



(86) Date de dépôt PCT/PCT Filing Date: 1993/04/21  
(87) Date publication PCT/PCT Publication Date: 1993/11/11  
(45) Date de délivrance/Issue Date: 2005/02/15  
(85) Entrée phase nationale/National Entry: 1994/10/12  
(86) N° demande PCT/PCT Application No.: FI 1993/000163  
(87) N° publication PCT/PCT Publication No.: 1993/021969  
(30) Priorité/Priority: 1992/04/23 (921802) FI

(51) Cl.Int.<sup>5</sup>/Int.Cl.<sup>5</sup> A61L 27/00, A61L 31/00  
(72) Inventeurs/Inventors:  
LI, PANJIAN, NL;  
KANGASNIEMI, ILKKA, FI  
(73) Propriétaire/Owner:  
VIVOXID OY, FI  
(74) Agent: SMART & BIGGAR

(54) Titre : NOUVEAUX REVETEMENTS BIOACTIFS, LEUR PREPARATION ET LEUR UTILISATION  
(54) Title: NOVEL BIOACTIVE COATINGS AND THEIR PREPARATION AND USE

(57) **Abrégé/Abstract:**

This invention relates to novel coating materials for biomedical applications, particularly for the use on biomedical implants, said coating material comprising gel-derived titania wherein said material is capable of inducing calcium phosphate formation onto its surface under in vitro conditions, e.g. in a simulated body fluid and/or under in vivo conditions. The invention further includes processes for the preparation of the coating materials as well as their use in biomedical implant technology.

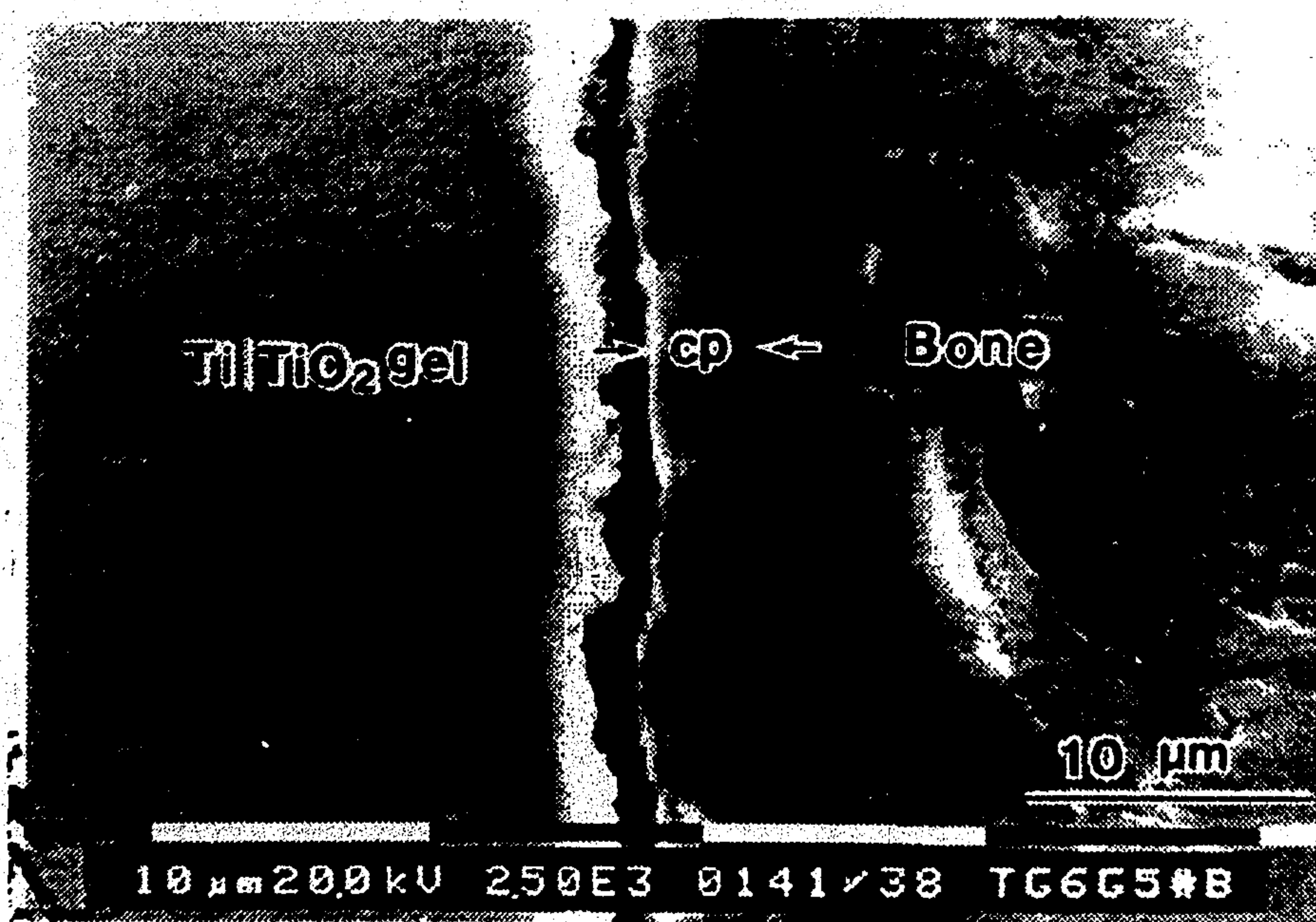




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> :  A61L 27/00	A1	(11) International Publication Number: WO 93/21969 (43) International Publication Date: 11 November 1993 (11.11.93)
(21) International Application Number: PCT/FI93/00163 (22) International Filing Date: 21 April 1993 (21.04.93) (30) Priority data: 921802 23 April 1992 (23.04.92) FI (71) Applicant (for all designated States except US): AXIDENTAL OY [FI/FI]; Yliopistonkatu 7 C 31, FIN-20110 Turku (FI). (72) Inventors; and (75) Inventors/Applicants (for US only) : LI, Panjian [CN/NL]; Endegeesterstraatweg 8, NL-2342 AJ Oegstgeest (NL). KANGASNIEMI, Ilkka [FI/FI]; Köydenpunojankatu 2 B 5, FIN-20300 Turku (FI).	(74) Agent: TURUN PATENTTITOIMISTO OY; P.O. Box 99, FIN-20521 Turku (FI). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published 2118036 With international search report.	

(54) Title: NOVEL BIOACTIVE COATINGS AND THEIR PREPARATION AND USE



## (57) Abstract

This invention relates to novel coating materials for biomedical applications, particularly for the use on biomedical implants, said coating material comprising gel-derived titania wherein said material is capable of inducing calcium phosphate formation onto its surface under in vitro conditions, e.g. in a simulated body fluid and/or under in vivo conditions. The invention further includes processes for the preparation of the coating materials as well as their use in biomedical implant technology.



## NOVEL BIOACTIVE COATINGS AND THEIR PREPARATION AND USE

This invention relates to novel bone-bonding gel-derived titania-based coatings. The invention also includes processes for the preparation of such coatings and their uses as surgical implants.

5 Titanium and its alloys are extensively used in reconstruction surgery as dental and orthopaedic implants because of their excellent biocompatibility with bone tissue (P.I. Brånemark, J. Prosthetic Dent. 50:399-410, 1983; D.I. Bardos, D. Williams (ed), Concise Encyclopedia  
10 of Medical & Dental Materials, Pergamon Press, Oxford 1990, pp 360-365; R. van Noort, J. Mater. Sci. 22:3801-3811, 1987). This can be explained by the unique characteristics of titanium-bone interface. The extremely slow growth of titanium oxide was observed during the implantation. The  
15 TiOH groups within the hydrated oxide layer were considered to be involved in the events leading to osseointegration of the titanium implants (P. Tengwall & I Lundström, Clinical Materials 9:115-134, 1992). The calcium and phosphorous groups were identified in the few nanometer thick oxide  
20 layer (D. Mcqueen et al, Clinical application of Biomaterials, John Wiley & Sons, Chichester, 1982, pp. 167-177). Although titanium implants could be fixed in bone bed through osseointegration by using appropriate surgical techniques, the fixation proceeds slowly and depends  
25 largely on surgery (L. Sennerby, PhD thesis, University of Gotenburg, Gotenburg, Sweden, 1991). To enhance the bonding process and improve the bonding strength, the plasma-sprayed coatings of apatite, more particularly hydroxyapatite, were developed and approved for clinical  
30 application (K. de Groot, J. Ceram. Soc. Japan 99:943-953, 1991). However, from a technical point of view, plasma spraying is cumbersome and essentially complex, because apatite powder is chemically unstable at elevated temperatures.



2118036

2

Implants can chemically bond to bone through apatite because bone mineral is hydroxyapatite. These bone-bonding implants could be wholly apatite ceramic or coated with apatite using specific techniques such as plasma spray coating process. Furthermore, apatite can also be used as a bioactive phase in some composites to make them bond to bone (K. Verheyen, Resorbable materials with bone bonding ability, PhD thesis, Leiden University, Holland, 1993). In contrast to those apatite-based materials, bioactive glasses and glass-ceramics develop apatite layer onto their surfaces after implantation within bone tissue (L. L. Hench, Bioceramics: from concept to clinics, J. Am. Ceram. Soc. 74:1487-510, 1991; T. Kokubo, Bioactive glass ceramics: properties and application, Biomaterials 12:155-163, 1991). This kind of apatite gives the glasses and glass-ceramics a bone-bonding strength stronger than apatite ceramics (T. Kokubo, Bioactivity of glasses and glass-ceramics, in Bone-bonding Biomaterials, P. Ducheyne, T. Kokubo and C. A. van Blitterswijk (eds), Reed Healthcare Communication, Holland, 1992, pp. 31-46). This bone-like apatite formation results from the interaction of these bioactive glasses and glass-ceramics with the surrounding biological tissue and especially with body fluid.

The potential for apatite formation can be evaluated for materials by using a metastable calcium phosphate solution, called a simulated body fluid (SBF,  $\text{Na}^+$  142,  $\text{K}^+$  5.0,  $\text{Mg}^{2+}$  1.5,  $\text{Ca}^{2+}$  2.5,  $\text{Cl}^-$  148,  $\text{HCO}_3^-$  4.2,  $\text{HPO}_4^{2-}$  1.0 and  $\text{SO}_4^{2-}$  0.5 in mM). The fluid has been used in in vitro studies to provide information about the process of bone-like apatite formation on these bioactive glasses and glass ceramics because of its ion concentrations nearly equal to those of human blood plasma (T Kokubo et al, J Biomed Mater Res 24, 721-734, 1990). Moreover, it does help a great deal to assess the possibility of bone-bonding for materials before their in vivo study. Those materials which can induce apatite formation on their surfaces in SBF can be placed in



the list of candidates for bone-bonding materials. Recent research showed that besides bioactive glass and glass-ceramics, also pure silica prepared by sol-gel method can successfully induce bone-like apatite formation on its surface whereas pure silica glass and quartz both synthesized at high temperature cannot (P Li et al "Apatite formation induced by silica gel in a simulated body fluid", J. Am. Ceram. Soc. 75: 2094-2097, 1992). One difference in characteristics among these three silica exists in the density of silanol groups (SiOH). The gel-derived silica has abundant SiOH groups whereas both silica glass and quartz do not have. Furthermore, bioactive glasses prepared by sol-gel process were reported to form apatite faster than the same glasses but prepared through conventional melting methods (R. Li et al, J App Biomater 2:231-239, 1991).

Based on these findings, we suspected that titania is also an apatite inducer if it is prepared by sol-gel method. In vitro study with the titania gel showed evidence to support our speculation. It was found that apatite is induced by the titania gel when soaked in SBF both as bulk and as coating. Figure 1 represents scanning electron microscopic (SEM) micrographs showing a) hydroxyapatite formation on the bulk (above) and b) coating (below) of gel-derived titania after they are soaked in SBF. The implantation with gel-derived titania coated titanium plugs in the femura of goats revealed that calcium phosphate could accumulate and deposit onto and/or within the titania gel coating. As shown in Figure 2, this calcium phosphate layer bridges the bone and the coating so that they can bond to each other. We consider that abundant TiOH groups remained in gel-derived titania are responsible for its high affinity for calcium and phosphate.

Swedish Patent No. 464911 describes a Ti-gel film produced by treating the titanium surface with hydrogen peroxide under certain conditions. The reaction was considered to

alter  $\text{TiO}_2$  into  $\text{TiO}_{4-x}(\text{OH})_x$ . The patent claimed such a surface to possess anti-inflammatory properties. The inventors suggested that "such a gel-surface resulting from the reactions in vivo might have something to do with a formation of chemical bonding of the bone to the titanium implants". However, the document did not show any evidence or indication that the treated titanium surface might be bioactive. There is no mention of a Ca,P-layer, which is generally accepted as a prerequisite for the bone bonding to occur. Our experiments clearly demonstrated that a Ca,P-layer forms onto the titania-gel derived coating both in vitro and in vivo, which is a basic difference from the Ti-gel surface described in the Swedish patent.

The apatite induction capacity of gel-derived titania could be enhanced by the corporation of, for instance,  $\text{CaO}$ ,  $\text{P}_2\text{O}_5$ ,  $\text{Na}_2\text{O}$  or  $\text{SiO}_2$  into the titania. They can be introduced during the process to make titania-based materials. As a matter of fact, the effect of these additive compounds on bone-bonding has been determined for bioactive glasses and glass-ceramics (L.L. Hench: "The compositional dependence of bioactive glasses and glass ceramics", P Vincenzine (ed), Ceramics in substitutive and reconstructive surgery, Amsterdam, Elsevier, 1991, pp. 259-274).  $\text{Al}_2\text{O}_3$ ,  $\text{B}_2\text{O}_3$ ,  $\text{MgO}$  and  $\text{K}_2\text{O}$  may be added as well. They can remain in the oxide form within the coating or, at least to some extent, release the corresponding ions.

In addition to the sol-gel process used for the preparation of titania having sufficient  $\text{TiOH}$  groups, a galvanic process can also be considered. Our studies have shown that the gel-like surface formed on a negative titanium pole when two pieces of titanium plates were placed at a distance in a hydroxide solution ( $\text{Ca}(\text{OH})_2$  in this case) with a proper pH value under certain voltage. Figure 3 shows SEM photograph of Ti-gel formed on the negative Ti-pole where SEM-EDX showed the accumulation of Ca and P when soaked in SBF (original magnification: 680x, bar (white) 100  $\mu\text{m}$ ).



74583-5

5

This gel was thus capable of attracting Ca and P ions from surrounding calcium phosphate solution. Such surface could be expected to promote bone-bonding compared to untreated titanium surfaces. Oxides of Ca, P, Na, Si, Al, B, Mg and K  
5 may also be added during the galvanic process to improve the coatings.

It can be expected that a strong bonding between titanium implant and gel-derived titania-based coating can be developed through a passivating titanium oxide layer which  
10 could secure a lasting strong bone bonding. Furthermore, it is simple in technique to develop the gel-derived titania coating on titanium and its alloys compared with plasmasprayed technique. Hence, the development of gel-derived titania-based coatings on titanium and its alloys is  
15 highly interesting from both scientific and application points of view. Such gel-derived titania-based materials are believed to give rise to an-entirely new generation of bone-bonding materials.

#### SUMMARY

20 In one aspect of the invention, there is provided a novel coating material for a biomedical application, characterized in that it comprises mainly a gel-derived titania-based material that has been treated at elevated temperature, wherein the material is capable of inducing calcium  
25 phosphate formation onto its surface under in vitro conditions and/or under in vivo conditions.

In another aspect of the invention, there is provided a process for the preparation of a coating material for use on a biomedical implant characterized in that a gel-derived  
30 titania-based coating is formed according to a sol-gel method.

74583-5

5a

In a further aspect of the invention, there is provided a process for the preparation of a coating material for use on a biomedical implant characterized in that gel-derived titania-based coating is formed according to a galvanic  
5 method.

In yet a further aspect of the invention, there is provided an implant for biomedical use comprising a substrate and a bone-bonding coating material thereon characterized in that the coating material is a gel-derived titania-based coating  
10 material that has been treated at elevated temperature.

In yet a further aspect of the invention, there is provided an implant for biomedical use comprising a substrate and a bone-bonding apatite layer thereon characterized in that the apatite layer has been grown on a gel-derived titania  
15 coating in an in vitro solution.

In yet a further aspect of the invention, there is provided an implant for biomedical use comprising a substrate and a bone-bonding layer thereon characterized in that the bone-bonding layer is essentially a mixture of gel-derived  
20 titania and apatite, the apatite component having been grown on a gel-derived titania coating in an in vitro solution.

#### DETAILED DESCRIPTION

Thus, one object of the invention is a novel gel-derived titania-based coating material having abundant TiOH groups  
25 for biomedical application, said coating material has been treated at elevated temperature and being capable of inducing apatite formation onto its surface under in vitro conditions, e.g. in a simulated body fluid, and/or calcium phosphate deposition under in vivo conditions. According to  
30 one aspect of the invention, the coating material can further comprise one or more of the following elements



74583-5

5b

either as ions or as oxides: Ca, P, Si, Na, K, B, Mg and Al. These additives are introduced to enhance calcium phosphate formation and improve the stability of the coating.

Another object of the invention is a method for the  
5 preparation of a gel-derived titania-based coating material according to a sol-gel method.

Another object of the invention is a method for the

74583-5

6

preparation of a gel-derived titania-based coating material by a galvanic process. Preferably the process is carried out in a hydroxide solution where titanium is used as the positive as well as the negative pole. According to this process a titania gel surface is formed on the negative pole.

Another object of the invention is a method for the preparation of a gel-derived titania-based coating material according to a sol-gel method or the galvanic method wherein one or more of the following oxides are added to the process:  $\text{CaO}$ ,  $\text{P}_2\text{O}_5$ ,  $\text{Na}_2\text{O}$ ,  $\text{SiO}_2$ ,  $\text{K}_2\text{O}$ ,  $\text{Al}_2\text{O}_3$ ,  $\text{B}_2\text{O}_3$  and  $\text{MgO}$ .

A further object of the invention is an implant for biomedical application comprising of a substrate and a gel derived titania-based coating material thereon, said coating material has been treated at elevated temperature and being capable of inducing apatite formation onto its surface under in vitro conditions, e.g. in a simulated body fluid, and/or calcium phosphate deposition under in vivo conditions.

According to one aspect of the invention the substrates are tooth, hip or other joint implant substrates, or other biomedical implant substrates.

According to another aspect of the invention the substrate is a polymeric, metallic, ceramic, carbon substrate or a composite substrate comprising one or more of said components.

According to a preferred aspect of the invention the substrate is titanium or a titanium alloy.

A further object of the invention is an implant for biomedical application comprising of a substrate and a gel-derived titania-based coating material thereon, said coating material being capable of inducing calcium phosphate formation onto its surface in vitro e.g. in a



simulated body fluid and/or in vivo, wherein the coating material further comprises one or more of the following elements either as ions or as oxides: Ca, P, Si, Na, K, B, Mg or Al.

- 5 According to a further aspect of the invention the implant comprises a substrate and an apatite layer, said layer having been grown on a gel-derived titania coating in a synthetic solution, preferably a SBF solution.

10 According to a further aspect of the invention the implant comprises a substrate and a layer being essentially a mixture of gel-derived titania and apatite, said apatite component having been grown on a gel-derived titania coating in a synthetic solution, preferably a SBF solution.

15 According to the sol-gel method, a titania gel coating was prepared by a dipping process. A substrate is dipped in a ready-to-use titania sol solution and withdrew at the speed of about 5-50 cm/min. After kept at ambient temperature for 5-10 minutes, the gel film on the substrate was treated at 350-750°C for 3-30 minutes and then allowed out the oven to  
20 cool in air. Subsequently, the coating was given a ultrasonic cleaning in: (a) acetone for 3-10 minutes; (b) ethanol for 3-10 minutes. After that, the coating was rinsed with deionized water and dried. The devices can be repeatedly coated for several time to obtain thicker  
25 titania gel coatings. The titania sol solution was prepared by hydrolyzation of tetraisopropyl orthotitanate ( $\text{Ti}(\text{C}_3\text{H}_7\text{O})_4$ ). 5-20 grams of this titanium alkoxide was dissolved into 10-30 grams of absolute ethanol. The hydrolyzation of titanium alkoxide takes place when the  
30 above solution is mixed at 0°C with another ready-to-use solution with the composition: absolute ethanol 5-15, ethylenglycolmonoethylether ( $\text{C}_4\text{H}_{10}\text{O}_2$ ) 2-5,  $\text{H}_2\text{O}$  0.5-1.5 and condensed HCl 0.5-1.5 in gram. The titania sol solution is then used for coating after its aging for 0.5-30 hours. A  
35 bulk titania gel was prepared by evaporating HCl-peptized



2118036

8

amorphous titania sol 50 nm in size in an oven at 80°C. The gel was heated at 400-700°C for 2 hours. A silica gel was prepared by hydrolysis of tetrahydroxysilane in an aqueous solution containing polyethylene glycol with average  
5 molecular weight of 10,000 and small amount of nitric acid. The organic phase was leached out in ethanol-water solution. The gel was heated at 400°C for 2 hours. An alumina gel was prepared by evaporating HCl-peptized amorphous alumina sol 100 x 10 nm in size in an oven at  
10 80°C. The gel was heated at 450°C for 2 hours.

A rectangular piece 6 x 6 x 1.5 mm<sup>3</sup> of the gels was soaked in 12 ml of SBF. The concentrations of Ca and P in the fluid were monitored with inductively coupled plasma (ICP) emission spectroscopy during the soaking. After various  
15 periods, the gel pieces were removed from the fluid and their surfaces were analyzed with a thin-film X-ray diffraction (TF-XRD), Fourier transform infra-red reflection spectroscopy (IRRS) and scanning electron microscopy (SEM).

20 ICP measurements showed that Ca and P concentrations in the fluid appreciably decreased with soaking of the titania and silica gel. Soaking of alumina gel did not affect the Ca and P concentration. Figure 4 shows SEM photographs of the surfaces of the silica gel (top) and titania gel (bottom)  
25 soaked in SBF for 2 weeks. It can be seen from Figure 4 that a certain kind of deposition is formed on the surfaces of both silica and titania gel. No deposition was observed on an alumina gel. The deposit on the silica and titania gels was identified as a carbonate-containing hydroxy-  
30 apatite of small crystallites and/or defective structure, similar to the apatite in the natural bone, by the TF-XRD and IRRS. It is apparent from the results that both gel-derived silica and gel-derived titania induces apatite formation.

35 A model is produced to explain the apatite induction from



physiological-related fluids. It is considered that both silica gel and titania gel are capable of inducing apatite formation due to their abundant OH groups and negatively charged surfaces at physiological pH 7.4. The surfaces with  
5 negative charge has high affinity for Ca ions which can be accumulated around the surfaces because of Coulomb's force. Meanwhile, phosphate groups are attracted by abundant OH groups as a result of hydrogen bond. Therefore, both calcium ions and phosphate ionic groups rally around the  
10 surfaces and accumulate to such extent that heterogeneous nucleation of apatite occurs.

CLAIMS:

1. A novel coating material for a biomedical application, characterized in that it comprises mainly a gel-derived titania-based material that has been treated at elevated temperature, wherein the material is capable of inducing calcium phosphate formation onto its surface under in vitro conditions and/or under in vivo conditions.
2. The coating material according to claim 1 characterized in that it further comprises as additive one or more of the following elements either as ions or oxides: Ca, P, Si, Na, K, B, Mg or Al.
3. The coating material according to claim 1 or 2, wherein the in vitro conditions are a simulated body fluid.
4. The coating material according to claim 1, 2 or 3 for use on a biomedical implant.
5. A process for the preparation of a coating material for use on a biomedical implant characterized in that a gel-derived titania-based coating is formed according to a sol-gel method.
6. A process for the preparation of a coating material for use on a biomedical implant characterized in that gel-derived titania-based coating is formed according to a galvanic method.
7. The process according to claim 6 characterized in that the process is carried out in a hydroxide solution where titanium is used as the positive as well as the negative pole.



74583-5

11

8. The process according to claim 5, 6 or 7 characterized in that one or more of the following oxides are added to the process: CaO, P<sub>2</sub>O<sub>5</sub>, Na<sub>2</sub>O, SiO<sub>2</sub>, K<sub>2</sub>O, Al<sub>2</sub>O<sub>3</sub>, MgO or B<sub>2</sub>O<sub>3</sub>.

5 9. An implant for biomedical use comprising a substrate and a bone-bonding coating material thereon characterized in that the coating material is a gel-derived titania-based coating material that has been treated at elevated temperature.

10 10. The implant according to claim 9 characterized in that the substrate is a tooth, hip or other joint implant substrate.

11. The implant according to claim 9 characterized in that the substrate is a polymeric, metallic, ceramic or  
15 carbon substrate or a composite thereof.

12. The implant according to claim 9 or 11 characterized in that the substrate is titanium or a titanium alloy.

13. The implant according to any one of claims 9 to 12  
20 characterized in that the coating material further comprises one or more of the following elements either as ions or as oxides: Ca, P, Si, Na, K, B, Mg or Al.

14. An implant for biomedical use comprising a substrate and a bone-bonding apatite layer thereon  
25 characterized in that the apatite layer has been grown on a gel-derived titania coating in an in vitro solution.

15. An implant for biomedical use comprising a substrate and a bone-bonding layer thereon characterized in

74583-5

12

that the bone-bonding layer is essentially a mixture of gel-derived titania and apatite, the apatite component having been grown on a gel-derived titania coating in an in vitro solution.

5 16. The implant according to claim 14 or 15, wherein the in vitro solution is a simulated body fluid solution.

17. The coating material according to claim 1, 2, 3 or 4, wherein the elevated temperature is less than 750°C.

18. The coating material according to claim 1, 2, 3, 4  
10 or 17, wherein the elevated temperature is greater than 350°C.

19. The implant according to claim 9, 10, 11, 12 or 13, wherein the elevated temperature is less than 750°C.

20. The implant according to claim 9, 10, 11, 12, 13  
15 or 19, wherein the elevated temperature is greater than 350°C.

SMART & BIGGAR  
PATENT AGENTS  
OTTAWA, CANADA



1/4

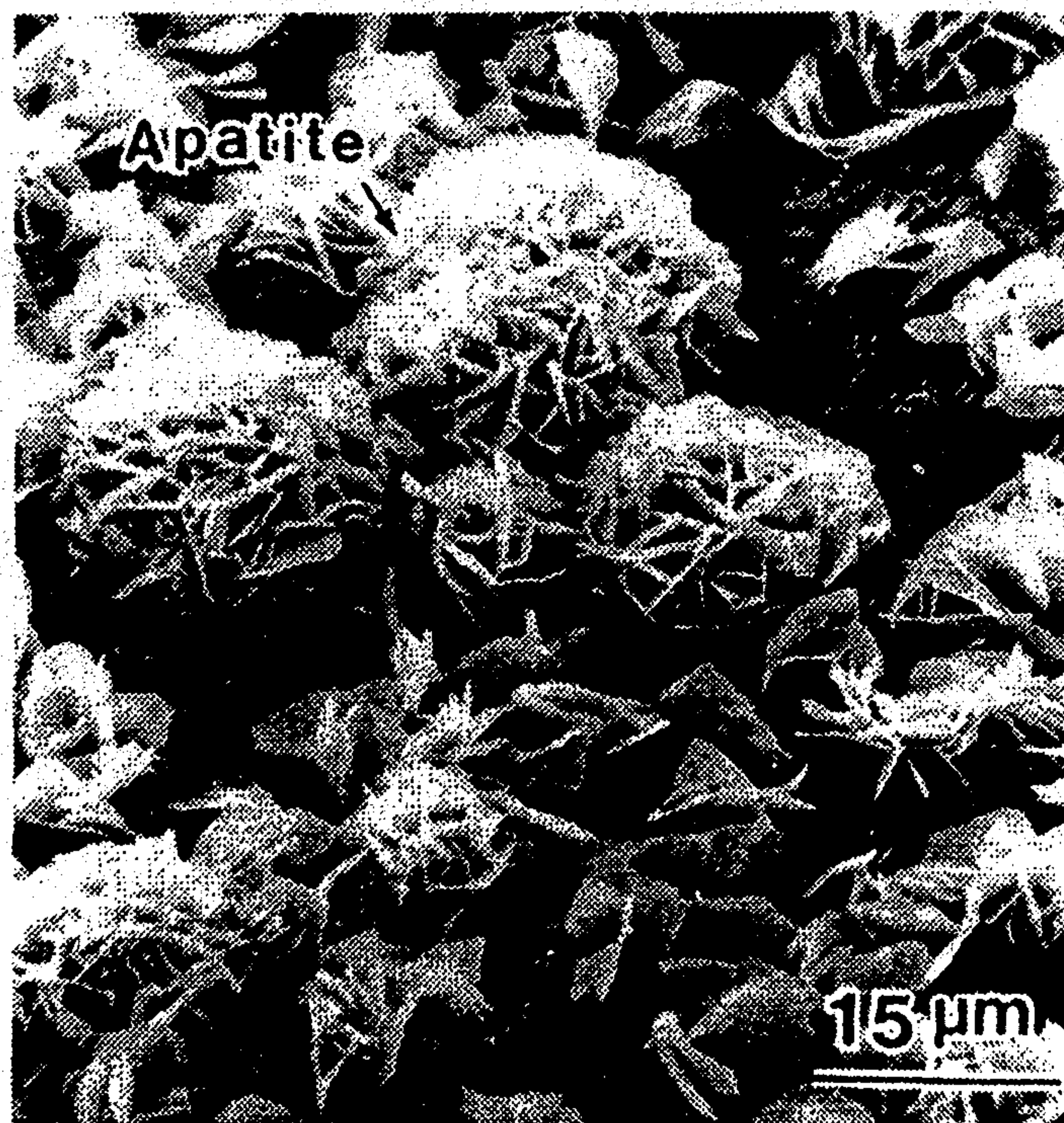
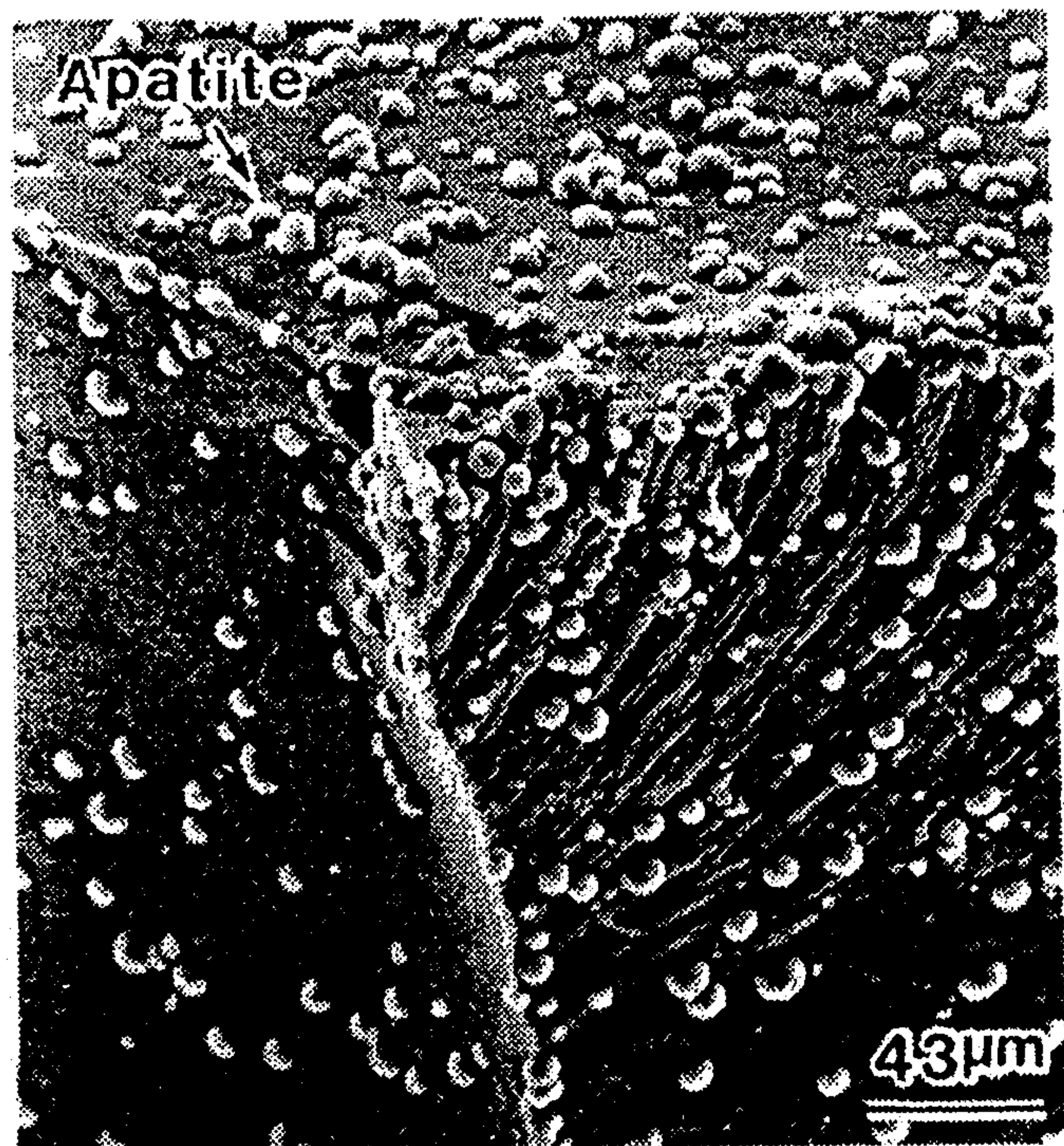


FIG. 1

SUBSTITUTE SHEET



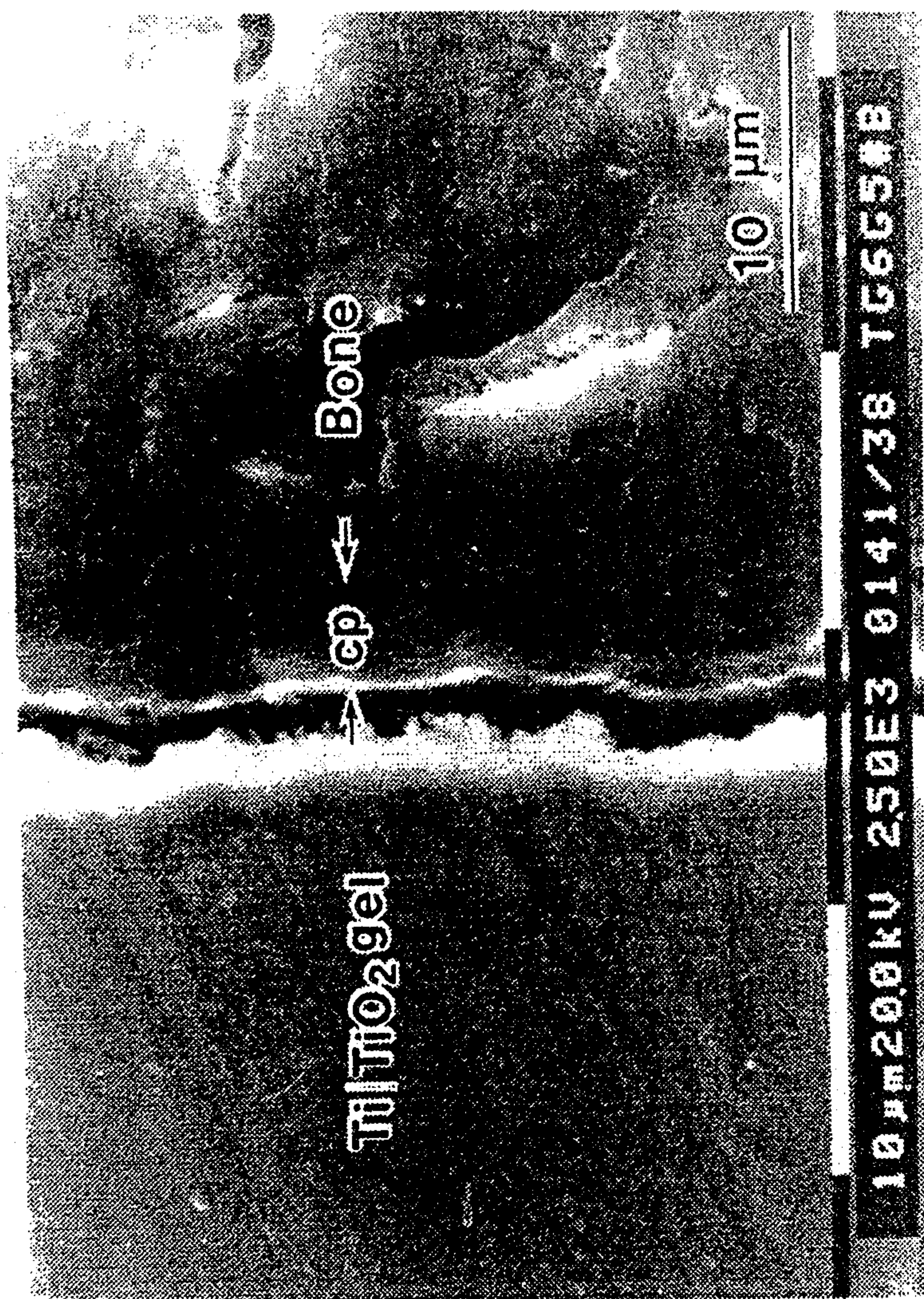


FIG. 2



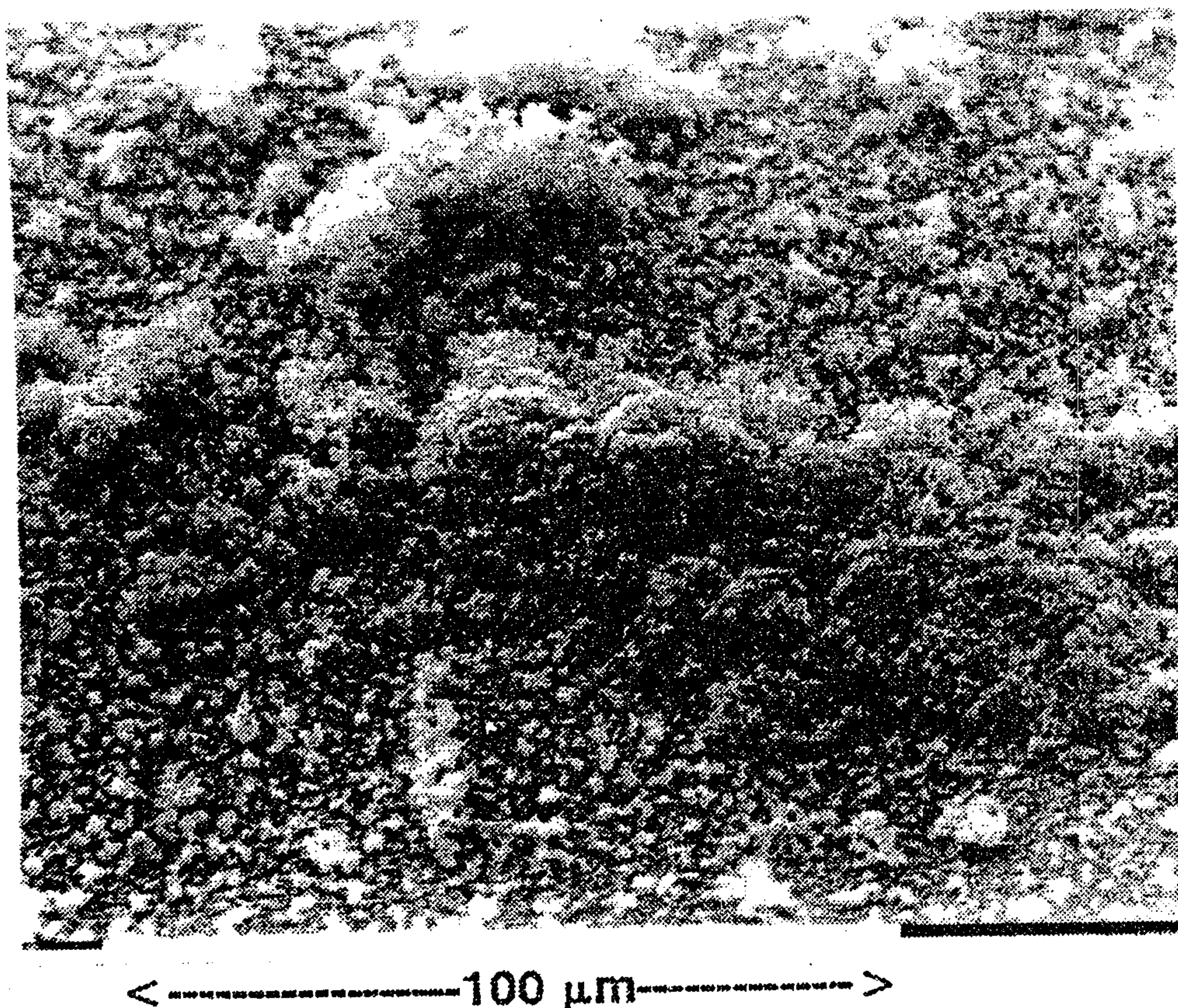


FIG. 3



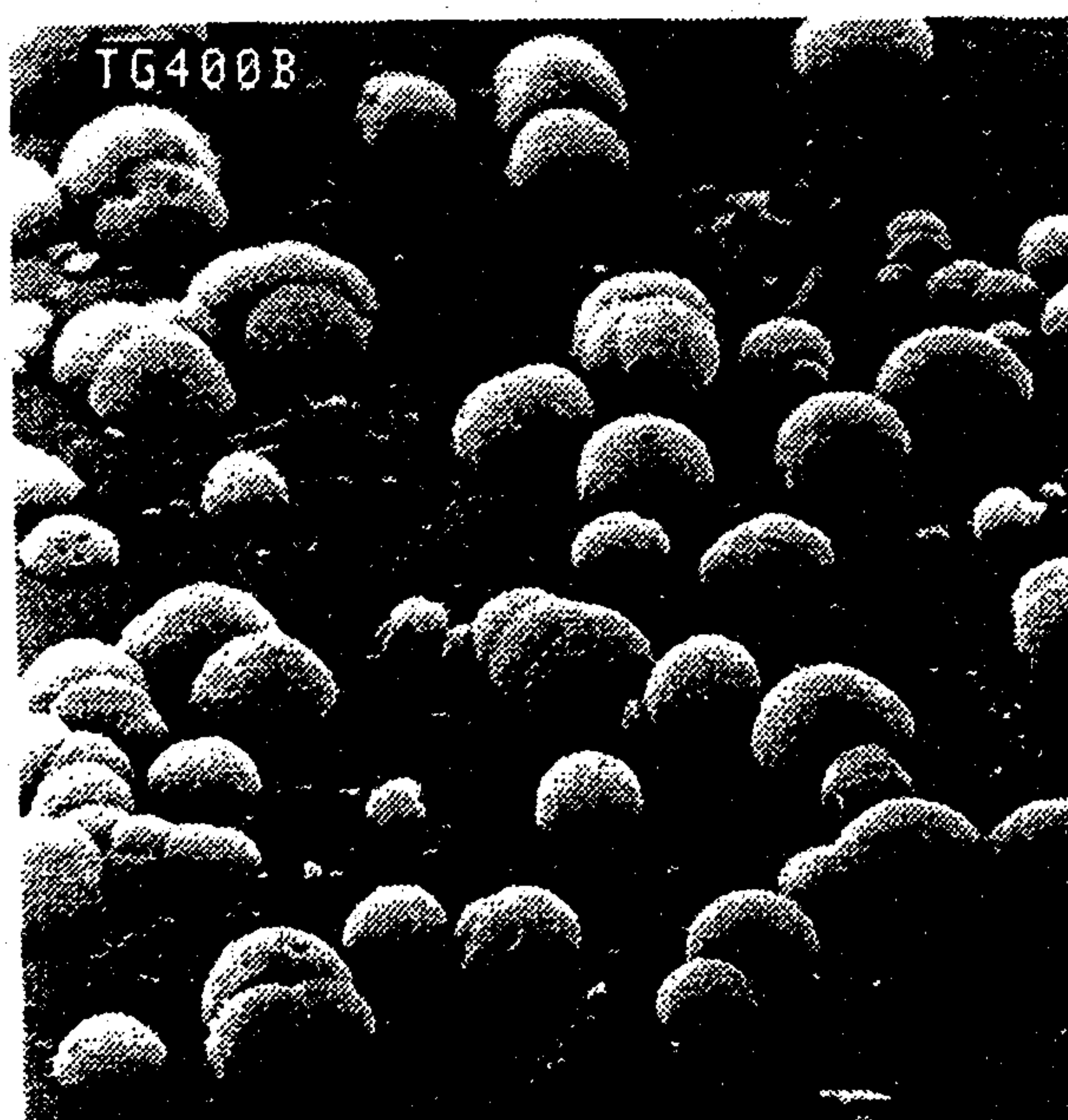
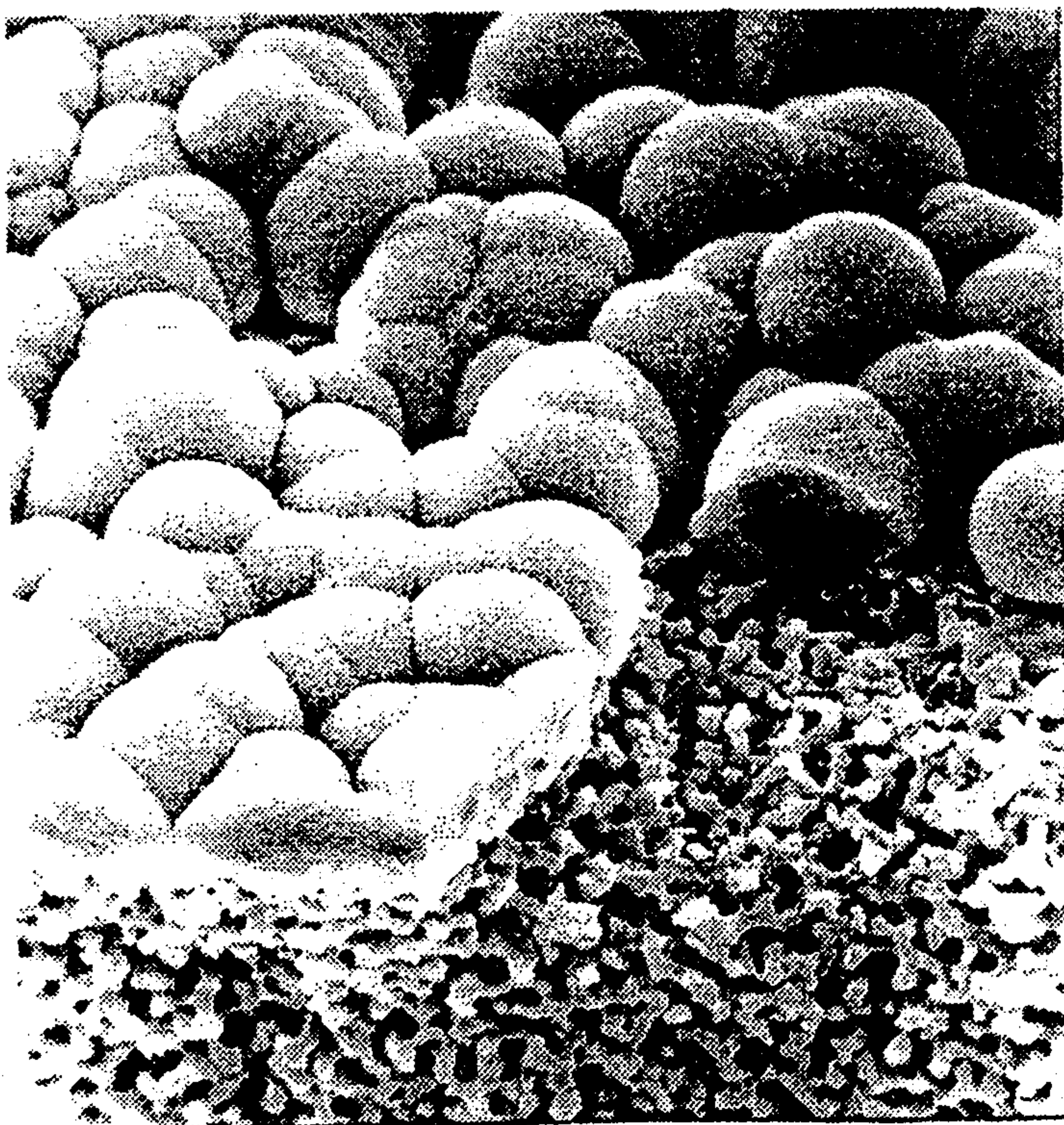


FIG. 4