Pharmacologic Effects in Man of a Specific Serotonin-Reuptake Inhibitor

Abstract. *Fluoxetine (Lilly 110140) caused a 63 percent inhibition of [³H]serotonin uptake into platelets obtained from normal volunteers to whom the drug was administered daily for 7 days. This dose had no effect on the usual pressor response produced by injections of norepinephrine or tyramine.*

Fluoxetine (Lilly 110140) has been studied extensively in animals (*1, 2*). Its specificity as a serotonin (5-hydroxytryptamine) reuptake inhibitor has created much interest, and fluoxetine has been used in evaluating the function of the serotonergic system. Here we describe the clinical pharmacology of fluoxetine in man and demonstrate its effects on noradrenergic and serotonergic systems.

Normal, healthy volunteers who had given their informed consent were hospitalized and maintained on a modified catecholamine-free diet throughout the entire study.

Four subjects were included in a study designed to determine the specificity of fluoxetine with respect to its effects on the serotonergic system. These subjects received placebo medication for 7 days in capsules identical in appearance to capsules containing fluoxetine. Throughout the next 7 days, subjects received fluoxetine capsules at a single daily dosage of 30 mg. All medications were administered at the same time each morning. Three hours after drug or placebo administration, on days 1, 4, 7, 8, 12, and 14, subjects were given bolus intravenous injections of tyramine (*3*), followed shortly thereafter by intravenous infusions of norepinephrine. The doses of tyramine and norepinephrine were adjusted to produce increases in blood pressure of 25 to 30 mm-Hg as previously described (*4, 5*). On these days blood was collected and centrifuged, and platelet-rich plasma was prepared for subsequent determination of the ability of the platelets to accumulate tritiated serotonin ([³H]5HT) and for the determination of the concentration of serotonin in platelets (*6*).

Three hours after the administration of a single placebo capsule (day 1), the doses of tyramine and of norepinephrine that would increase blood pressure elevations by about 25 mm-Hg were determined. The response to specific doses of these biogenic amines remained unchanged throughout the placebo period (days 4 and 7). Blood pressure responses to tyramine were similar on days 1, 4, and 7 after the subjects had received daily fluoxetine (30 mg) administration. These findings are indicative that fluoxetine at this dosage is devoid of effects on peripheral noradrenergic neurons. Platelets from subjects receiving placebo medication were capable of concentrating [³H]5HT in their usual manner, whereas when these subjects were receiving fluoxetine (30 mg daily), the uptake of [³H]5HT into platelets was significantly inhibited by 55 percent on day 4 and 63 percent on day 7 (Fig. 1). The degree of inhibition of [³H]5HT correlated well with the concentrations of fluoxetine in the plasma. Moreover, when the drug was discontinued, platelets regained their ability to accumulate [³H]5HT. Endogenous platelet serotonin levels varied from day to day within subjects; however, the mean concentration of serotonin in subjects treated with fluoxetine was less than when these individuals were receiving placebo medication. When fluoxetine administration was discontinued, the serotonin concentration in the platelets returned toward the concentration before treatment.

The administration of up to 90 mg of fluoxetine as a single dose to normal volunteers was without any demonstrable subjective or objective effects. There were no perceptible changes in the behavior of these subjects, nor were any adverse side effects reported. No difference in responses to a modified Cornell Medical Index Questionnaire was seen when a comparison was made between days of placebo administration and those days when subjects were receiving fluoxetine. Likewise, no subjective or objective behavioral or other overt pharmacologic or psychologic effects were observed in normal volunteers receiving fluoxetine (30 mg daily; total dose 210 mg), a dosage schedule which blocked [³H]5HT uptake into platelets by greater than 65 percent.

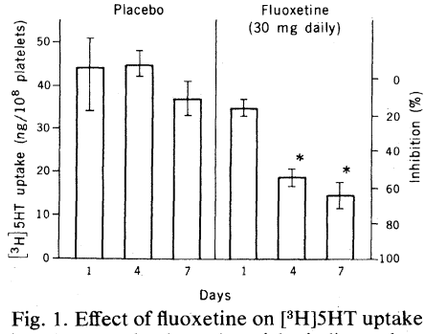

Fig. 1. Effect of fluoxetine on [³H]5HT uptake into human platelets. Asterisks indicate data significantly different ($P < .005$) from placebo treatment for that day.

It has been postulated that patients afflicted with the affective disorders represent a heterogeneous group, some patients suffering from a deficiency in the catecholamines (that is, norepinephrine) (*7*), while others may have a deficiency in the indolealkylamines (that is, serotonin) (*8*). The tricyclic antidepressants currently used in treating these disorders possess varying degrees of effectiveness in preventing the reuptake of norepinephrine and serotonin. Our experiments demonstrate that fluoxetine is a specific inhibitor of serotonin reuptake and suggested that it may be useful in evaluating the role of serotonin in the pathophysiology of mental diseases. Furthermore, the drug may be a potential therapeutic agent in treating these disorders.

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3. Tyramine solution was prepared by A. Fites of the Lilly Research Laboratories at a concentration of 5 mg/ml in saline. The solution was sterile and pyrogen free. Commercially available Levophed (Winthrop) was diluted to the desired concentration and infused over a 10-minute period by means of a constant infusion pump. All subjects had a 19-gauge needle inserted into the antecubital vein through which an infusion of 5 percent dextrose and water was administered and maintained at a continuous rate. All injections were made into the rubber tubing of this continuous infusion which was designed to deliver the drug into the antecubital vein.
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6. Platelet-rich plasma was prepared by centrifuging citrated samples of whole blood at 130*g* for 30 minutes. The [³H]5HT uptake into platelets was determined as previously described by a modification of the methods of Horng and Wong (*2*) and Lemberger *et al.* (*4*). Briefly, the uptake of [³H]5HT was determined by incubating 0.2 ml of human platelet-rich plasma in 1.8 ml of a Krebs bicarbonate buffer containing 0.1 m*M* glucose, 0.1 m*M* iproniazid, ascorbic acid (0.2 mg/ml) and EDTA (0.05 mg/ml). Uptake was terminated after 10 minutes of incubation by placing the tubes in an ice bath and quickly adding

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0.1 ml of 20 percent formaldehyde. The platelets were harvested by centrifugation at 12,000*g* for 25 minutes. After decanting the supernatant, the platelets were digested in hydrogen peroxide and poured into scintillation vials for liquid scintillation spectrometry. The amount of serotonin that accumulated at 4°C was subtracted from each sample.

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Silicon Identification in Prosthesis-Associated Fibrous Capsules

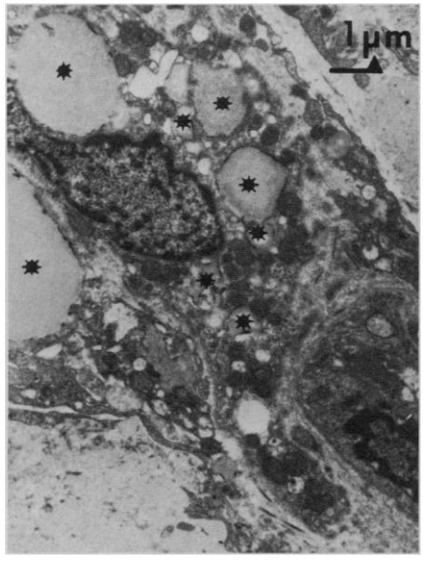
Abstract. *The use of correlated microscopic techniques, including the scanning electron microscopic modes of backscattered electron imaging and energy dispersive x-ray analysis, aid in defining the process of dispersion of silicon-containing material around silicone rubber (polydimethylsiloxane) prosthetic devices.*

Fibrous capsule formation after the implantation of a relatively large, inert object in tissue is a basic wound-healing response. Breast prosthesis implantation in humans, a major surgical market for silicone prostheses, generates a capsule which, when contracted (*1-3*), affects the success of mammary augmentation. Contraction of the breast capsule causes disfigurement or pain, or both, often leading to further surgery or even to the removal of the prosthesis and implantation of a new device. Although silicone breast prostheses have had extensive clinical use for more than 10 years, the conditions leading to a poor clinical course have not been systematically or experimentally evaluated by using adequate scientific techniques.

The polydimethylsiloxane polymers (silicone rubber) used in the construction of all types of currently used prosthetic devices may undergo substantial change once they are localized at a tissue site (*4-6*). Electron microscopic studies (*2, 7*) have described unique intra- and extracellular vacuoles associated with breast implants. To date, the in situ localization of silicon in those vacuoles has not been proved. The only precise identification of silicon in previous studies has been with standard bulk chemical spectroscopic techniques. The literature contains a single case report (*8*) of the identification of polydimethylsiloxane by atomic absorption spectrophotometry in human tissues. Infrared and ultraviolet spectroscopy have been used in experimental studies (*3*).

The data presented here are, to our knowledge, the first that conclusively demonstrate both cell-localized and extracellular silicon-containing material away from a polydimethylsiloxane implant. We were able to obtain these data only by using optical visualization and spectrometry in combination. Our study indicates that while the techniques of transmission electron microscopy are useful for describing the relationship between prosthesis-associated materials and the cells or tissues within which they are contained, the scanning electron microscopy (SEM) procedures of backscattered electron imaging and energy dispersive x-ray analysis (EDXA) identify and demonstrate the exact extent of silicon-containing material within tissue blocks. The SEM procedures have been used in other diagnostic applications, including the identification of inorganic silicon compounds (*9*), and their use by investigators working with any formulation of polydimethylsiloxane should provide a more accurate analysis of the movement of silicon-containing material away from a silicon-based device. More importantly, possible differences in electron scatter or differential x-ray intensities might allow the discrimination and identification of the source of tissue-localized material.

Ten fibrous capsule biopsies were obtained at the time of reimplantation of gel-filled mammary augmentation devices. The devices consisted of a silicone rubber envelope surrounding a less viscous silicone gel. All of the long-term prosthetic devices removed were intact and were grossly similar to the new implants. In one case the prosthesis removed at the time of resurgery was also taken. All samples, including a section of the prosthesis, were first fixed in an alde-



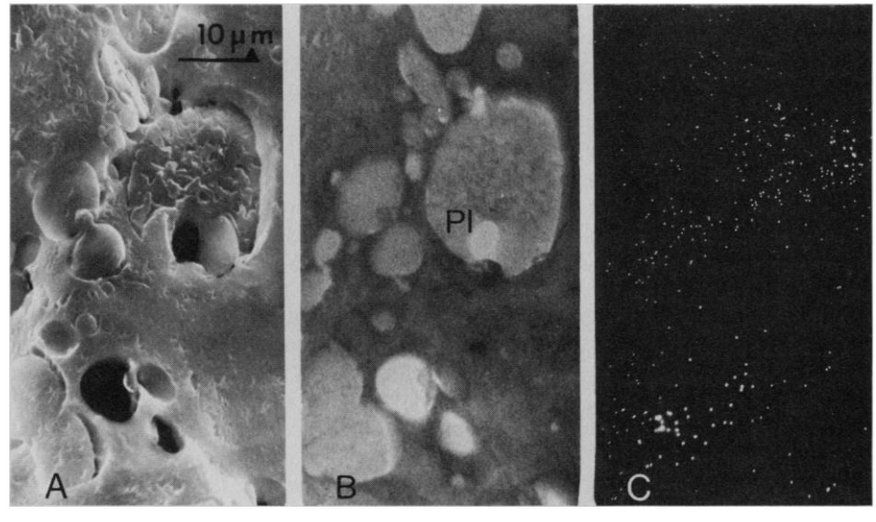


Fig. 1 (left). Transmission electron micrograph illustrating a diverse assortment of vacuoles (*) presumed to contain silicone and apparently located within a contracted capsule fibroblast (× 6500). Fig. 2 (right). Series of scanning electron micrographs of a thick section adjacent to the thin section shown in Fig. 1: secondary electron (A), backscattered electron (B), and EDXA (C) modes. The backscattered electron image here, and the one in Fig. 4B, are shown with reversed signal polarity to facilitate comparison with the more familiar transmission electron microscopic image. Regions of higher atomic number thus appear darker because of greater electron scatter. The EDXA silicon map demonstrates the presence of silicon localized in the vacuoles. Other elements (Cl, Os, U, and As) present in the sections were not selectively distributed. Point *PI* is the site of the spectral peak intensity analysis (× 1100).

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