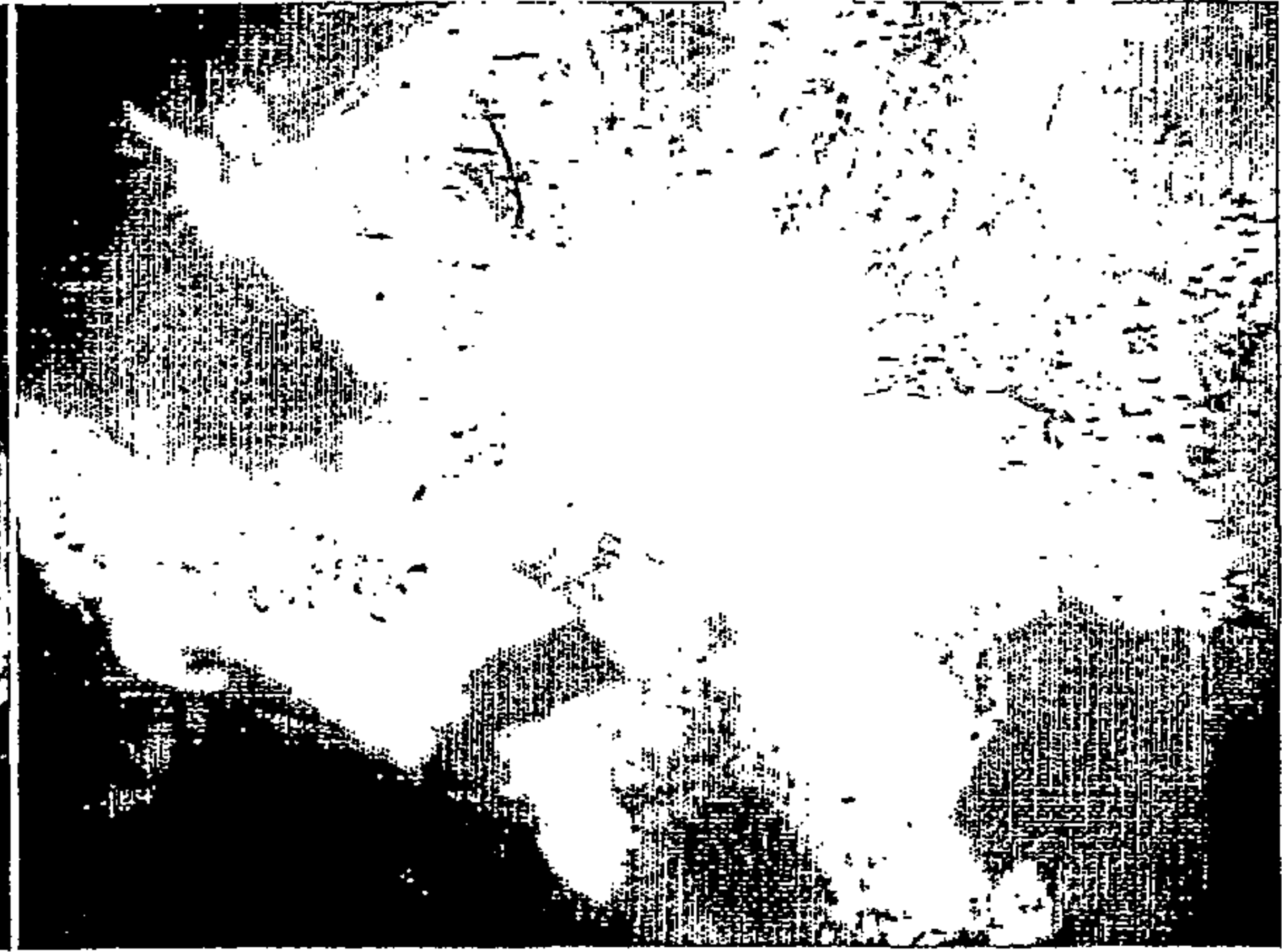


Figure 16

~d

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14 days after wound

AP

K17

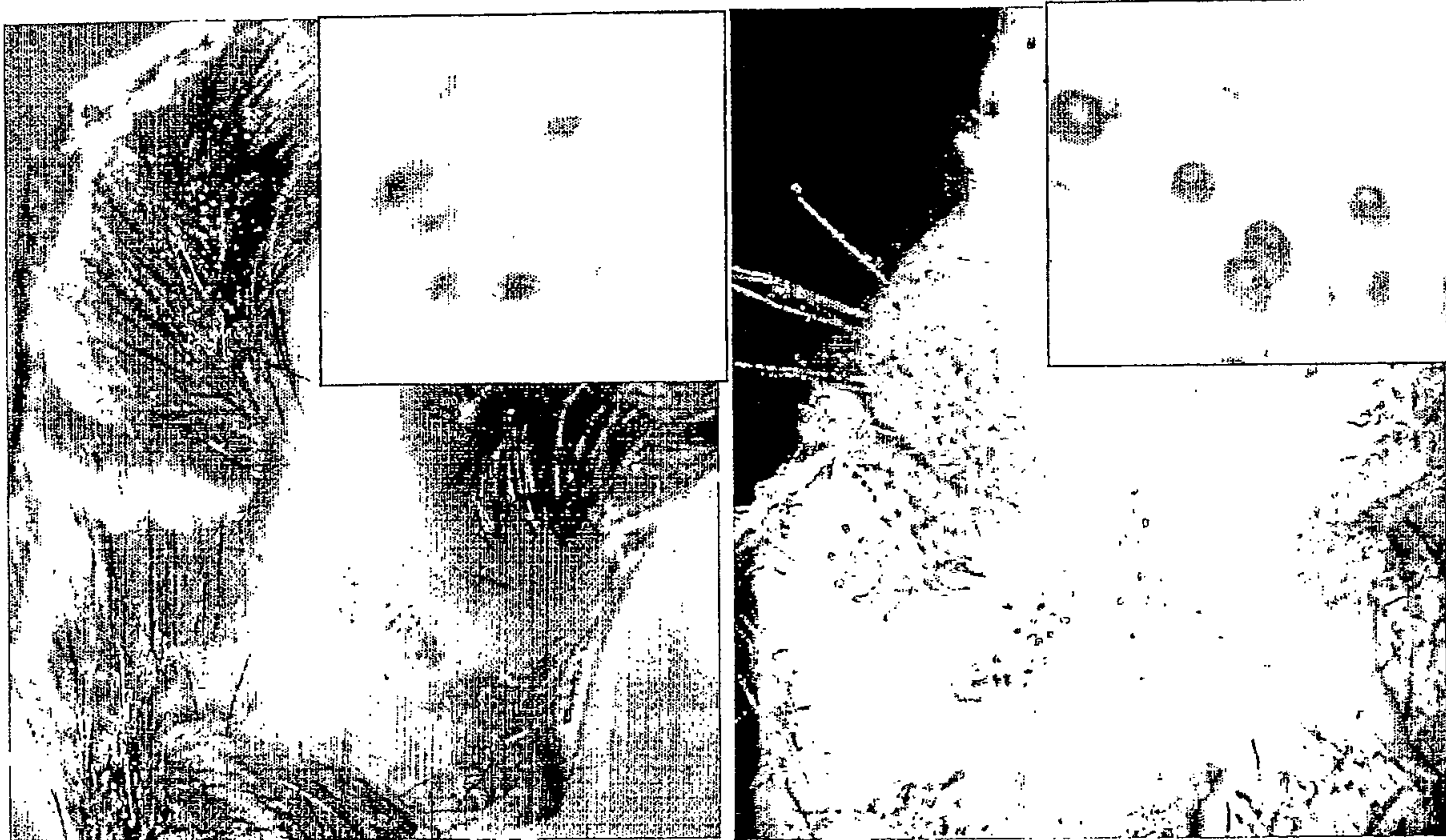


Figure 17

17 days after wound

AP

K17



Figure 18

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8 weeks old mice (2nd telogen)

Depilation x Wound wound

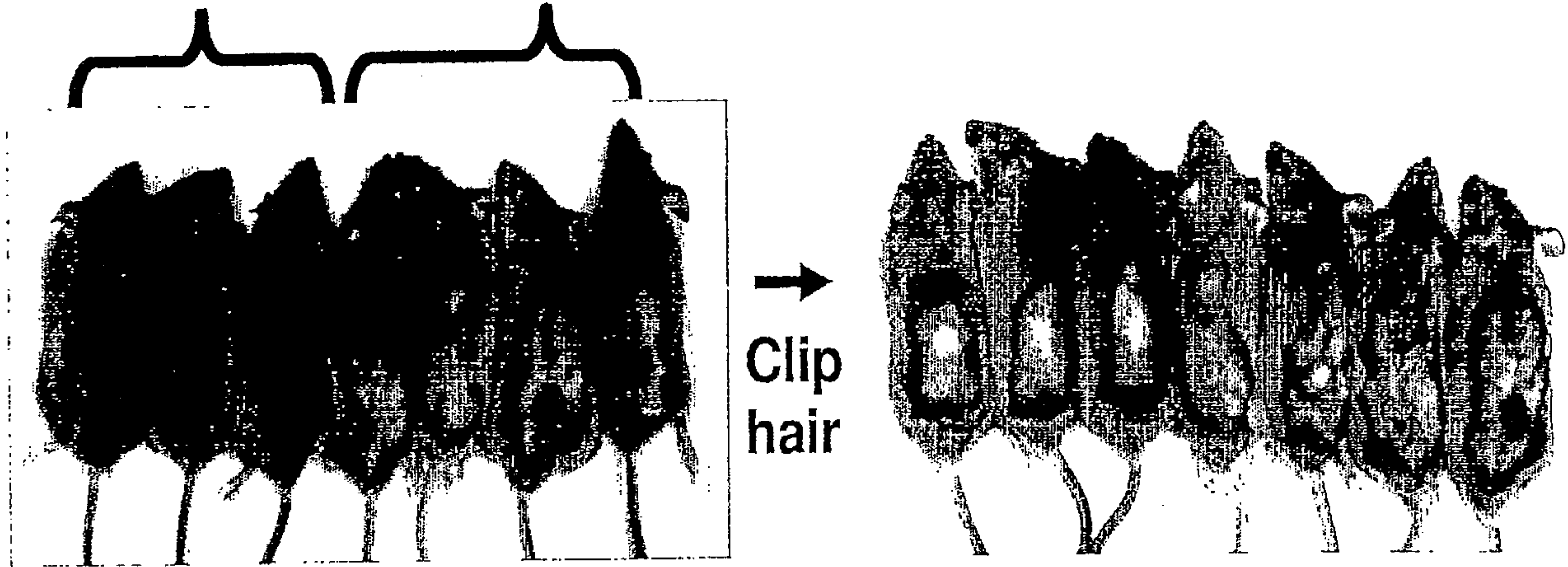
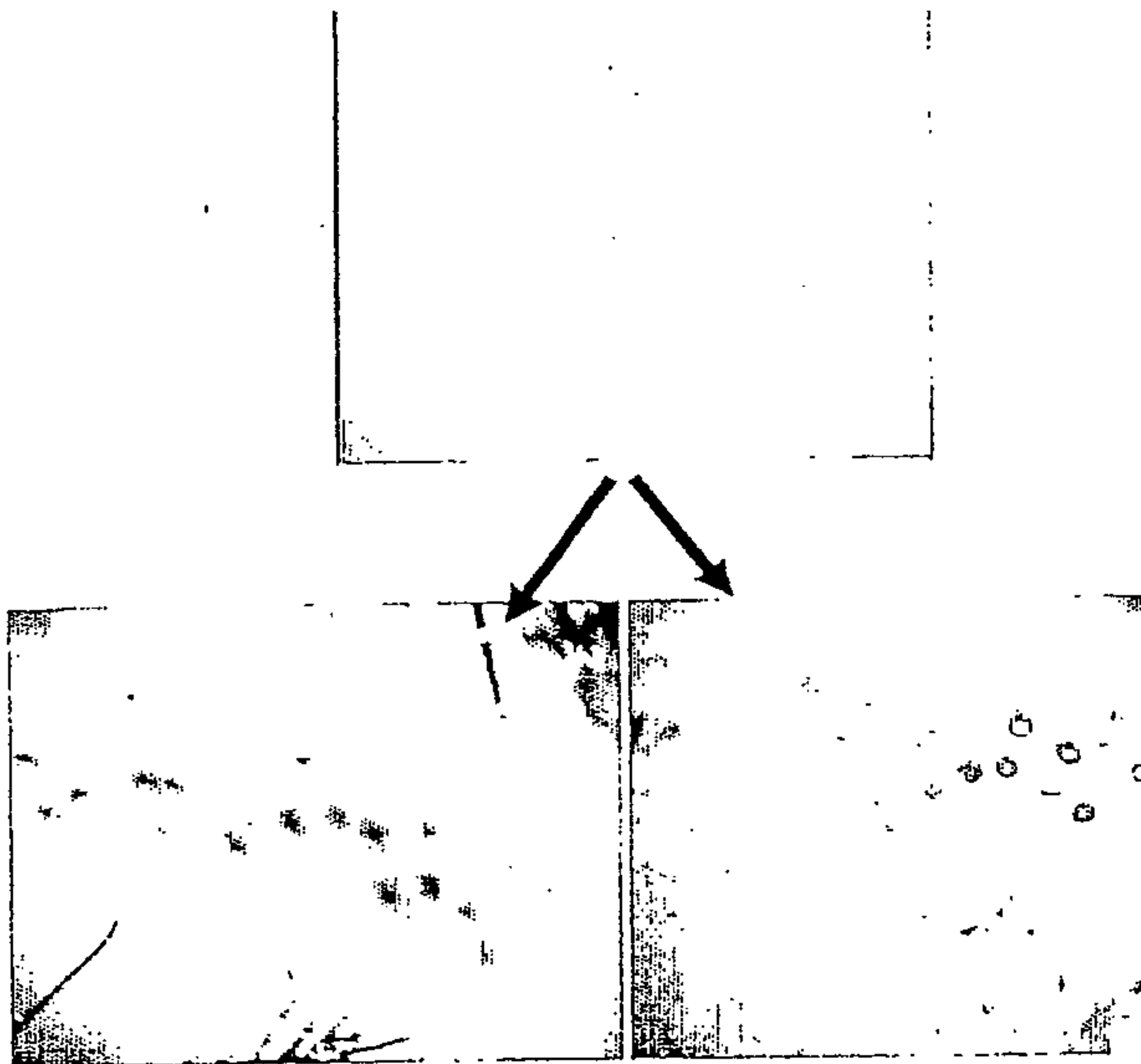


Figure 19

A.**AP****K17****B.**

WIHN assay :30 days after wound

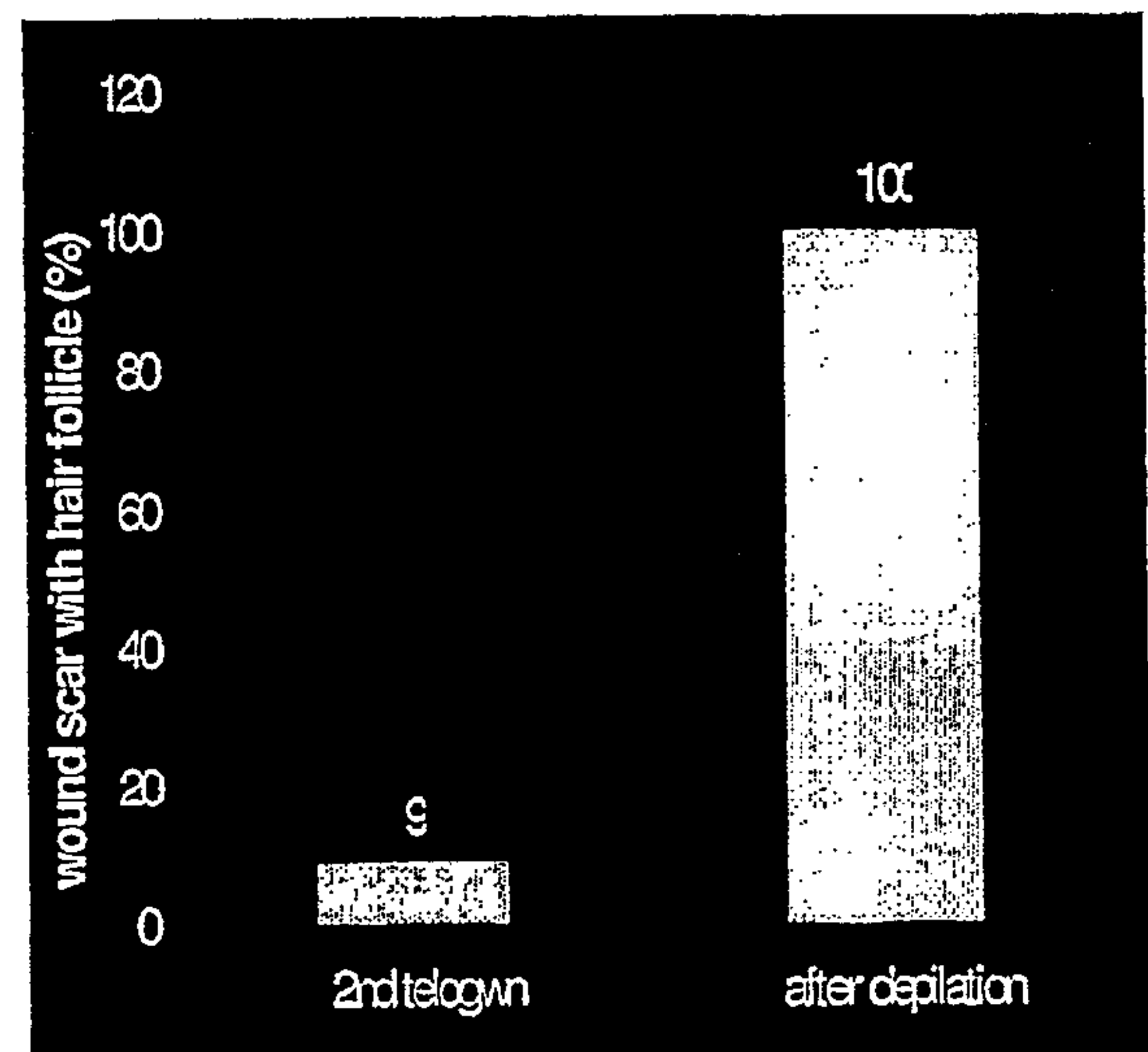


Figure 20

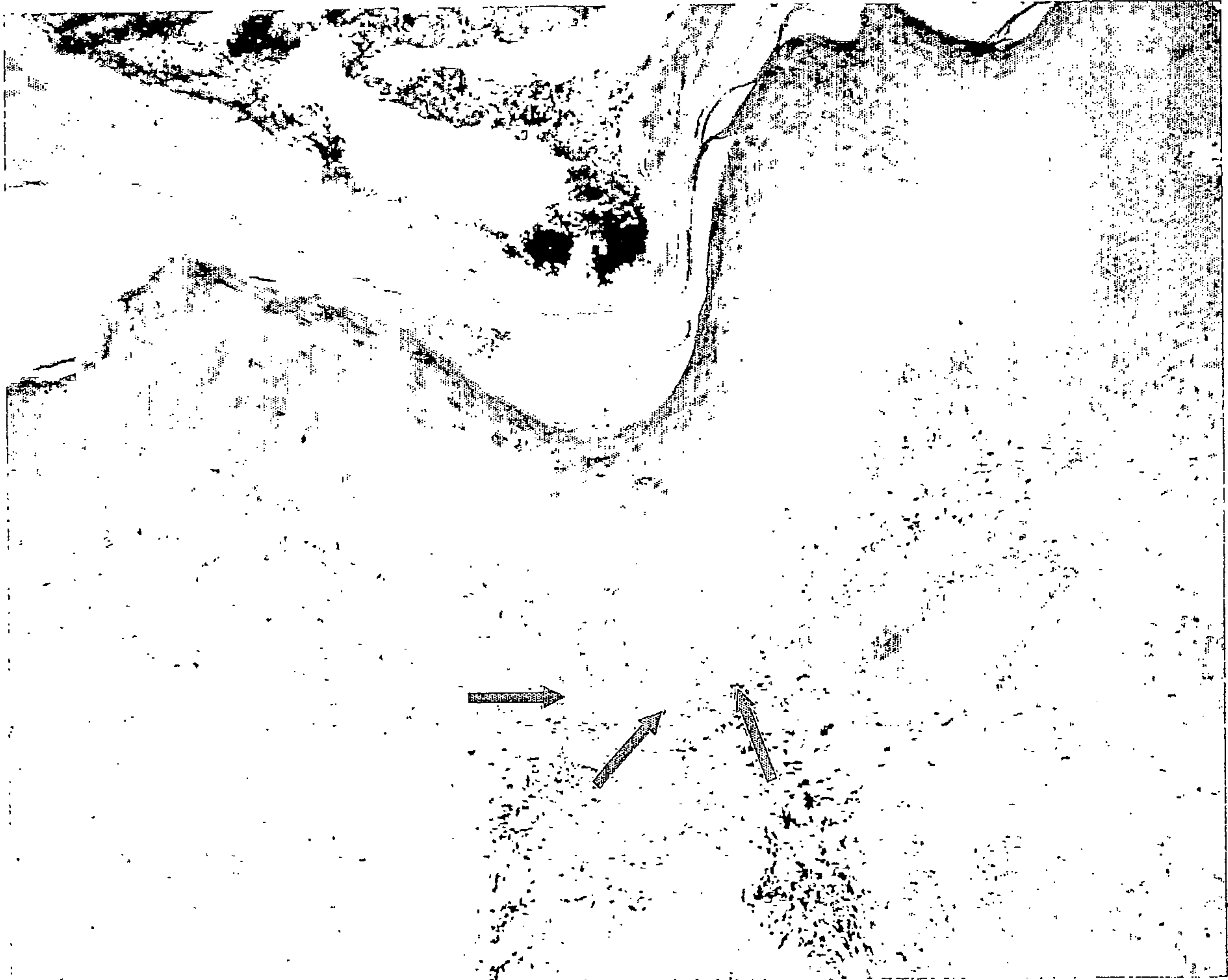


Figure 21A

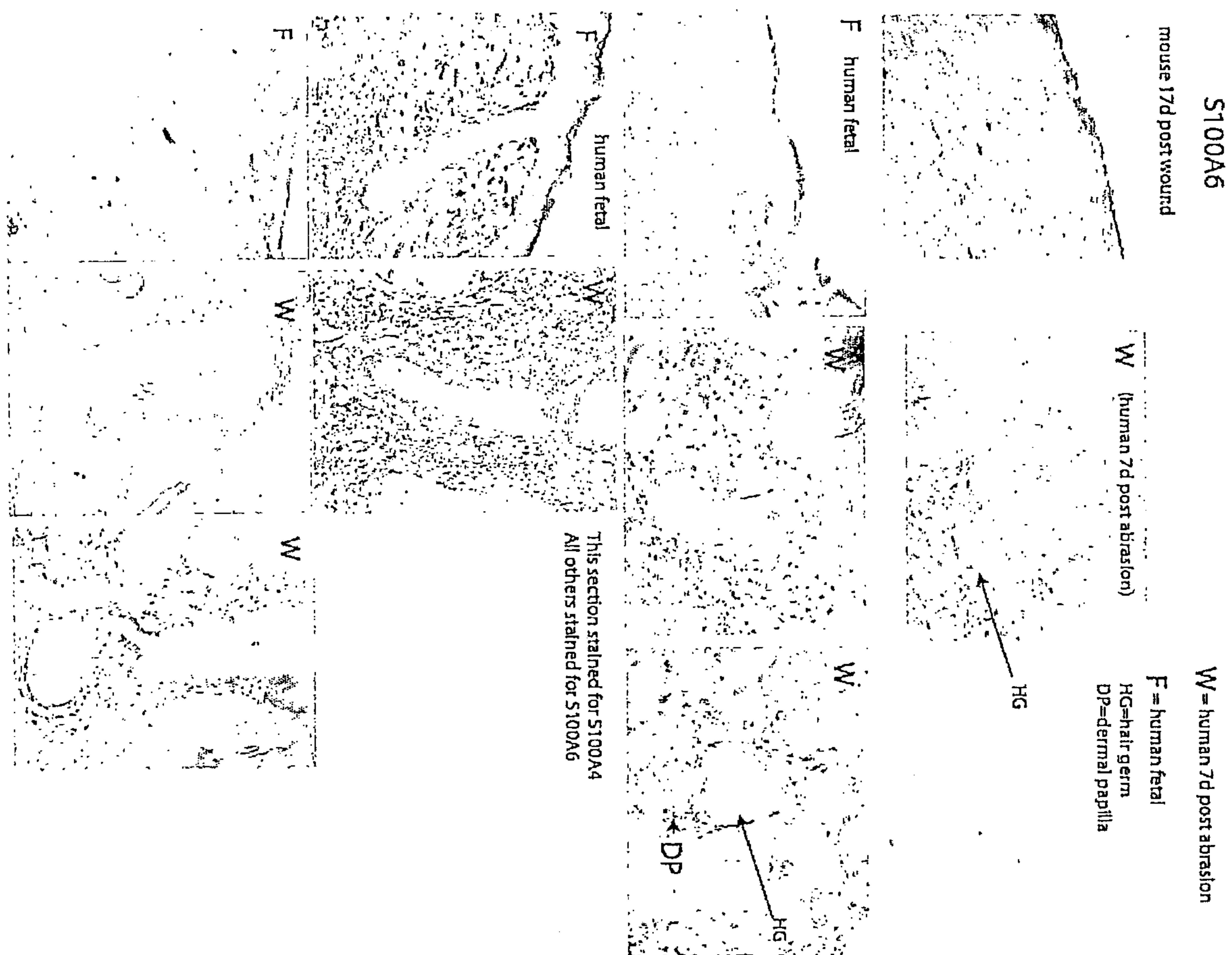


Figure 21B

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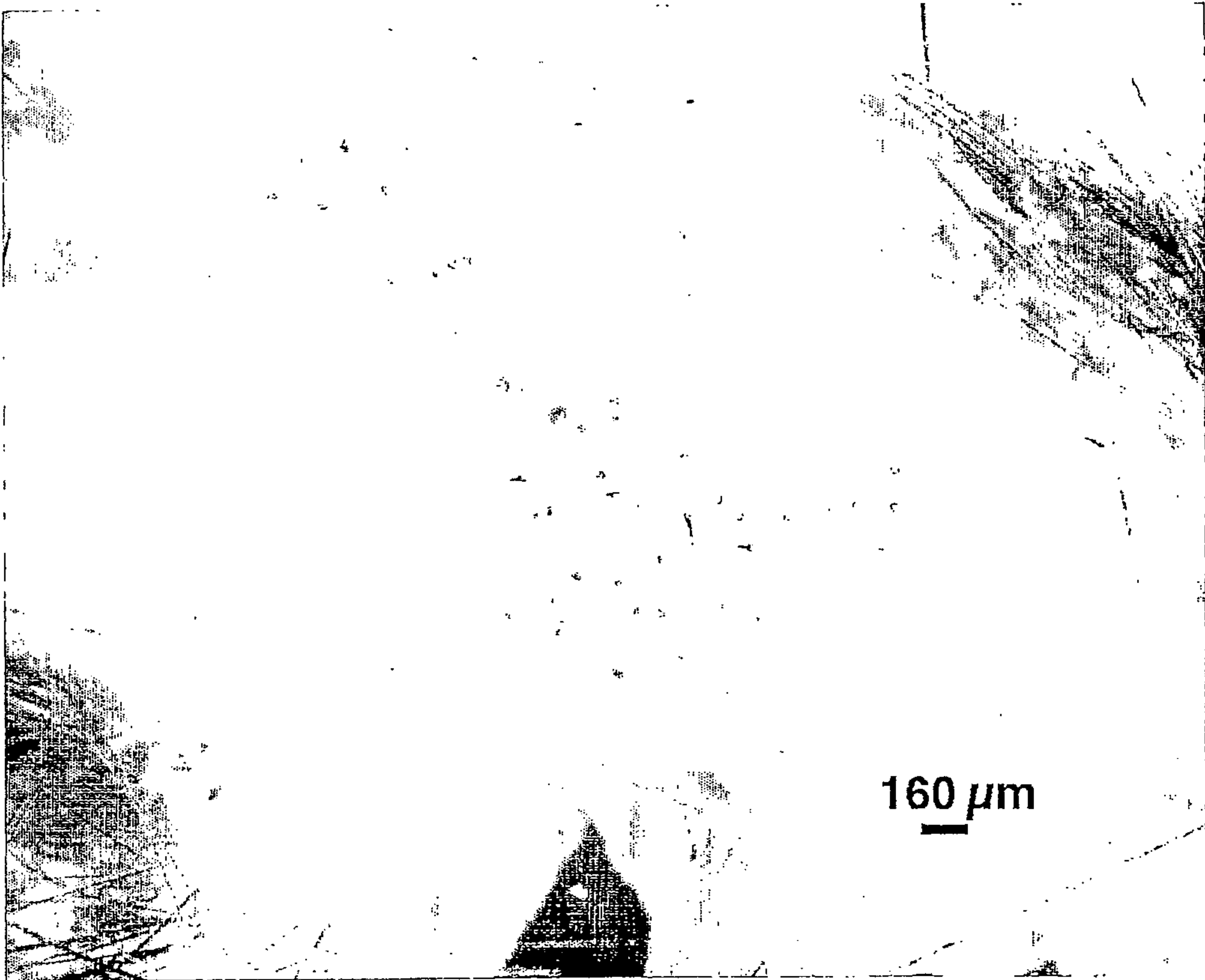


Figure 22A

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Figure 22B

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Figure 23

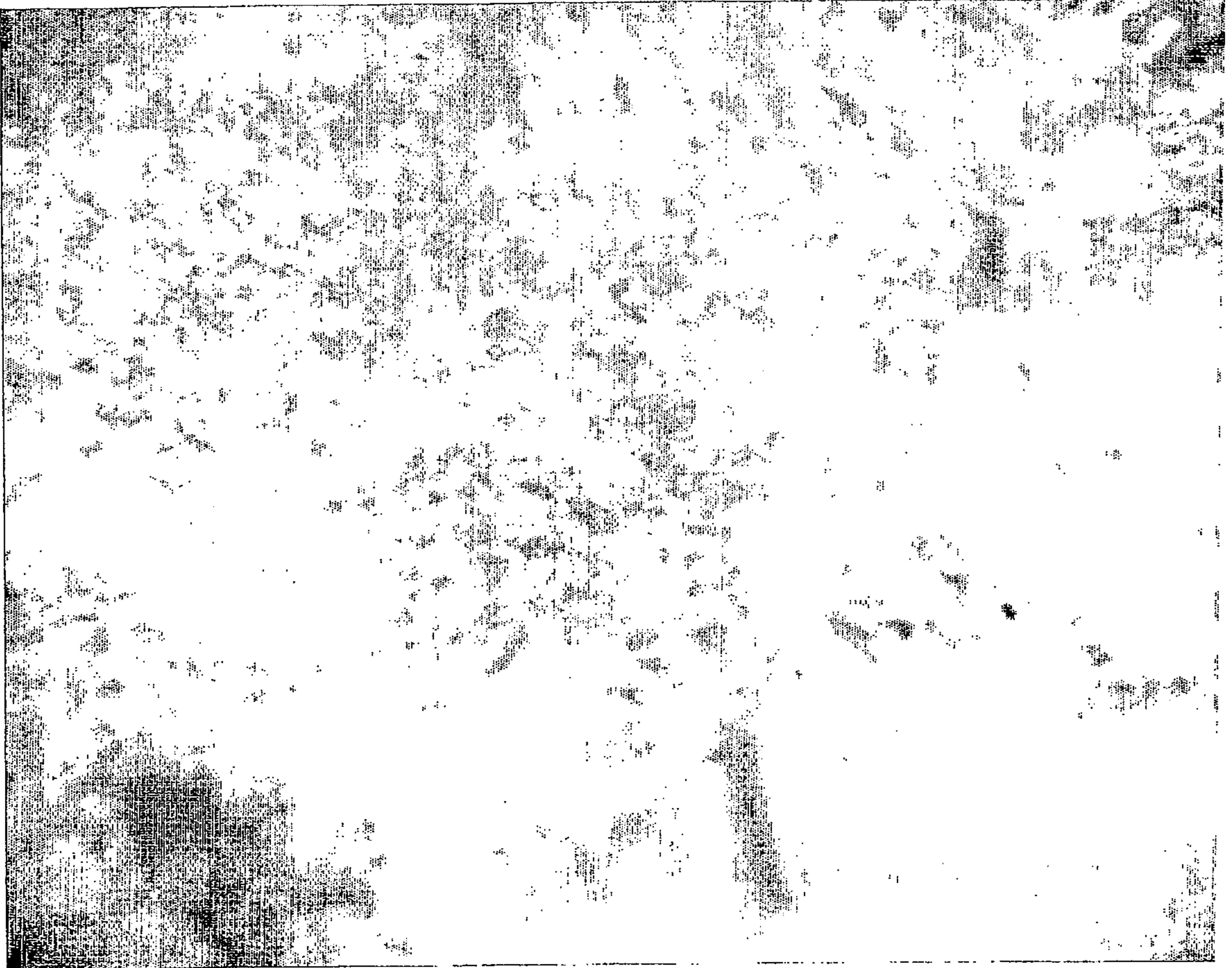


Figure 24A

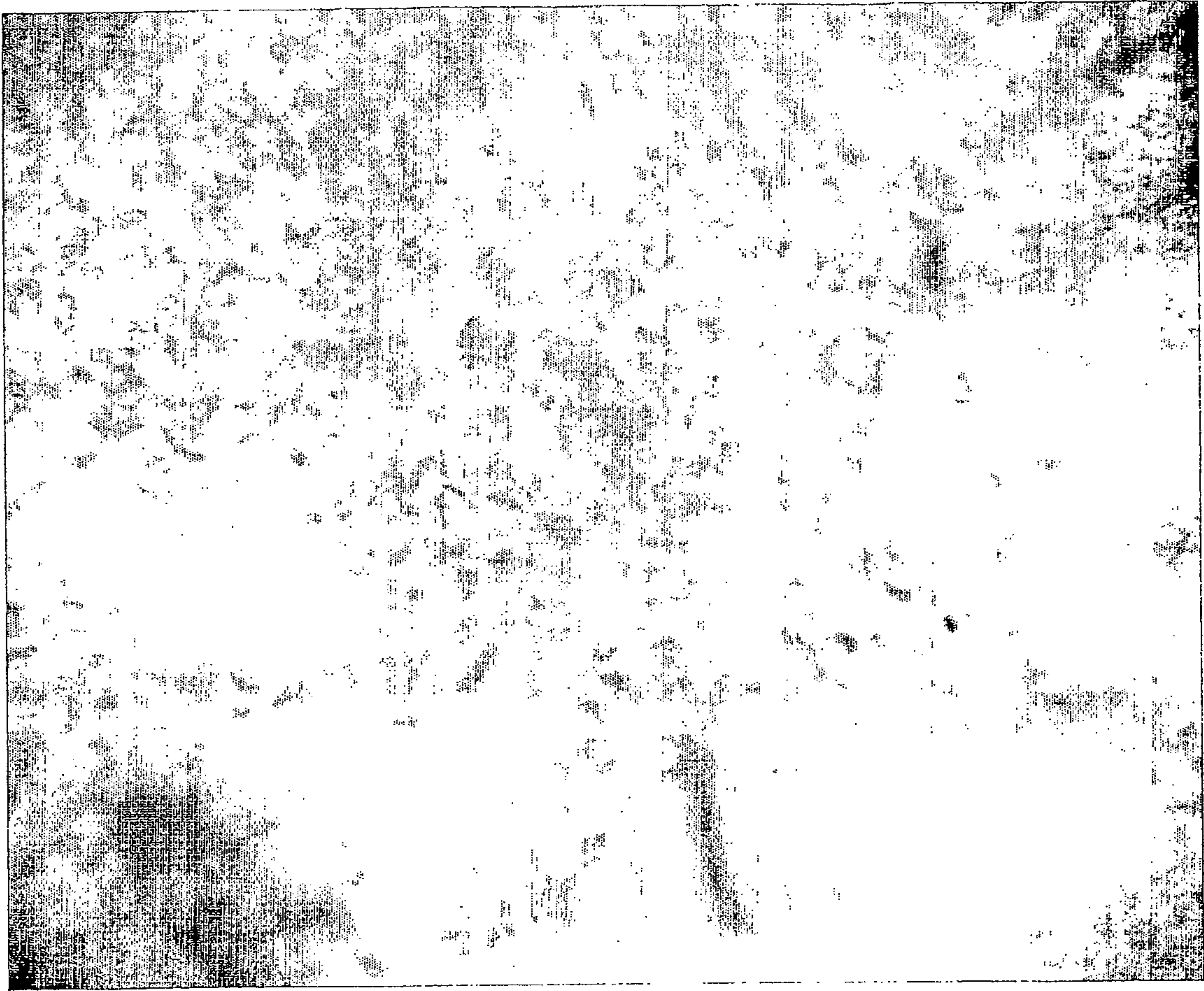


Figure 24B

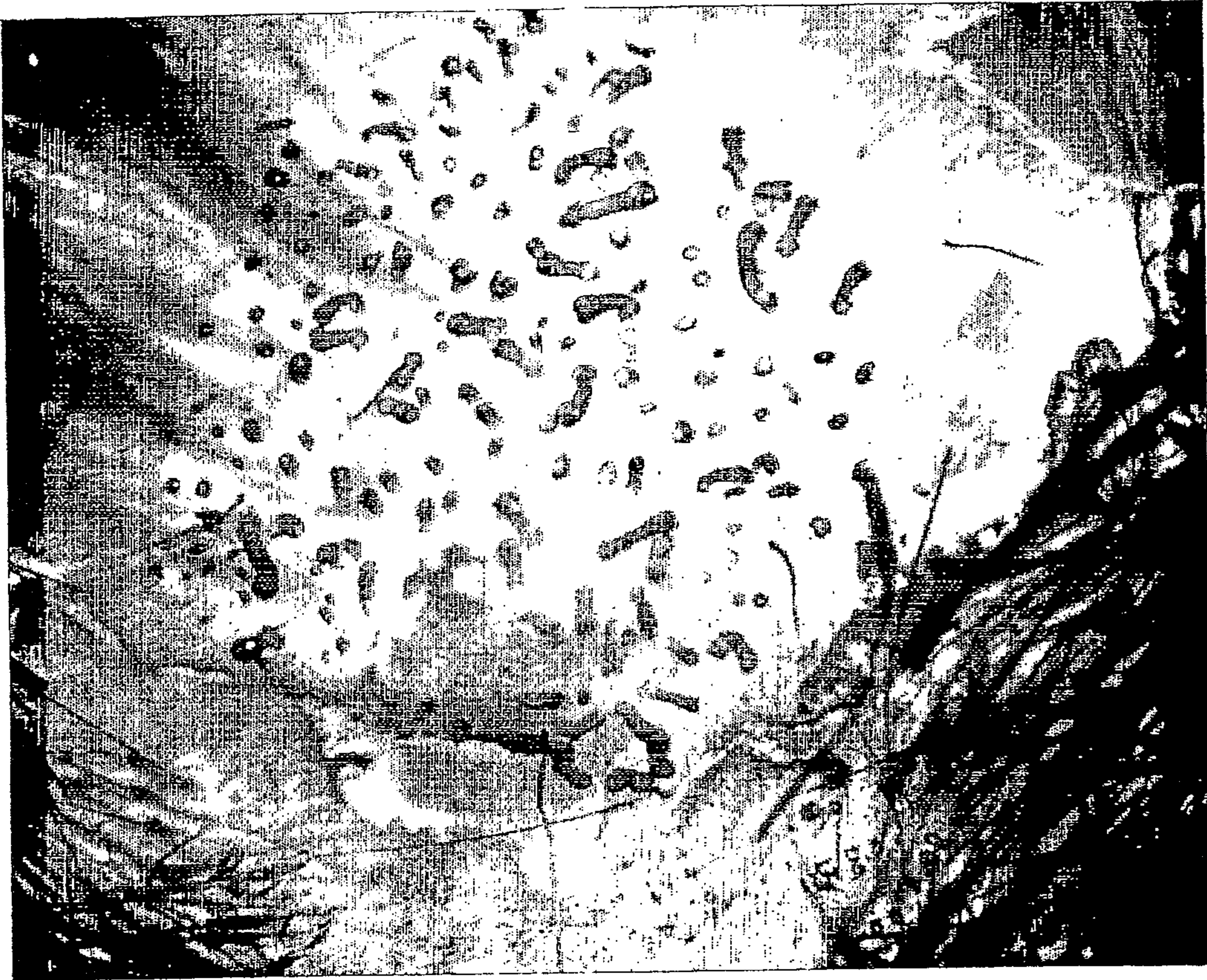


Figure 24C

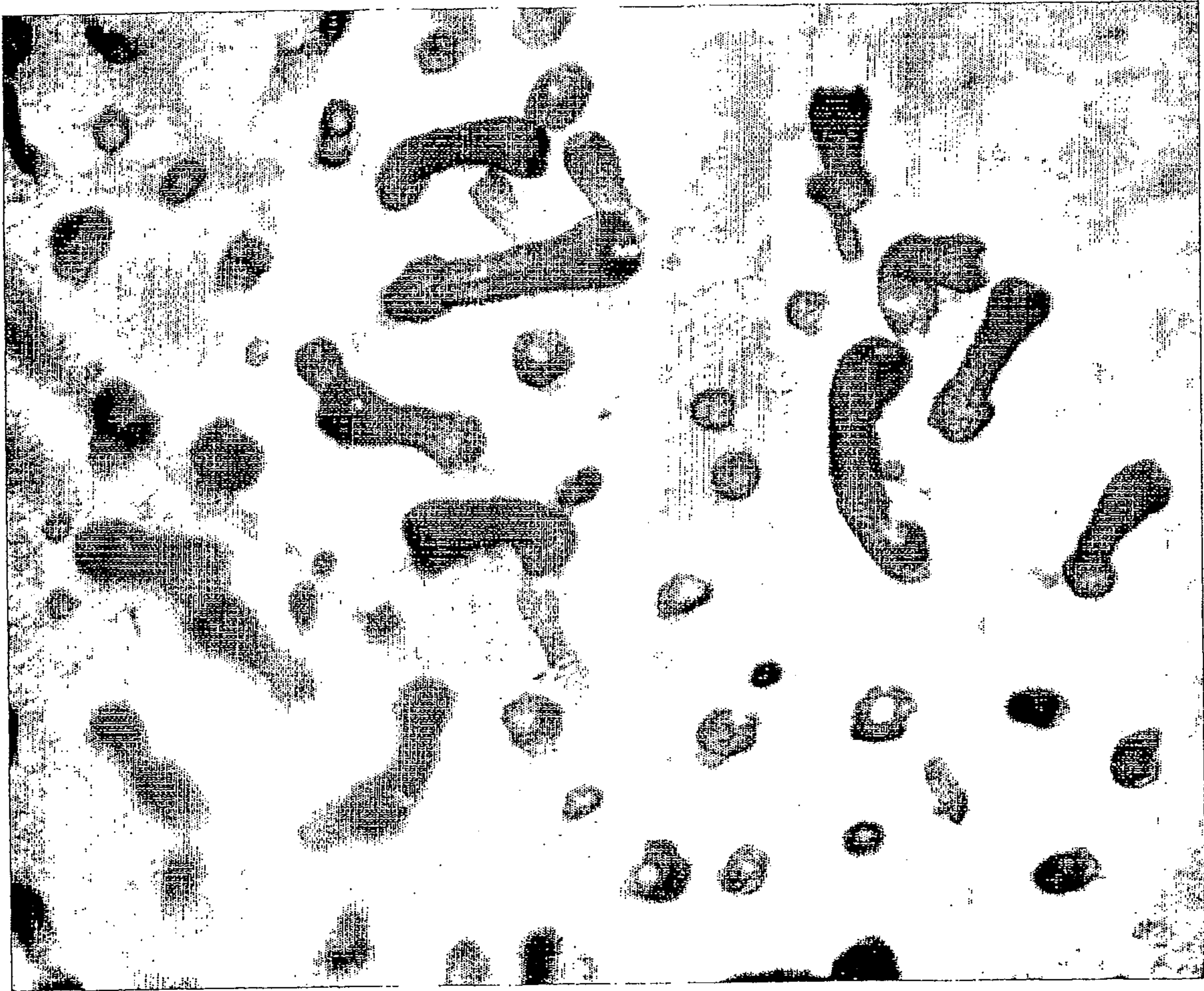


Figure 24D

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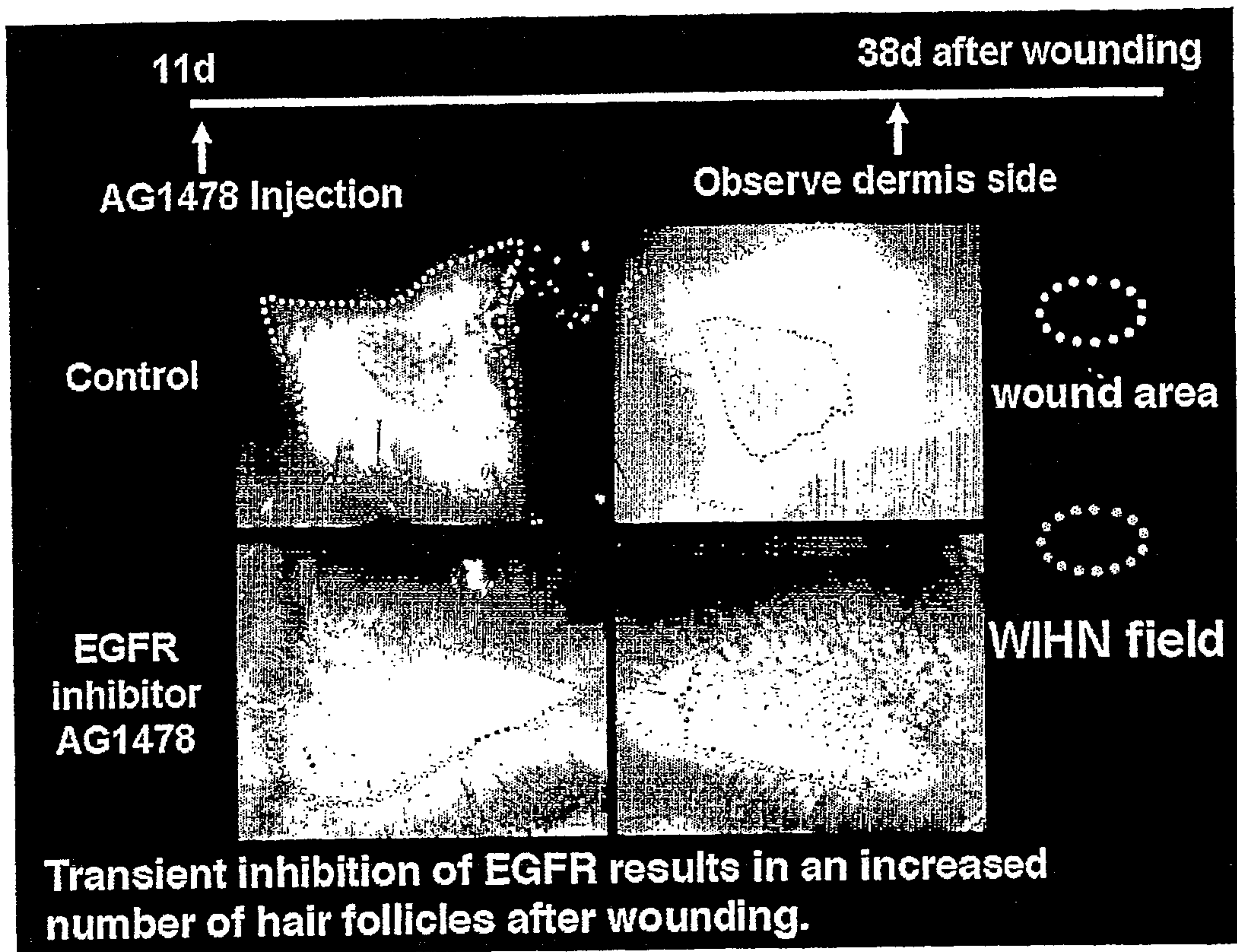


Figure 25A

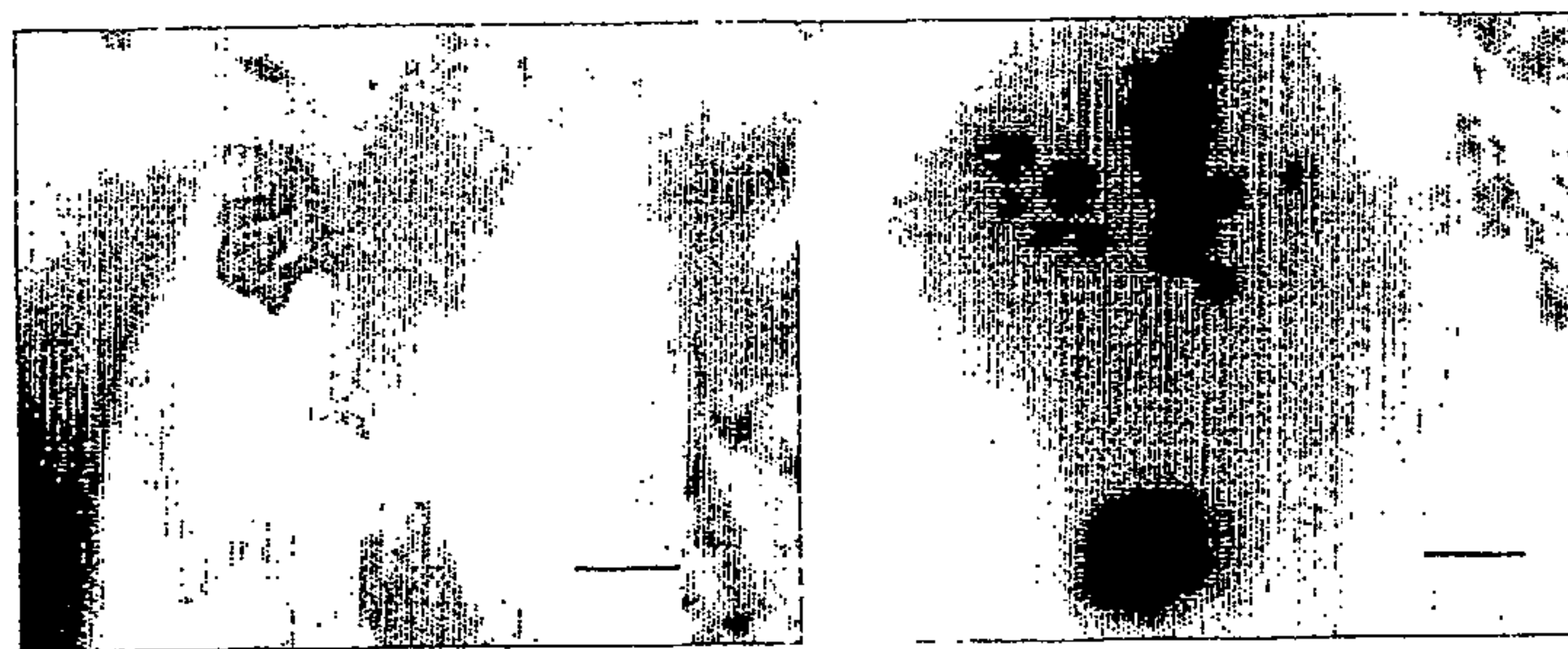


Figure 25B

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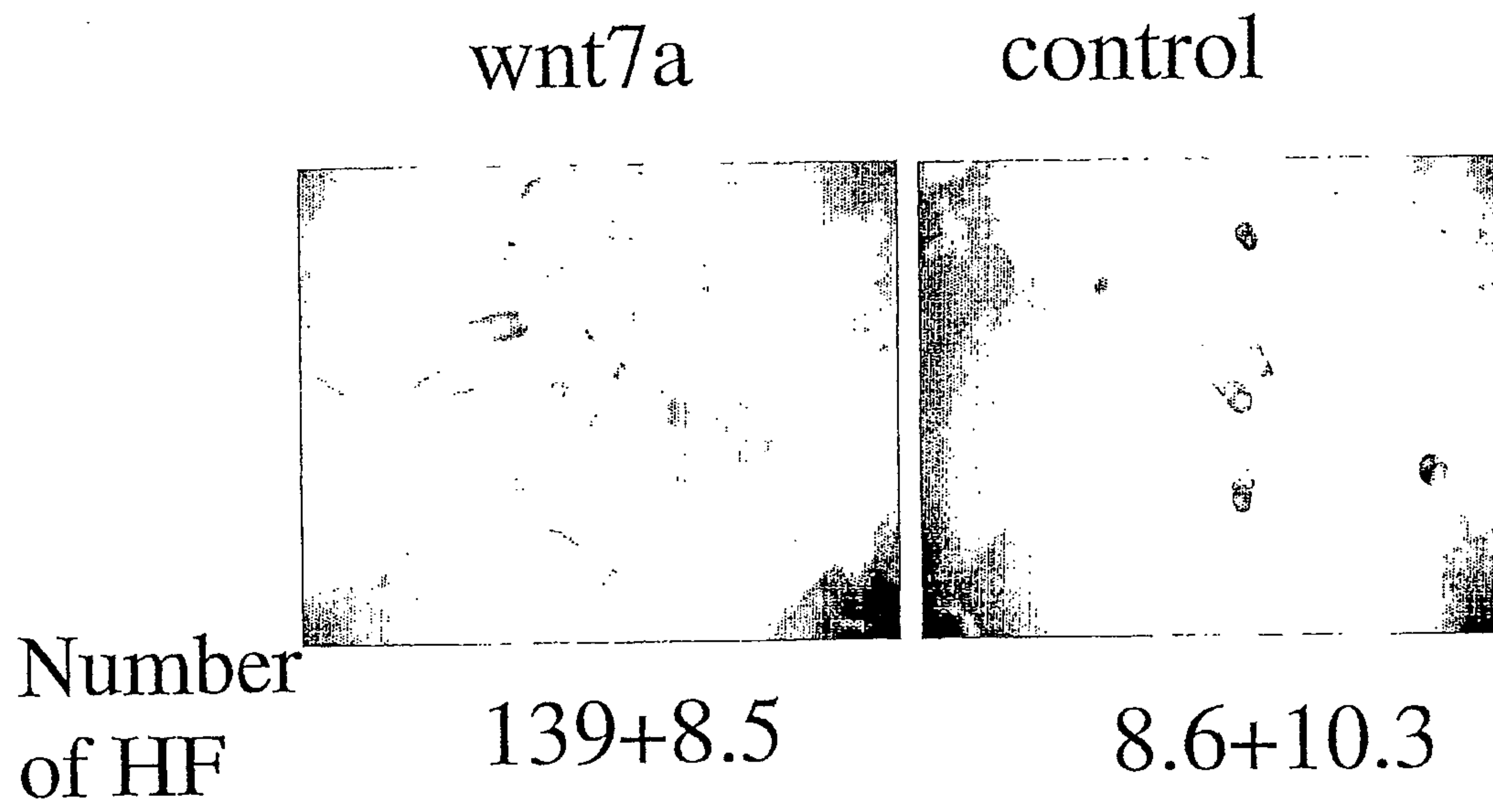


Figure 26A

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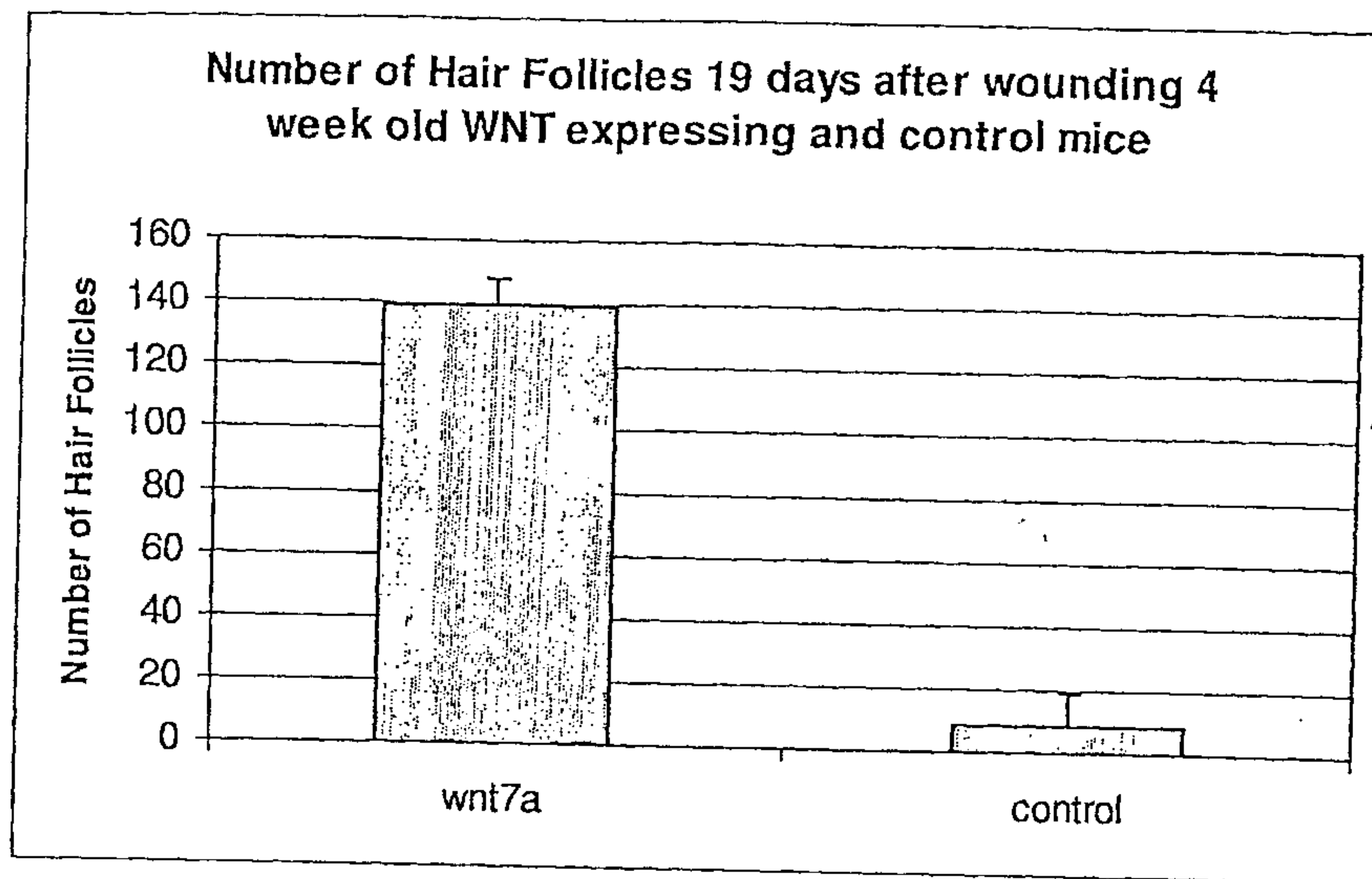


Figure 26B

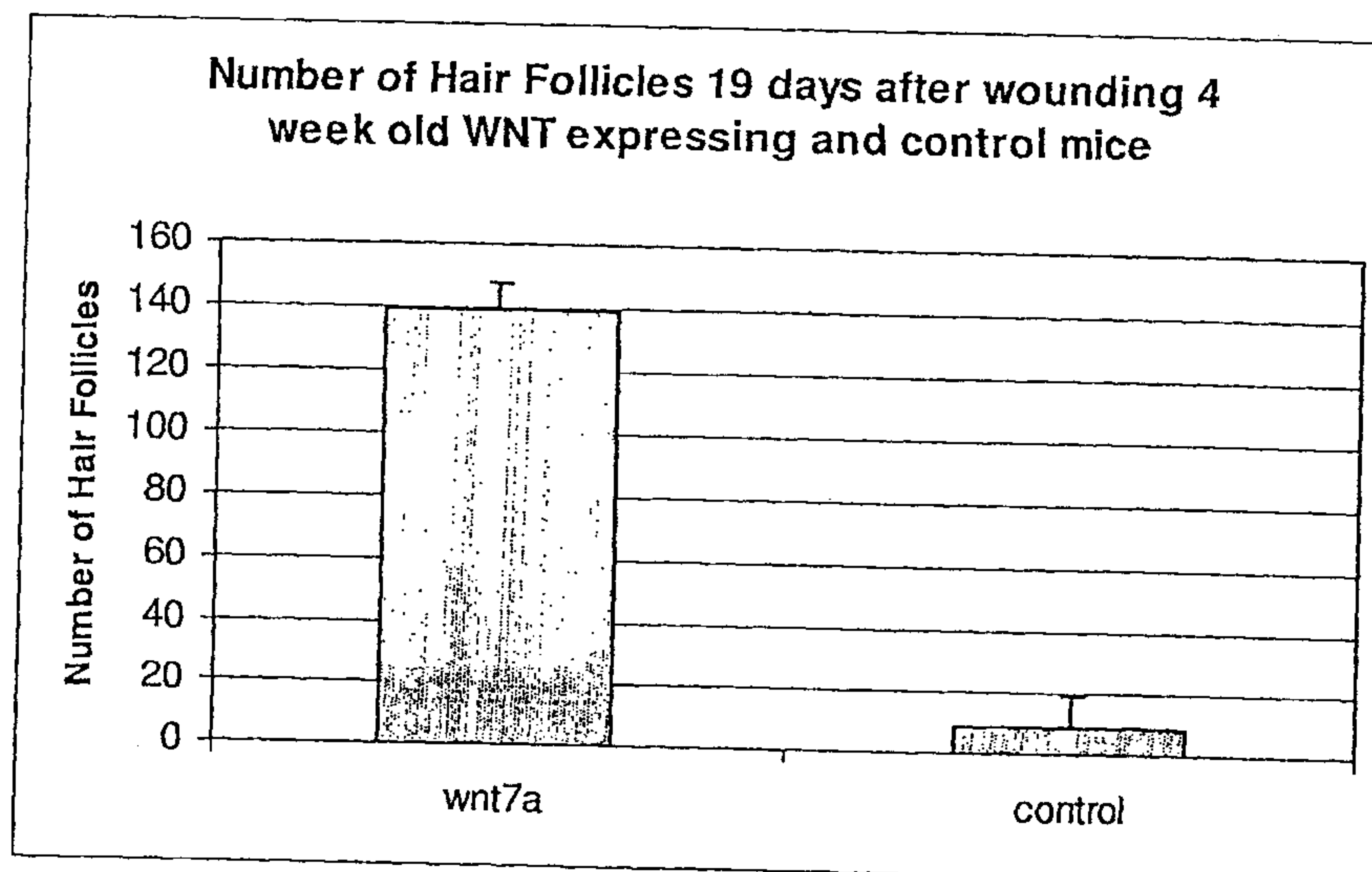


Figure 26C