COPY

August 25, 1962
Department of Surgery

Dr. W. Raab, M.D.
Active Em. Professor of Experimental Medicine
Director Cardiovascular Research Unit
The University of Vermont College of Medicine
Burlington, Vermont

Dear Doctor Raab:

Thank you for your kind letter of August 12. I am sorry to be so late inasnswering, but apparently your letter was delayed in being forwarded from the Naval Medical Research Institute, Bethesda, because I am no longer on active duty.

Our work using capsules of silicone rubber (Silastic) as slow release carriers for implantation of certain drugs, was submitted to Circulation Research and as soon as it is published I will be happy to send you a reprint. However, I can give you a summary of information which might be useful to you.

Essentially we have found that Silastic, an inert silicone rubber usedfforaprostbbtic aortic valves etc., will allow some drugs to dissolve in its wall and diffuse through the other side. For example if a capsulesof Silastic 14 mm long, 3.5 mm I.D., and 0.75 mm thick is filled with 30,000 micrograms of dry tri-iodothyronine powder, approximately 10 micrograms per day will diffuse from the external surface. When this capsule is implanted in the myocardium of a dog with complete heart block 8 hours after implantation a steady tachycardia originates from the site of implantation and averages about 100 beats/minute above the control level.

Theoretically such a pacemaker should last at least 3-4 years, but in our dogs a thin layer of fibrosis develops around the capsule after 1-2 weeks and then it functions only intermittently.

We can prove that the Silastic capsule continues to secrete however, because if it is removed from the fibrous layer and re-implanted in another area of the same heart or in another heart it continues to work indefinitely. Our present research is partly aimed at preventing the fibrosis. There are a number of ways of attacking this problem, for example including hydrocortisone in the lumen of the capsule. Even sterilization contributes to some of the fibrosis as most of the common sterilizing agents are absorbed into the Silastic wall.

Many drugs will not go through at all. We also tested hundreds of dyes since they were simple to assay. In general, only those dyes soluble in fats or the hydrocarbon solvents would diffuse through the Silastic others would not even after 5 months of observation. So far we have found that tri-iodothyronine, digitoxin, versene, penicillin and isoproterenol will go trough a solid wall of Silastic. Therefore I would expect that you could use this material to release other catecholamines. The rate of release is dependent on the surface area of the capsule not on the amount of drug inside. The latter determines the theoretical lifetime of the implanted capsule.

I am not sure over how long a period you wished to expose the myocardium to catecholamines, but after a few weeks you may get some fibrous tissue formed around the Silastic implant.

We make our own capsules by using Silastic tubing with a wall thickness of .75 mm and an I.D. of 3.5 mm. One end is sealed with a drop of Silastic cement and allowed to cure at room temperature for 24 hours or at 160 C. for 1 hour. The drug (either powder or liquid form) is then inserted into the lumen and the other end sealed with Silastic cement. These materials may all be obtained through the courtesy of Mr. Silas Braley, of The Dow Corning Center For Aid to Medical Research, Midland, Michigan. Also since there are literally hundreds of kinds of Silastic (liquid, sponge, gels, etc.) all with the same properties, you might describe your particular problem to Mr. Braley. He is an excellent physical chemist and was very helpful to us in our many experiments.

I have enclosed a copy of our original endocrine pacemaker paper, the work which led to our search for slow release agents. Since I have conducted several other experiments to study the relationship of thyroid and catecholamines using this technique of local myocardial thyrotoxicity, I would be very interested in receiving any papers you might have on the myocardial effects of catecholamines.

When we have the fibrosis problem solved I will let you know.

Sincerely yours,

Judah Folkman, M.D.