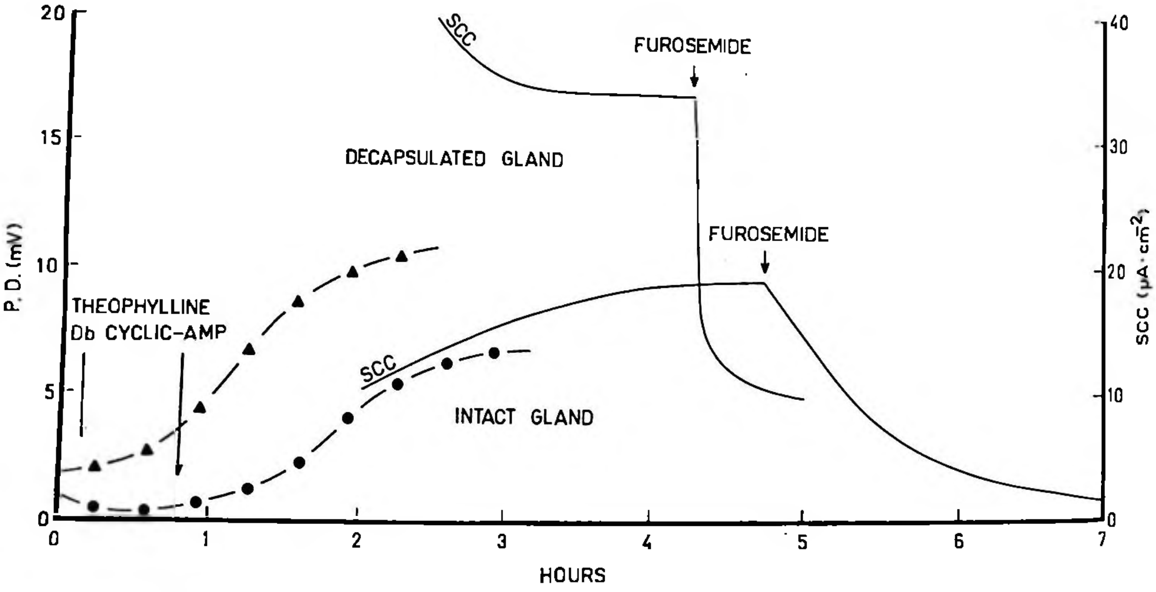


Figure 2. Time course of development of electrical properties of two rectal glands of *Squalus* stimulated first with theophylline ($10^{-4}$ M) and Db cyclic AMP ($10^{-5}$ M) and inhibited afterwards with furosemide ($10^{-3}$ M). Note that the decapsulated gland develops the potential difference and short-circuit current to higher levels and more promptly while the inhibition by furosemide is immediate in comparison with the intact tissue.

of tissue utilized in our experiments does not rule out the probability that the center of the tissue is n well oxygenated during the performance of the flux determination. Calculations kindly provided by Dr. Joh Stephenson from the National Institutes of Health based on the known oxygen uptake and thickness of the la of tissue utilized by us, support the notion that some degree of anoxia might exist in the tissue. Howeve this will have the effect of producing an overall reduction in metabolic rate that will reflect in lower rates of chloride transport. From evidence collected at this Station on the secretory characteristics of gland (see Silva 1976, this Bulletin) and the evidence presented here it can be safely stated that the dri force for the secretion of sodium chloride by the rectal gland of the shark is mainly a chloride active transport operating in the direction capsule to duct.

## CENTRAL NERVOUS SYSTEM DISTRIBUTION OF BLEOMYCIN IN *Squalus acanthias*

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Little is known about the entry of Bleomycin into the central nervous system, even though it is an important anti-cancer therapeutic agent. The dogfish was used as an animal model to study Bleomycin beca of the background of material available on central nervous system studies in the dogfish and the small quantity of albumin present in dogfish plasma to potentially impair interpretation of data. Three goals w pursued:

1. To compare the distributional space of Indium Bleomycin with Indium Chloride to determine fastness of Indium to Bleomycin in the model being studied;

2. To evaluate the cerebrospinal fluid to plasma activity ratio of Indium Bleomycin and compare it with Indium Chloride; and
3. To assess the uptake of Bleomycin by brain.

Two types of studies were done, one group of dogfish received Indium-111 Bleomycin, and a control group received Indium-111 Chloride for comparison of the distribution of the isotopes. The second group of studies consisted of two series of dogfish who received Indium-111 Bleomycin with studies in one group terminated in 20 hours and the other group terminated in 43 hours. Measurements were based on weights. Tared syringes were filled with approximately two ml of isotope in dogfish Ringers and re-weighed with the volume of isotope administered being determined by difference in weight. The isotope, in dogfish Ringers, was then injected intravascularly and the syringe was flushed three times with blood that was reinjected. Samples of plasma or tissue were placed in tared counting tubes and re-weighed. For determination of water content in samples the counting tube was dried to constant weight, and the water content determined by change in weight.

Following sacrifice of the animal spinal fluid was harvested and the brain was removed. The olfactory and cerebral lobes were separated from the brain, blotted and placed in a tared tube. In three dogfish the choroid plexus was separated from the brain and separately processed. The Indium activity was measured using its gamma emission in an automated gamma counter. Due to the short half-life of the isotope, the samples were counted prior to being taken to dry weight.

Small male dogfish of comparable weight were used in the studies and maintained in tanks with continuous circulating fresh sea water.

In the studies comparing Indium-111 Bleomycin with Indium-111 Chloride the mean space of distribution per fish was greater for Indium Bleomycin (N = 5) than for Indium Chloride (N = 3). In one hour the mean Indium Bleomycin space was 4.17 times the mean Indium Chloride space, at four hours it was 3.42 times the Indium Chloride space, and at eighteen hours it was 2.93 times the mean Indium Chloride space.

Mean cerebral spinal fluid to plasma ratios at 18 hours were 0.058 for Indium-111 Bleomycin and 0.008 for Indium-111 Chloride. Mean brain water to plasma water ratios at 18 hours were 0.067 for Indium Bleomycin and 0.028 for Indium Chloride. Mean brain water content in the Indium Bleomycin fish was 81.4 percent and was not measurably different from the Indium Chloride fish.

In the two series of fish studied at different times with Indium Bleomycin comparisons were made of Indium Bleomycin distribution. The mean distributional space for Indium Bleomycin was 454 ml/Kg fish (N = 12) at one hour, 654 ml/Kg fish (N = 12) at twenty hours, and 778 ml/Kg fish (N = 6) at forty-three hours. Mean cerebral spinal fluid to plasma ratios were 0.071 at twenty hours and 0.099 at forty-three hours. Mean brain to plasma ratios, expressed as counts per minute per gram brain water over counts per minute per gram plasma water were 0.082 at twenty hours and 0.090 at forty-three hours.

The small samples of choroid plexus ranging from 12 to 36 mg in the three fish sampled showed a mean tissue to plasma ratio based on counts per minute per gram weight of 0.526 at forty-three hours.

Indium Chloride distributed in an area approximating plasma volume. Indium Bleomycin, however, distributed in a larger volume, presumably representing tissue distribution. Failure of Indian Bleomycin to show major increase of distribution with time indicated that the isotope remains attached to the Bleomycin during the period of the study.

Bleomycin gained access to the cerebral spinal fluid and was accumulated in the highest concentration in the samples of central nervous system tissue studied in the choroid plexus. The increased concentration of Bleomycin in spinal fluid may be secondary to an accumulation of Bleomycin in the choroid plexus.