

CHAPTER 3

An *In Vivo* Examination of the Fate of the Components of a Root Canal Filling Paste made of Calcium Hydroxide and Iodoform with Silicone Oil

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《Abstract》

Using radioactive compounds, we investigated the fate of the calcium hydroxide and dimethylpolysiloxane (silicone oil) components in a root canal filling paste. The paste was made of calcium hydroxide and iodoform with the addition of silicone oil. Whole body, light, and electron microscopic autoradiographic surveys were used. Additionally, quantitative analysis using a liquid scintillation spectrometer was performed on the component dimethylpolysiloxane.

The calcium component moved to the bone tissue through the body fluid and blood, and some of it was excreted through the digestive tract. The calcium came partly from the calcium components of the paste in both types of heterotopic calcifications: dystrophic and matrix vesicle. Some of dimethylpolysiloxane component also passed into the digestive tract. Furthermore, the dimethylpolysiloxane played some part in the calcification caused by the embedded paste.

Introduction

Histopathological investigations of tissue reactions to the root canal filling materials, pulp capping agents, and other related chemicals have been conducted [1-8], especially on the root canal filling paste Vitapex [9-11]. In these reports, there have been some discussions on the behavior of the components of the paste [4-8]. The literature shows that the components were phagocytosed by macrophages and they appeared in the cytoplasm [9, 10]. Furthermore, the

features have also been examined electron microscopically [9, 10]. However, there are no data on the fate and/or movement of the embedded paste components *in vivo*. Therefore, we examined the fate of the component of the embedded root canal filling material paste, made of calcium hydroxide and iodoform with a silicone oil, Vitapex. In this Chapter, we introduce the results of our animal examinations [9, 12-14].

Fate of ^{45}Ca -labeled calcium hydroxide in the root canal filling paste

Regarding the fate of calcium hydroxide, Sciaky and Pisanti [6] studied the localization of calcium after amputation using the radioactive tracer ^{45}Ca . As far as we know, however, no other reports on the fate of these filling materials, especially about calcium hydroxide, have been published. We investigated the root canal filling paste, Vitapex, using ^{45}Ca -labeled hydroxide, with whole body, light microscopic, and electron microscopic autoradiographies. The radioactive ^{45}Ca -labeled Vitapex was subcutaneously injected into the rat abdominal subcutaneous connective tissues. Each animal received a total of 500mg of the paste with 1000 μCi of ^{45}Ca . These were examined at two different experimental intervals, 1 and 2 weeks.

Whole-body autoradiography showed that the bone tissues were labeled intensely in both the 1- and 2-week specimens, as shown in Figure 1. The tracer was also concentrated rather strongly in the digestive tract, but was very scanty in other tissues. There were heavy depositions in the abdominal subcutaneous tissues of the embedded area. The ^{45}Ca concentration in the digestive tract was stronger in the 1-week specimen than in the 2-week specimen (c, d). In this examination, we could not get any autoradiographs of the kidney. On the other hand, there was no radioactivity at all in the control autoradiographs made of specimens taken at the 2 experimental intervals.

Histopathologically, in the control specimens, granulation tissue gradually formed around the embedded paste [2, 9, 10, 15]. Irregular but strongly hematoxylin-stained structures had formed adjacent to the paste in the 2-week specimens. These structures reacted positively to von-Kossa's stain. As observed autoradiographically in the experimental specimens, the ^{45}Ca concentration in the granulation tissues around the paste was very high. The ^{45}Ca compound existed mainly in the tissues near the embedding site and seemed to be absorbing into bold capillaries. In the granulation tissues, macrophages had phagocytosed the ^{45}Ca compound within their cytoplasm (Figure 2, a). Furthermore, the capillaries show positive reactions in the capillaries (Figure 2, b). The calcified structures which appeared adjacent to the paste indicated strong ^{45}Ca deposition (Figure 3, c, d). Foam cells showed no evidence of having phagocytosed or of containing ^{45}Ca .

With electron microscopic observation of the control specimens, the calcium salts, phagocytosed within macrophages, were demonstrated as electron-dense masses in the granulation tissues. In the area of these granulation tissues, evidence of matrix vesicle formation was observed in the 1-week specimens. The growth of electron-dense crystals beyond the calcified matrix vesicle and some crystals on the collagen bundles were noted in the 2-week specimens.

As observed autoradiographically in the experimental specimens, a high level of radioactivity was present in the electron-dense materials that had been phagocytosed by macrophages in the granulation tissue (Figure 3, a). The labeled compound also appeared in the dystrophic calcification on the collagen bundles (Figure 3, b), and at the initial sites of matrix vesicle calcification caused by the paste (Figure 3, c, d).

The tissue reactions to the root canal filling paste, made of calcium hydroxide and iodoform

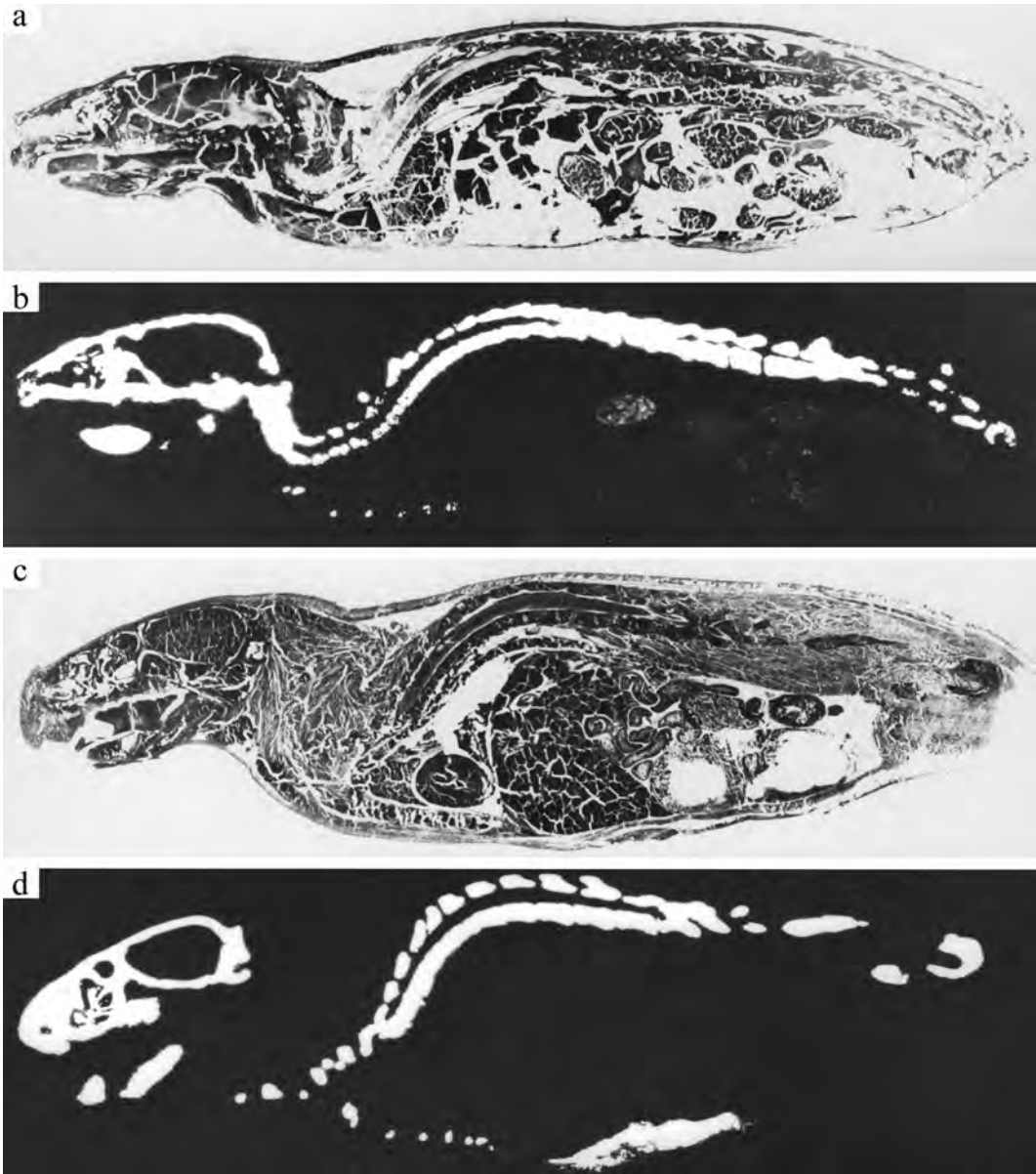


Figure 1 Whole-body section (a) and the autoradiogram (b) of 1-week specimen. ^{45}Ca deposition was strong in the bone tissue and slight in the digestive tract (a, b, arrows). 2-week specimen is the nearly the same as the 1-week specimen (c, d).

with the addition of silicone oil, Vitapex, have already been observed by radiography, histopathology, enzyme photochemistry, and electron microscopy [2, 9, 10, 11]. As observed radiographically, the embedded paste gradually diffused and finally disappeared approximately 40 days later. The findings that components of the paste were phagocytosed by macrophages were observed by both light and electron microscopy [2, 9, 10]. To follow-up on these findings, we decided to examine two different experimental intervals: 1 and 2 weeks. In these stages, through a variety of histopathological appearances, dystrophic and matrix vesicle calcification

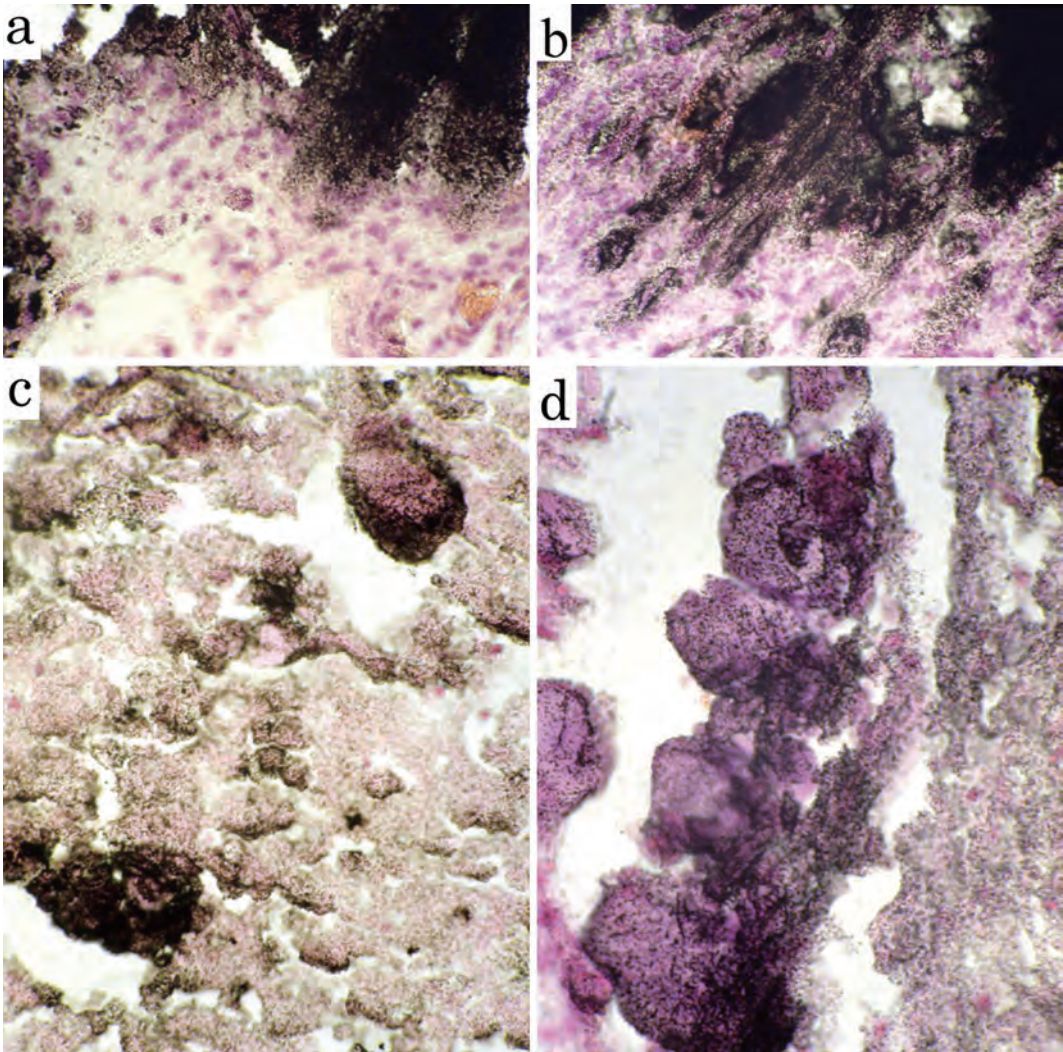


Figure 2 ^{45}Ca -autoradiogram of the granulation tissue due to the embedded ^{45}Ca -paste show the positive signals appearing in the cytoplasm of macrophages (a), capillaries (b), calcified bodies appearing in the granulation tissues around the paste (c, d).

and phagocytosis were observed.

Eda [4] reported that von Kossa's positive granules were deposited under the necrotic tissue formatted after pulpectomy using calcium hydroxide, and the calcium in the granules was considered to have come from tissue fluid. Moreover, there are numerous published reports regarding the movement of calcium hydroxide in paste. Schroder and Granath [5] reported that the calcium came from tissue fluid. However, their discussions relied solely upon morphological investigations. On the other hand, experimental study using a radioactive tracer of ^{45}Ca was presented by Sciaky and Isanti [6] and Sciaky [8]. They reported that the calcium ions from hydrozide did not directly enter the formation of a new dentin bridge after pulp amputation using calcium hydroxide. Moreover, by means of autoradiography using ^{45}Ca , Yoshida [16] studied pulp healing following pulpotomy with calcium hydroxide. He found that the von Kossa's

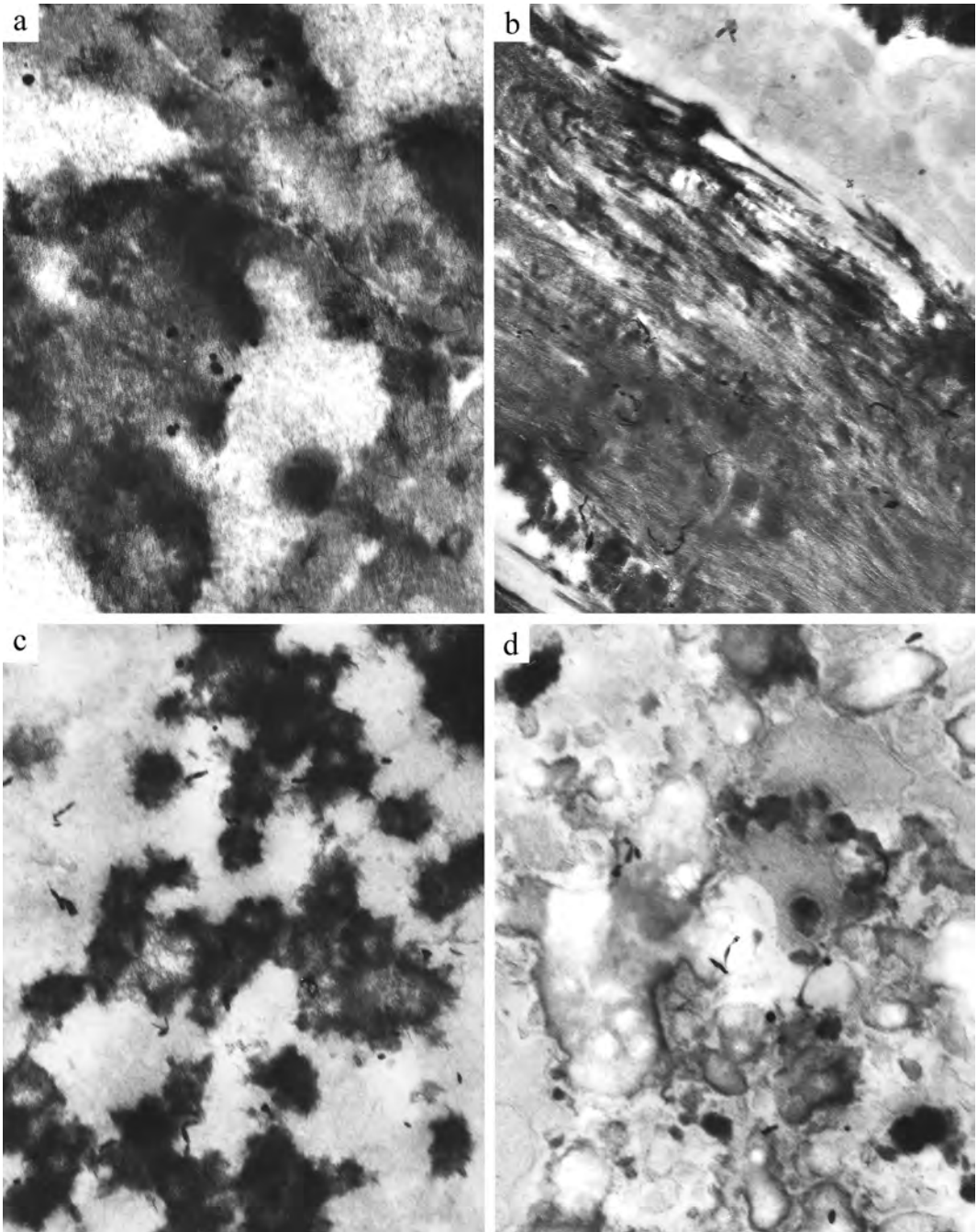


Figure 3 Electron-microscopic level autoradiogram shows radioactivity in the phagocytosing macrophage (a), dystrophic calcified collagen bundles containing ^{45}Ca (b), and matrix vesicle calcification containing radioactivity (c, d).

positive granules deposited underneath amputation wounds were definitely calcium salts that had originated not from the paste or the body fluid. As far as we know, there are no other autoradiographic examinations using ^{45}Ca in root canal filling materials and other related chemicals. There are no reports on the movement of embedded root canal filling materials and other related chemicals inside the body.

By means of the light microscopic autoradiography in the present chapter, we determined that ^{45}Ca localization in the granulation tissues around the embedded paste was the same as that of von Kossa's positive granules [2]. Electron microscopic autoradiography revealed that the electron-dense materials being phagocytosed by macrophages were definitely calcium salts which originated from the embedded paste. Those results were thought to be the first findings of the movement of root canal filling materials and other related chemicals inside the body [9, 12]. This was different from the reports of Yoshida [16], Pisanti and Sciaky [6], and Sciaky and Pisanti [8], which described no movement of the material. It is considered that the difference might be attributed to the nature of the chemicals used: we utilized a silicone oil-based mixture, while Yoshida used a water-based one. The water-based paste caused necrosis because of the higher alkalinity of calcium hydroxid, while the silicone oil-based paste (Vitapex) showed no necrotizing effect. Therefore, we believe that the ^{45}Ca component in our examination was able to move into the granulation tissue.

Through observation of whole-body autoradiography, we also noted movement of ^{45}Ca . Its strong presence in bone was especially evident; it is also quite clear that the calcium component moved into the bone tissue through the blood, since the ^{45}Ca was shown by light microscopic autoradiography to be absorbed into the blood capillaries. Furthermore, the existence of radioactivity in the digestive tract leads us to believe that the calcium component traveled through the blood and some of it was absorbed by the digestive tract. Because our experimental rats were kept in metabolic cages, we thought they could not eat the contaminated radioactive tracer.

In conclusion, the behavior of the calcium hydroxide component of a root canal filling paste, Vitapex, was investigated using ^{45}Ca . It was found that (1) the calcium component moved into the tissues and some of it was excreted through the digestive tract; and (2) calcium came partly from the paste in both types of calcifications: normal bone tissues and hetrotopic (dystrophic and matrix vesicle) calcifications caused by the paste.

Fate of ^{14}C -labeled dimethylpolysiloxane (silicone oil) in the root canal filling paste embedded in rat subcutaneous tissues

Dimethylpolysiloxane (silicone oil) is a well-known biomaterial used in the human body, especially in the field of plastic or reconstructive surgery. The fate of embedded dimethylpolysiloxane has been investigated histopathologically, and electron microanalytically [17-21]. Ben-Hur and Newman [17] and Ben-Hur et al. [18] reported the presence of dimethylpolysiloxane in phagocytizing giant cells of the lymph nodes after embedding. Furthermore, other investigators described the absorption and movement of embedded dimethylpolysiloxane [19-21]. However, these data were based upon morphological observation only. Because no autoradiography studies had been heretofore reported on this subject, the present study was undertaken to investigate the fate of dimethylpolysiloxane in a root canal filling material by autoradiography of the ^{14}C -labeled compound.

The rats were given the root canal filling paste, Vitapex, with ^{14}C -labeled dimethylpolysiloxane (silicone oil), a total of 500mg of the paste containing 500 μci of ^{14}C into subcutaneous connective tissue embedding into the abdominal site. 1-week or 2-week after the injection, the

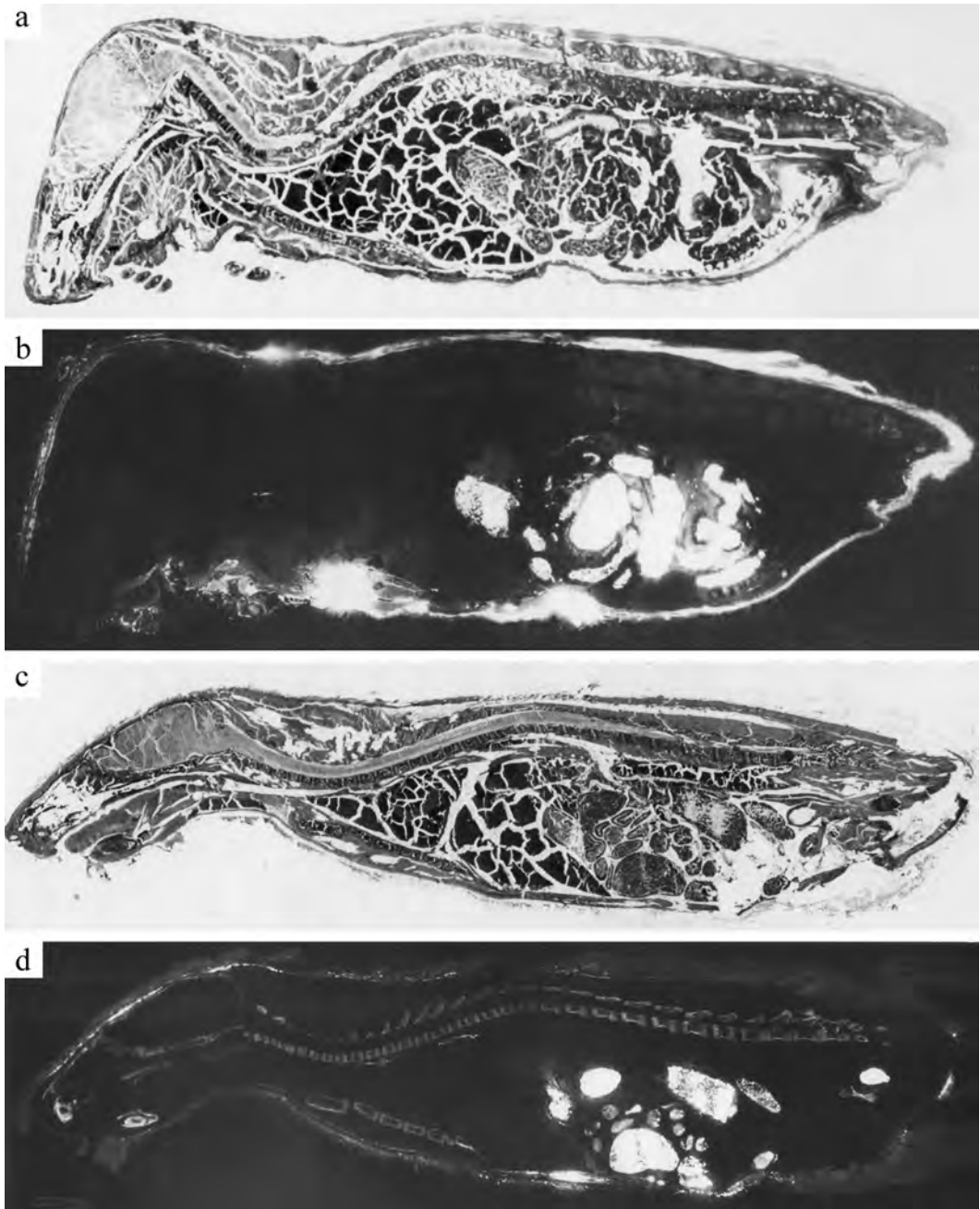


Figure 4 Whole-body section (a) and the autoradiogram (b) of 1-week specimen. ^{14}C deposition was strong in the digestive tract and in the cutaneous tissue, but slight in the liver (a, b). 2-week specimen (c section; d autoradiogram) shows radioactivity presenting in the digestive tract and weakly present in the bone tissue in the whole body.

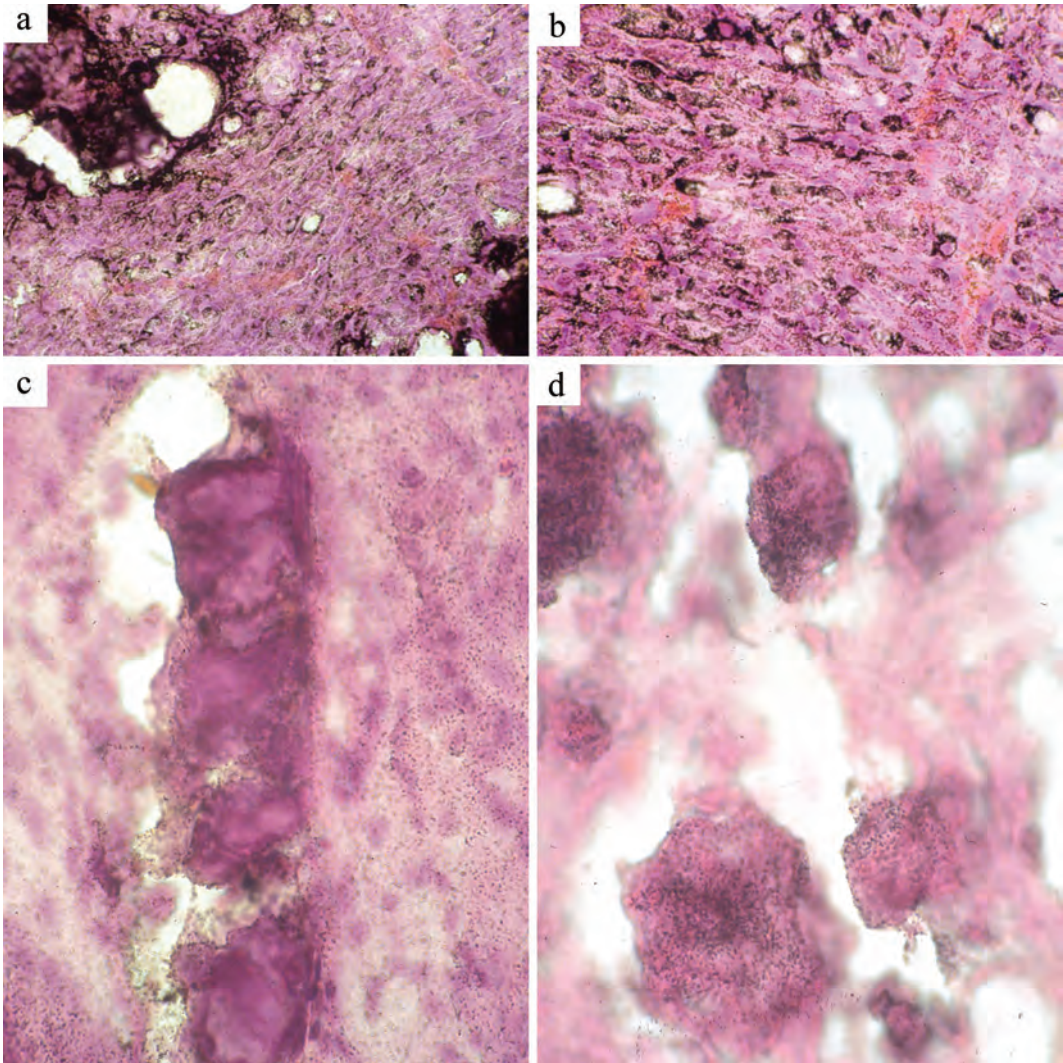


Figure 5 Labeled compound phagocytosed by foam cells appearing in the granulation tissues (a, b). Radioactive calcified materials forming in the granulation tissue (c), and absence of radioactivity in calcified materials (d).

following three types of autoradiography were applied: whole-body, light-microscopic and electron-microscopic.

Whole-body autoradiography showed that the ^{14}C -compound embedded into the abdominal connective tissue was inside the digestive tract and in the coetaneous tissues at 1-week after the embedding of the paste (Figure 4, a, b). The bone tissue was labeled slightly by ^{14}C , and the tracer was also concentrated rather slightly in the liver (Figure 4, b). The distribution pattern of 2-week specimens varied little from that of 1-week specimens; however, the relative concentration of the label was different; especially in the bone tissue it was higher than that in 1-week specimens (Figure 4, c, d). On the other hand, there was no radioactivity at all in the control autoradiographs made of specimens taken at the 2 experimental intervals.

In the control specimens, granulation tissue gradually formed around the

embedded site, which was separated into small masses. In these sites, the dimethylpolysiloxane component of the embedded paste was phagocytosed by macrophages, whose appearance then changed to that of foam cells having clear cytoplasm. In the granulation tissue elicited by the embedded paste, some calcified materials stained with hematoxylin had formed. These materials also reacted positively to von Kossa's stain.

As shown by autoradiography of the experimental specimens, the concentration of ^{14}C in the granulation tissue was observed to be very high in the foam cells, but low in the macrophages (Figure 5, a). There was rather abundant labeling of the wide cytoplasm of foam cells (Figure 5, b), but little labeling of the cytoplasm of macrophages and fibroblasts (back ground). ^{14}C -labeled material penetrated into blood capillaries in the granulation tissues. Furthermore, the calcified materials indicated various concentrations of ^{14}C : some were labeled (Figure 5, c), and others, unlabeled (Figure 5, d).

By electron microscopic observation of the control specimens, the embedded dimethylpolysiloxane component that had been phagocytosed by foam cells appeared as many lipid-like droplets in the granulation tissue. In the area of these granulation tissues, two types of heterotopic calcification, dystrophic and matrix vesicle, caused by the paste were observed. In the experimental specimens, radioactivity was highly concentrated in the above-mentioned droplets (Figure 6, a, b). Furthermore, the radiolabel was also present in the electron-dense materials in the cytoplasm, which was phagocytosed by the macrophages (Figure 6, c). Moreover, there was strong labeling of ^{14}C in the heterotopic, matrix vesicle type, calcified structures adjacent to the embedded paste (Figure 6, d).

Histopathological studies have already been done on tissue reactions to root canal filling materials [2, 10, 22, 23]. Block et al. [24] reported on the root canal filling material N2 labeled with a ^{14}C tracer. That report described the labeled compound to be distributed throughout the body, especially in the blood, regional lymph nodes, kidney, and liver, and the amount of radioactivity to decrease with time. We presented the fate of ^{45}Ca -labeled calcium hydroxide in a root canal filling material paste embedded in rat subcutaneous tissues, and concluded that the calcium component moved into the tissues and that some of it was excreted through the digestive tract. Also, some of the calcium came from the paste that appeared in calcification sites: normal physiological bone tissues and heterotopic, dystrophic and matrix vesicle, calcification sites caused by the paste [12].

We already reported the tissue reactions to Vitapex as assessed by radiography, histopathology, enzyme histochemistry, and electron microscopy [2, 9]. These morphological investigations revealed that the dimethylpolysiloxane component of "Vitapex" was phagocytosed by macrophages and appeared as small droplets within foam cells. To follow up on these findings, we decided to examine two different experimental intervals: 1 and 2 weeks. From the changes seen in the histopathological features at these time points, ongoing events of phagocytosis and formation of dystrophic and matrix vesicle calcification sites were considered to have occurred.

Regarding the fate of dimethylpolysiloxane (silicone oil) inside the body, many histopathological investigations have been published. Ben-Hur and Newman [17] observed giant cells which had phagocytosed embedded dimethylpolysiloxane, and Ben-Hur et al. [18] reported that the giant cells which had gathered in the lymph nodes appeared to contain dimethylpolysiloxane. In addition, other papers have dealt with the absorption and movement of embedded dimethylpolysiloxane into various organs, liver, adrenal gland, ovary, lymph nodes, and kidney [25, 26]. These reported data considered only light microscopic observations; therefore, there was no proof of the absorption and/or movement of the embedded

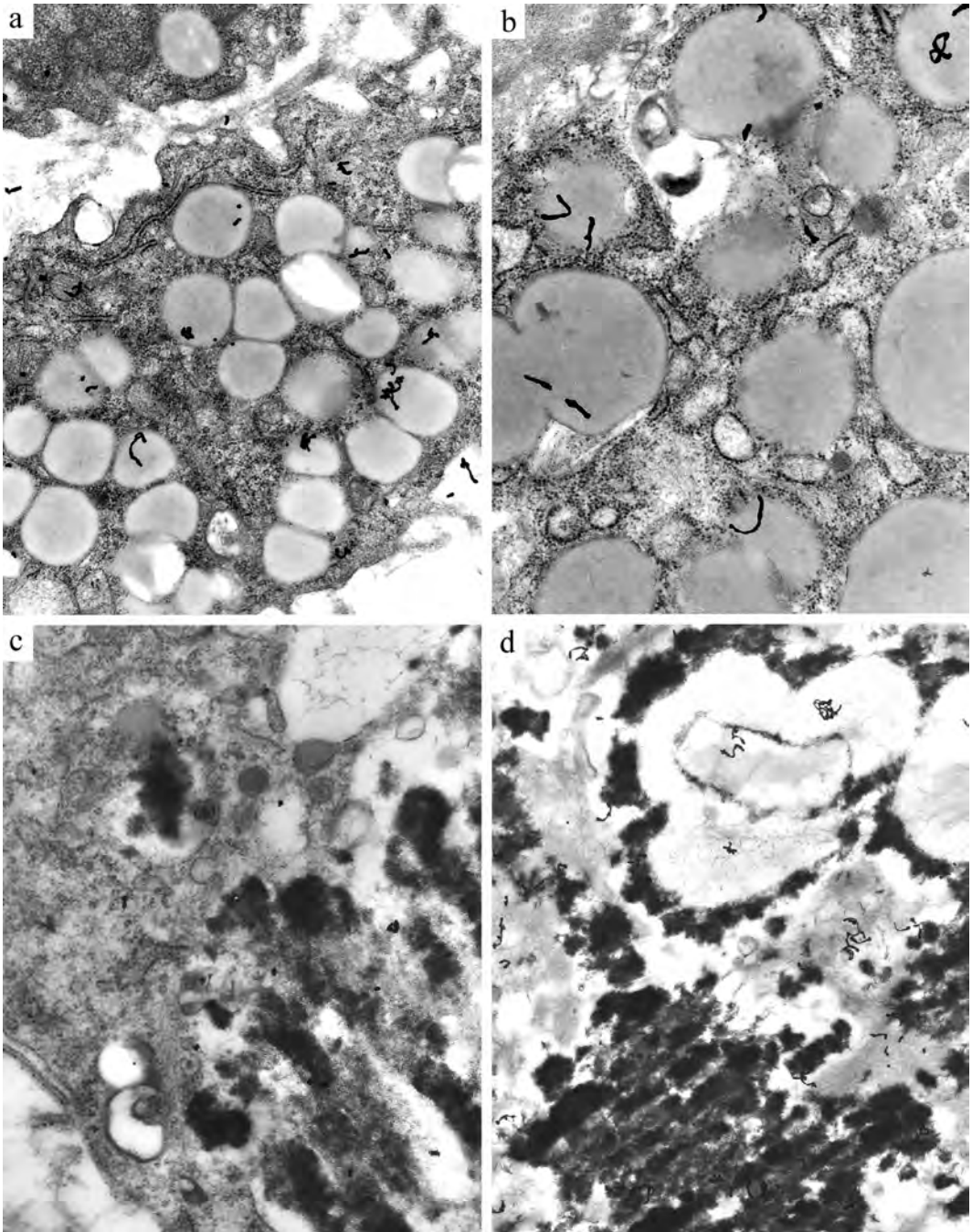


Figure 6 EM autoradiogram of 2-week specimen. The ^{14}C deposition was strong in the droplets within the cytoplasm of foam cell (a, b). The ^{14}C present in the phagocytosed electron-dense materials (c), and paste-inducing heterotopic calcification site containing ^{14}C (d).

dimethylpolysiloxane inside the body. However, by energy dispersive X-ray microanalyses Wickham and Rudolph [19] did prove the presence of silicon (Si) in droplets contained in the cytoplasm of phagocytes.

Through observations of whole-body autoradiography, movement of ^{14}C -labeled material was recognized. Its strong presence in the digestive tract and the cutaneous tissue was especially evident; and it is also quite clear that the label moved into the bone tissue. These data lead us to conclude that the ^{14}C component traveled through the blood and that some of it was absorbed by the digestive tract. Because our experimental rats were kept in metabolic cages, we can rule out the possibility of gut-associated radioactivity due to injection of previously extracted radioactive tracer. For the same reason, we believe that the presence of the tracer in the cutaneous tissue was not due to contamination.

We observed in the granulation tissues elicited by the paste that there were two types of calcifications: one dystrophic, the other matrix vesicle. These heterotopic calcifications were described in detail in our published papers [2, 9]. In the present chapter, the localization of radioactivity around the embedded paste was nearly the same as that of von Kossa's-positive granules. Regarding silicon (Si), Carlisle [27] concluded that it is associated with calcium in the early stage of calcification. Since dimethylpolysiloxane is a silicon (Si) compound, we believe that it may play some part in the matrix vesicle calcification process in the granulation tissue induced by the embedded paste.

In conclusion, we observed the distribution of ^{14}C -labeled dimethylpolysiloxane inside the body by means of whole-body, light, and electron microscopic autoradiography. Our data suggest that dimethylpolysiloxane passes into the digestive tract through the blood, and that the ^{14}C -label is also concentrated in bone tissue and in calcification sites in the resulting granulation tissues.

Quantitative analysis of the fate of embedded dimethylpolysiloxane

Regarding the fate of silicone oil inside the body, a number of histopathological and electron microscopical investigations have been published [17-21]. The fate of the silicone oil component of the root canal filling paste Vitapex, consisting of calcium hydroxide and iodoform with the addition of silicone oil, has been previously reported [10, 13].

Therefore, the present data was undertaken to investigate by quantitative analysis, using a ^{14}C -labeled compound, the excretion of silicone oil embedded in rat subcutaneous tissue. An adult female SD rat of about 100g in weight was used. (U^{14}C -labeled silicone oil (about 500 cs) with a specific activity of 4.91 mCi/g was purchased from New England Nuclear (NEN; Boston, MA, USA). It was mixed with other non-labeled components of Vitapex (Neo Dental Chemical Product Co. Ltd., Tokyo, Japan). The composition is shown in Table 1.

Under anesthesia induced by a subcutaneous injection of pentobarbital solution, a total of

Table 1 Components of the paste

Iodoform	40.4
Calcium hydroxide	30.3
^{14}C -silicone oil	22.4
Others	6.9
Total (g)	100.0

Table 2 Amount of silicone oil excreted

Day	Feces ($\mu\text{Ci}\times 10^{-2}$)	Urine ($\mu\text{Ci}\times 10^{-3}$)	Total ($\mu\text{Ci}\times 10^{-2}$)
1	9.2007	6.3798	9.8387
2	2.8749	4.0038	3.2753
3	3.5974	3.5022	3.9476
4	1.8247	9.2977	2.7545
5	2.4712	5.8272	3.0839
6	2.6147	3.4259	2.9573
7	2.1018	2.9383	2.3956
8	2.4472	3.2141	2.7686
9	3.0409	1.8645	3.2274
10	2.7794	1.4432	2.9237
11	5.2878	1.5758	5.4454
12	4.0475	2.4246	4.2900
13	3.5300	1.7425	3.7043
Total	45.8182	47.6396	50.5823

500mg of the paste ($500 \mu\text{Ci}$ of ^{14}C) was embedded in the dorsal subcutaneous connective tissue. The animal was kept in a metabolic cage. The same amount of normal (non-radiolabeled) paste was applied to an additional rat as a control. The feces and urine were collected every day for 13 days and weighed. The samples were treated with the tissue and gel solubilizer Protosol (NEN), and the solubilized material was then added to universal LSC cocktail Aquasol-2 (NEN). The radioactivity was determined in an Aloka model LSC 651 liquid scintillation spectrometer with automatic quenching monitor (Aloka, Tokyo, Japan).

Some of the ^{14}C -compound embedded in the connective tissues was excreted into the feces and the urine (Table 2). The average amount excreted into the feces were $3.1217 \times 10^{-2} \mu\text{Ci/day}$, and the total amount over the experimental period was thus $4.5818 \times 10^{-1} \mu\text{Ci}$ (13 days). In the urine, the ^{14}C level averaged approximately 10-fold loss, or $3.6646 \times 10^{-3} \mu\text{Ci/day}$, and $4.7640 \times 10^{-2} \mu\text{Ci}$ was excreted over the experimental period. The total amount excreted by the animal (in feces and urine) was $5.0582 \times 10^{-1} \mu\text{Ci}$, and this was equal to about 0.1% of the total dose ($500 \mu\text{Ci}$) embedded.

Silicone oil is a well-known biomaterial, but its fate once embedded has been investigated only histopathologically, ultrastructurally, and electron microanalytically [17-21]. Since these studies were morphological, they were unable to demonstrate the absorption and/or movement of the silicone oil inside the body. However, using analytical electron microscopy, Wickham and Rudolph [19] and Rudolph et al. [21] did demonstrate the movement of silicone (Si).

Histopathological investigations of tissue reactions to the root canal filling material Vitapex have already been conducted [10, 11]. These reports showed that the silicone oil component was phagocytosed by macrophages and appeared as small droplets in the cytoplasm. Furthermore, we observed the distribution of ^{14}C -labeled silicone oil component embedded in rat subcutaneous tissues by means of whole-body, light and electron microscopic autoradiography, and reported that the silicone oil passed into the digestive tract through the blood [10, 13]. The results of the present study were similar to those given in the aforementioned reports, but demonstrate, by quantitative analysis, the excretion of the silicone oil in the feces. Additionally,

the excretion of the compound into the urine was confirmed, although the amount was quite small.

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