Silicone Degradation Reactions

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INTRODUCTION

Silicone (polydimethylsiloxane, PDMS) is generally a very stable polymer. Because of this, it is used in a wide variety of adverse environments such as those with high temperature or as electrical insulation. However, a great deal of this stability derives from the fact that hydrolysis reactions which occur are reversible and the polymer essentially heals itself. It is likely that such reversibility would not occur in the surface region where high concentrations of other components, such as water, can exist. Because of the significant concern about the fate of silicone released from breast implants in particular, it is important to understand the types of chemical changes which may occur in silicone upon exposure to physiological environments so that the data on various silicon-containing species can be correlated with other physiological studies on known compounds. Accordingly, this chapter will focus on the known silicone degradation reactions which occur within normal physiological ranges (37 and mixed aqueous environment). Various other studies will be drawn upon to evaluate the possible changes since the literature on silicone modification under physiological situations is sparse at this time. Three main reactions discussed are hydrolysis, oxidation, and addition.

The physical form of the silicone is also an important parameter in this evaluation since one expects changes and tissue interaction to occur on the surface. Hence, the greater the dispersion, the greater the amount of surface area and consequently, the greater possibility for reaction. As shown in Table I a drop of silicon oil with a radius of one centimeter can be divided into smaller droplets and this will sharply increase the total surface area. Hence, such a drop, if divided to smaller drops with a radius of approximately one micron (as is seen in normal tissue slides of phagocytized silicone) would generate 10 12 spheres with a total surface area of about 10 square meters. If the particles were smaller, for instance 0.1 micron radius, there would be 10 15 particles with about a 100 square meter surface area. With particles this small, the surface chemistry becomes a major determinant of the properties of the material and needs to be determined as carefully as the bulk properties.

Table I: Changes in radius, volume and area of spheres as their size is reduced from dividing a 1 cm. radius drop of liquid (adapted from Hiemenz, 1986)

Radius (cm)	Number of Spheres	Volume per Sphere (cm^3)	Area per Sphere (cm^2)	Total Area (cm^2)
1	1	4.2	12.6	12.6
0.5	8	0.5	3.1	25.1
1.25×10^{-1}	512	.008	.19	101
10^{-4} (1μ)	10^{12}	4×10^{-12}	1×10^{-7}	1×10^{5} (10m^2)
10^{-5} (0.1μ)	10^{15}	4×10^{-15}	1×10^{-9}	1×10^{6} (100m^2)

Assuming that no changes take place in silicone, four basic questions can be asked about an implant: How much silicone is released from ir) What is the composition of the material which is released? Where does the material go within the body? What effects does it have when it gets there') We will address only the first two questions and will also discuss the changes which

might occur in the silicone during the course of its dispersion through the body which may influence some of the behavior seen.

The phenomenon of gel bleed has been known for two decades and has been described as "inevitable" (Brody, 1977). An early in vitro bleed study of silicone gel-filled breast implants (Bergman and van der Ende, 1979) consisted of placing an implant on a pre-weighed piece of filter paper in a desiccator for 2 and 12 weeks. At each time period the paper was weighed and the weight gain calculated. Bergman, et al. concluded that there was a "progressive oozing" of silicone gel through the implant shell in all five implant manufacturers. One method used to measure silicone release rate in simulated body fluid at 37°C gave a value of about 1 mg./day for most implants (Yu, et al.).

There is little data in the literature on the composition of gel bleed. The most comprehensive study (Varaprath, 1991) showed very little vinyl siloxane contained in gel bleed (about 100 ppm). Most oil from gel bleed was somewhat reduced in molecular weight as described below.
A significant amount of very low molecular weight material was found in the gel bleed from several implants which may represent octamethycyclotetrasiloxane (D4), the cyclic tetramer (mol.wt = 297). The unreactive internal fluid used to make the bulk of the gel was shown by Varaprath to have a weight average molecular weight (Mw) of about 37,000 and a number average molecular weight (Mn) of about 14,000. There was no low molecular weight material reported. In contrast, the gel bleed from an implant was found to have mostly material with a slightly lower molecular weight (Mn = 5,000-13,000 and Mw = 9,000-24,000), but also included about 4% of very low molecular weight components (approximately Mn = 530 and Mw = 540) and 3-15% very high molecular weight components (about 300,000 molecular weight).

An analysis of extraction liquids from gel sheeting used as a topical, semi-occlusive dressing found that the most abundant siloxane oligomers were cyclic components, octamethycyclo-tetrasiloxane (D 4), decamethycyclopentasiloxane (D5)' dodecamethycyclohexasiloxane (D6)' and other larger cyclic siloxanes (Haggard, et al., 1993). The identification of these low molecular weight components is of interest because they can diffuse faster and enter a cell more readily than higher molecular weight components, and thus may show changes in degradation.

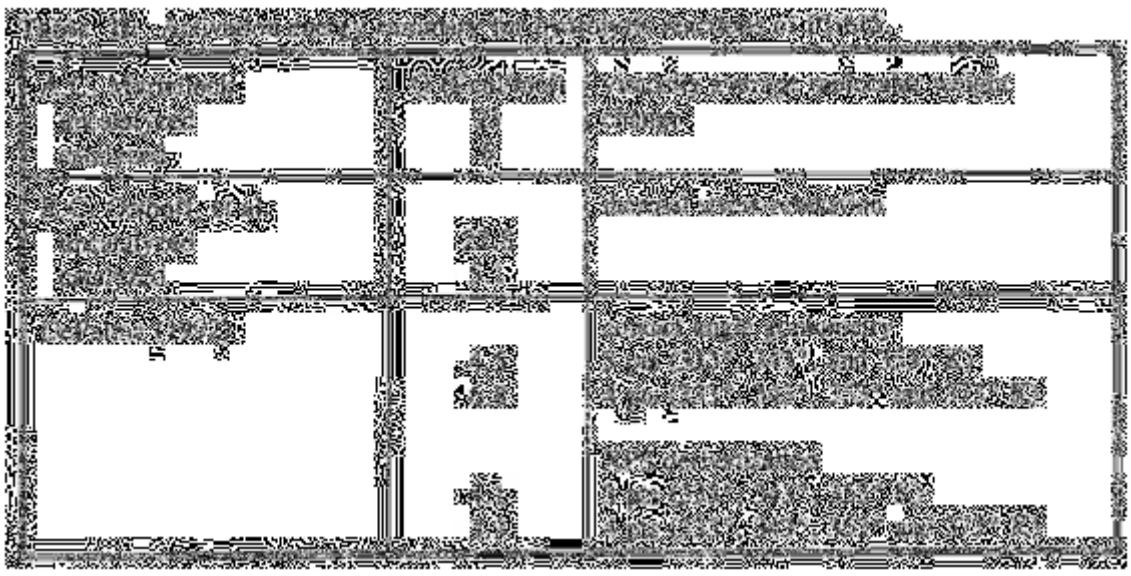
In Figure 1 is a schematic diagram showing the interface between an implant and the fibrous capsule and surrounding tissue. The "gel" filling material consists of a true cross-linked section called a gel making up roughly 10-20% of the material and a lower molecular weight soluble fraction (sol) which can be extracted and can also largely pass through the elastomer shell. This sol can be picked up by the synovium-like cells and transported to the tissue much as in a synovial capsule. The fibrous capsule appears to reach a certain saturatable concentration of silicon which is transported through this structure. However, very high levels of silicone can build up between the fibrous capsule and the implant, depending on the relative rate of release from the implant and the rate of transport through the capsule. Trapped silicone will continuously be released from an essentially zero order release device into the surrounding tissue. There is indication that macrophages and other cells pick up this silicone which is then transported to lymph nodes and other locations, including the liver. It is uncertain how much other silicone is emulsified at this point and carried with interstitial fluid to distant locations,

although it is likely that this occurs to some extent because of the large number of natural surfactants present in interstitial fluid and blood (e.g., membrane components, oligopeptides).
The main point of interest here is that these mechanisms produce a large surface area of particulate material which will have a significant surface chemistry. This ignores rupture and migration along tissue planes by large pieces of PDMS, although there is indication that subsequent to rupture. the material is also incorporated into cells by phagocytosis and distributed to distant locations. Because of the present poorly characterized distribution of this variable material, establishing dose response relationships is difficult. A number of studies suggest that the capsule, as well as the blood. is a saturatable transport system for the distribution of this finely divided silicone. This is inferred from demonstration of increased levels of silicone in blood and capsules of women with implants. and its detection in distant organs. In a similar manner, low levels of PDMS may be degraded actively when phagocytized, but higher levels may swamp cellular degradation mechanisms.

HYDROLYSIS
As shown in Figure 2, the siloxane bond can be hydrolyzed by exposure to water, creating two silanol groups. As mentioned. this reaction is highly reversible, tending to form the siloxane bond when high enough concentrations of silanol groups are present. This explains, for instance. the equilibrium aqueous solution concentration value of about 50 parts per million for silicic acid Si(OH)4' in glass containers. Above 50 parts per million, silanol groups condense and reform silica. The same reaction occurs with silicone polymers and is accelerated greatly in both directions by the presence of acid or base catalysts. This can happen even in cross- linked networks in air at room temperature if the air is moist, as seen in stress relaxation studies (Vondracek. 1982). Some of the catalysts for the condensation reaction have been strong acids and bases and also amines (Saam. 1990).

We conducted a hydrolysis study as part of a master's thesis (DePalma, 1992). The surface chemistry of silicone is somewhat difficult to follow because of the extreme mobility of the polymer which allows low molecular weight materials to routinely rise to the surface and create a fresh silicone layer whenever the material was exposed to air. In addition, many of these changes happened rapidly due to the low glass transition temperature ofthe silicone. Eventually we settled on working with a piece of elastomer which had been extracted extensively with toluene to remove the approximately 5% extractable, low molecular weight material present.

The elastomer was a peroxide-cured silicone film which would have the same general properties as the platinum-cured elastomer used in most breast implants. Studies were conducted at elevated temperatures to speed the reaction and the results were extrapolated to 37°C. The extrapolations were not strictly linear and showed a lag period before the reaction seemed to follow a linear period. This lag, we feel, was due to the influence of silanol groups on subsequent reaction, i.e., it acted as a catalyst itself and hence, speeded up the reaction once it formed. Despite these variations, there was generation of a more hydrophilic surface in each case after extended exposure of a PDMS solid to a saline solution. Other groups reported similar behavior [M. Morra, et aI., "on the aging of oxygen plasma-treated PDMS surfaces" J. Col. & Interface Science 137, 11-24 (1990)], in that control samples which had been stored in water at room temperature eventually became hydrophilic. Most of our study was directed towards understanding the kinetics of this reaction and extracting an activation energy for it. The activation energies determined and those reported in the literature for similar systems are indicated in Table III (DePalma, 1992)



Surface changes were monitored by two methods. The first method used contact angle goniometry for air measured under water. The other method involved a surface derivatization method combined with x-ray photoelectron spectroscopy and, we believe, showed reaction with surface silanol groups. The two methods yielded essentially the same general numbers, which give us the activation energy reported and allowed us to produce the following extrapolation for the surface hydrolysis reaction at 3rc. As seen in Addendum, a fairly rapid initial reaction would take place which would slowly increase with time. leading to a significant fraction (about 25-30% change) in somewhere between two and ten years. The exact numerical agreement between this saline. elevated temperature study and the in vivo environment may vary, however, it is very likely that the hydrolysis reaction occurs on the surface relatively slowly over a period of roughly five years in both saline and tissue. The change in the surface from a siloxane bond to a silanol containing structure would lead to profound changes in behavior. Silanols are acidic and have a pK. similar to that of phenol. Hence, they would likely be ionized to some extent. Because of the presence of "reactive silanol groups" on fumed amorphous silica the particles are treated with silicone polymer to reduce their surface density (Levier. 1993). The presence of the silanol group has been linked to the activity of silica in various biological evaluations such as fibrosis and cell lysis (Razzaboni. 1990). There are numerous reports indicating that crystalline silica is more damaging than amorphous silica. However if the materials are adjusted for similar surface silanol concentration, they both appear to be about as physiologically damaging to nearby cells. The crystalline/amorphous difference appears to result from the difference in the method of preparation of the materials. Crystalline silica or quartz is ground in water. which leads to hydrolysis of the fractured siloxane bonds. In fact the crack propagation velocity in silica is much higher in the presence of water than it is in the absence of water because of the enhanced effect on breaking this bond (Ritter, 1991). Amorphous silica, on the other hand, is formed in a high temperature fuming process and generates siloxane bonds on the surface (Kingery. et aI., 1976). These siloxane bonds have been detected by a variety of methods and are shown to slowly hydrolyze on storage in a moist environment to produce surface silanol groups. When the amorphous silica has been so allowed to hydrolyze on the surface, it also has activity similar to that of the crystalline material. Relating this to the PDMS behavior, it appears that the hydrolyzed particles would likely be more physiologically active than the unhydrolyzed PDMS.

The binding of PDMS to proteins is an interesting area where the presence of silanols would likely lead to different behavior (Shi. et al.. 1989). In electrophoresis, for instance, it is considered important to block surface silanol groups to prevent binding of proteins (Towns, 1990). However proteins also have hydrophobic regions which would bind strongly to the siloxane area. Many questions remain in this area and it is uncertain at this point whether the binding of the hydrophobic interior of the proteins would cause a different kind of response than binding of the hydrophilic exterior of many proteins, exposing a more hydrophobic interior. It is likely that the binding will be different in quantity as well as quality and lead to different types of denaturization as well as amounts bound depending on the state of the PDMS.

Silanol groups can also interact with carbohydrates to form structural polymers in animals (Mathews. 1990).

The hydrolysis reaction occurs also in the bulk to some extent, possibly due to the transport of acids and bases into the gel by complexation with cyclic siloxane species (Saam, 1990). This degradation was demonstrated in a study (McCoy, 1987) of factors influencing the stability of mammary gel. It was shown that residual catalyst concentrations above about two parts per million led to depolymerization when the gel was stored at 36°C. The degradation in this case was measured by a penetrometer and essentially measured the extent of cross-linking of the gel.

Concentrations above this level occasionally occurred during production and the recommendation of the report was that extraction be carried out with testing afterwards to keep the levels low.

OXIDATION

As shown in Figure 3, oxidation basically involves the removal of a methyl group from the PDMS side chain, replacing it with a silanol group. It would be expected that such a reaction would occur through free radical attack on the methyl hydrogens, leading to substitution. It has been demonstrated that having a silicon adjacent to an alkyl carbon hydrogen bond increases the propensity for free radical extraction by a factor of about five (Barton, 1990). As shown in Figure 3, the oxidation leading to production of silanols on side chains would lead to gelation if the main backbone chain was intact. In other words, the formation of a gel from a liquid would occur if oxidation were occurring and the silanol groups were, in tum, reacting with each other. This kind of reaction might be expected from superoxide or hydroxyl radical generation, such as has been postulated to occur in an oxidative burst during an inflammatory response. If this reaction were occurring, one would expect the liquid "gel bleed," which had been through the elastomer shell, to slowly tum into a gel (cross-linked) material. This point would be significant because it has shown (Nairn, 1993) that the gel form of PDMS is a strong adjuvant while the liquid form is not. The NMR methods developed by Garrido in this volume demonstrate that oxidation occurs since silicon is observed with more than two oxygens attached to it. Additionally, one can look at the physical state of silicone in preserved tissue slides.
During normal processing of histological samples, the tissue is extracted with various solvents of decreasing polarity, eventually being extracted with xylene before being infiltrated with paraffin wax. Such a processing would remove liquid which is soluble in xylene, but would not remove gel, which could only swell. We attempted to determine whether the small amounts of silicone remaining in tissue slides were soluble in xylene and the results are shown in Figure 4.

We concluded that some cross-linking had taken place in this tissue sample which is from a woman with a non-ruptured implant. This shows that liquid released by gel-bleed has gelled at the point where a tissue analysis has taken place. These results are consistent with oxidation during residence in the tissue or during tissue processing. The specific mechanism shown in Figure 3 (first step) is for high temperature oxidation of PDMS. Other physiological oxidants such as superoxide, hypochlorous acid or hydroxyl radical may not proceed through a hydroperoxide intermediate, but would also lead to a cross-linked structure as a final product.

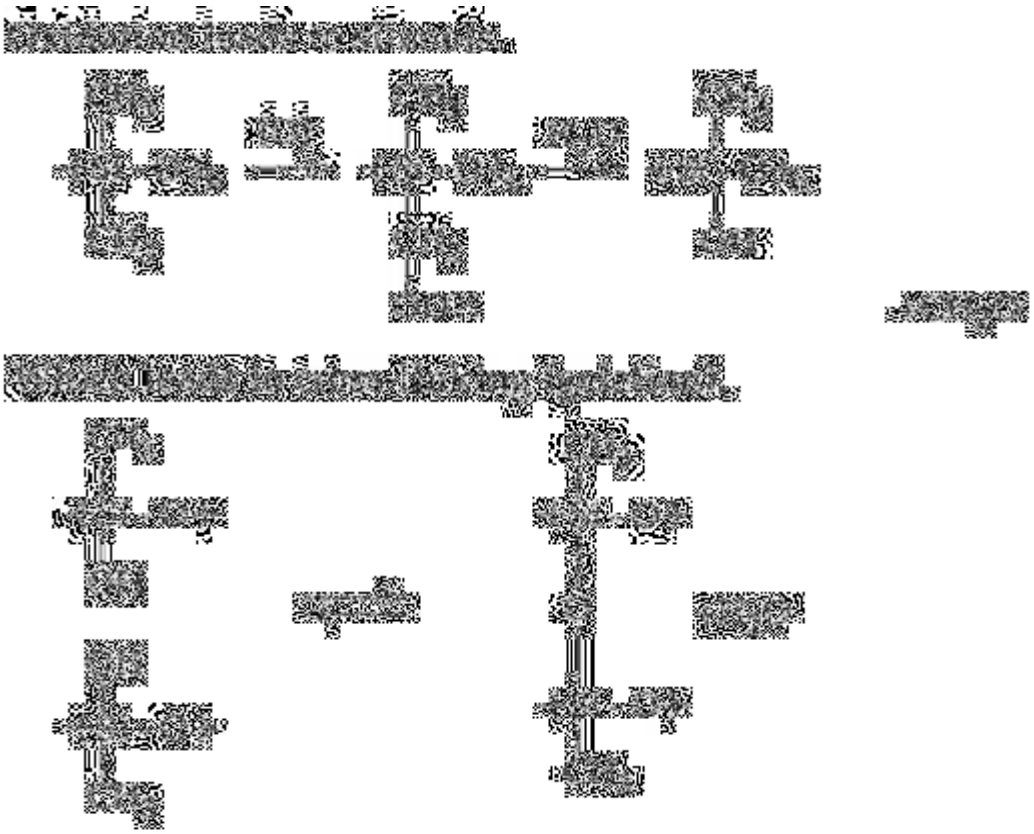


Figure 3: Removal of methyl groups from PDMS by oxidation with subsequent cross-linking.

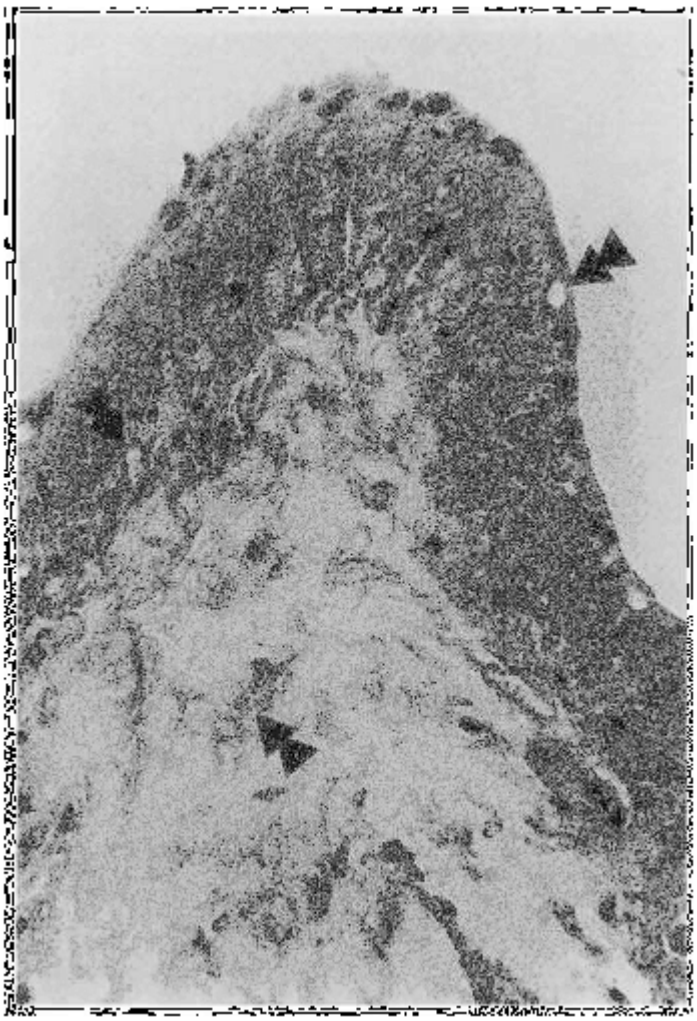
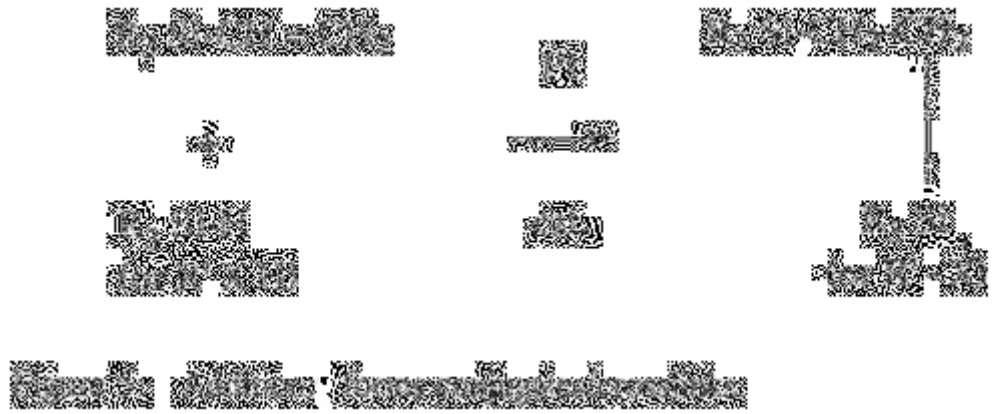


Figure 4: This patient underwent bilateral subcutaneous mastectomies for fibrocystic disease with subsequent placement of silicone gel filled implants. Three years after surgery she developed signs and symptoms of autoimmune disease, and was eventually diagnosed with scleroderma. She did not improve after medical therapy, and the implants were removed. At surgery, the elastomer shells were intact. The capsular tissue was routinely processed with xylene as a dehydrating agent. During hematoxylin and eosin staining, xylene was again used as a clearing agent. Microscopic examination of the capsules revealed numerous intracellular vacuoles of refractile, water clear, foreign material (arrows). The identity of this material was confirmed to be silicone using microscopically guided Fourier transform infrared spectroscopy. Since the elastomer shell was intact, the origin of the silicone is presumed to be gel bleed. Hematoxylin and eosin at 200

ADDITION TO VINYL GROUPS

As shown in Figure 5, the small amount of vinyl groups which are present in gel bleed can react with other components having them add to the vinyl groups. This reaction is the basis for the platinum cross-linking reaction, leading to the gel originally. However, other functional groups are known to add to vinyl substituants in various organic molecules and such behavior would also be expected here. Almost no information on this reaction has been found in the literature.



CONCLUSION

These various results suggest that at the surface of PDMS droplets, hydrolysis and oxidative changes take place, leading to a surface which is a cross-linked silanol containing composition.
This composition would not be unlike that of silica which had been hydrolyzed to a form which would have a significant biological effect. The interior of such droplets may be largely normal PDMS at this point, depending on their size. If this mechanism is true, then methods which would address silicosis may also function, to some extent, to ameliorate other silicone induced diseases. One method proven to be successful with silicosis is treatment with polyvinylpyridine- N-oxide. The N-oxide group is believed to complex selectively with the silanol groups and block them from interacting in an adverse way with cell membranes (Shi, et aI., 1989).

ACKNOWLEDGEMENT

We acknowledge the Society of Plastic Surgeons Educational Foundation for partial support of this project

* Chris Batich has worked with attorneys representing women in suits against some manufacturers.

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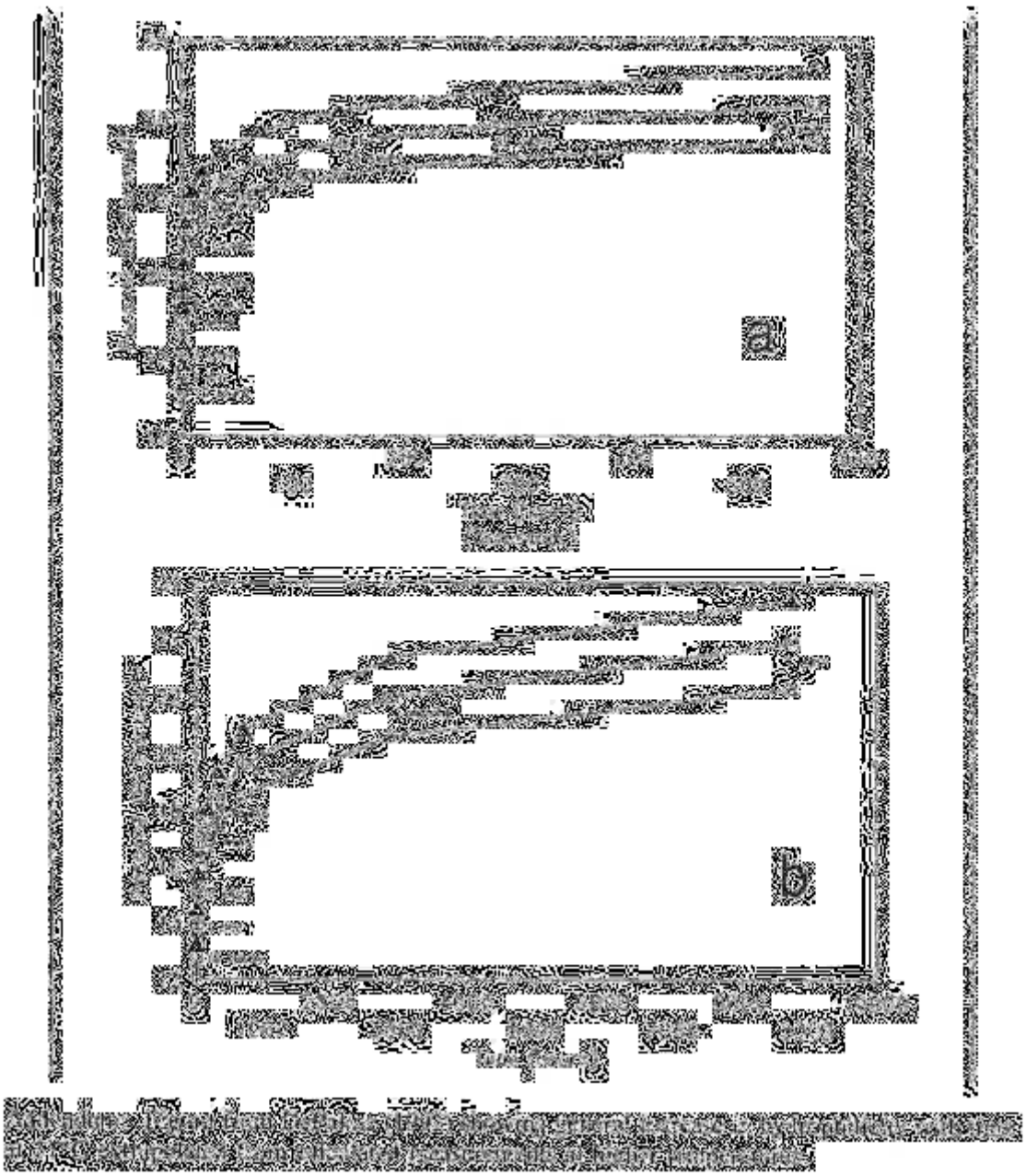
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