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Clifford Grobstein (1916-1998) and the developing kidney

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Clifford Grobstein, one of the leading post-war developmental biologists and a pioneer in studying inductive tissue interactions in mammalian embryogenesis, died of pneumonia at the age of 82 in La Jolla, California on September 6, 1998. He was an Emeritus Professor of Biology and former Chancellor of Public Relations at the University of California, San Diego.

Clifford Grobstein was born in New York City where he also received his Bachelor's degree in 1936. Having his PhD degree in zoology completed at the University of California, Los Angeles, Grobstein moved to Bethesda where his scientific career began at the National Cancer Institute. A series of key articles was subsequently published from 1953 to 1957 when Grobstein accepted a chair in Biological Sciences at Stanford University, which brought him back to his beloved California. There, in the windowless basement of the biology building, Grobstein established a small laboratory with an excellent animal colony and a technical staff of only two, three people. Since the group was small and the administrative duties modest, Grobstein could peruse the scientific literature extensively and work actively at the bench in the laboratory together with a small number of graduate and postdoctoral students who were privileged to join the already famous scientist. In 1965 Clifford Grobstein moved to San Diego, where he acted as Chancellor of Public Relations but still kept a small laboratory with a few students. He never felt a need to expand his research group beyond a few people and a small technical staff, which allowed close collaboration within the team and created an intimate, friendly atmosphere in the laboratory.

The experimental work of Clifford Grobstein, which would make him one of the best recognized post-war developmental biologists, can be largely timed to the fifties. The concept of "embryonic induction" launched by Hans Spemann in the early twenties had initially led to vivid, worldwide research activity, but the enthusiasm had gradually faded. The basic idea of an interaction between embryonic cells and tissues governing development had, indeed, been confirmed by many developmental biologists who had been focusing mainly on the early stages of amphibian development. However, the nature of this intercellular signaling had remained obscure, and no signal substances acting in normal embryogenesis had been properly characterized. Moreover, such interactions operating during the later stages of development were poorly understood when Grobstein first tackled the problem.

Earlier experimental work on amphibian and avian embryos, and observations on mutant mice had suggested that morphogenesis of the parenchymal organs might be governed by interactions between the various cell lineages within the rudiment. This was confirmed in Grobstein's early experiments published in 1953. By enzyme treatment combined to delicate microsurgery he managed to separate the two major components of certain glandular organs (salivary gland, kidney) and showed that both the epithelium and the mesenchymal blastema failed to differentiate in isolation. Apparently, a morphogenetic interaction between these components was a prerequisite for organogenesis (Grobstein, 1953a). In 1956 Grobstein emphasized that such morphogenetic interac-

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Clifford Grobstein, the unbeatable master of microsurgery *(admired by Niklas Saxén).*

tions, earlier known as embryonic induction, take place *"whenever in development two or more tissues of different histories and properties become intimately associated and alteration of the developmental course of the interactants results."* (Grobstein, 1956b).

By that time, Grobstein had concentrated his experiments on the developing mouse kidney, the metanephros. This organ develops from two major cell lineages: a mesenchymal blastema and an epithelial bud invading the mesenchyme to branch therein. The epithelial branches were shown to be pivotal for the subsequent development of the mesenchyme, which undergoes an epithelial conversion into secretory kidney tubules including the glomerular epithelium. Reciprocally, the mesenchyme controls the regular branching of the epithelium (Grobstein, 1955). This process soon proved an excellent model-system for further analysis of inductive tissue interactions during organogenesis. Especially, the "trans-filter" technique has been successfully applied in search of signal substances carrying messages between the two cell lineages (Grobstein, 1953b, 1956a). The method involves the separation of the interacting tissues by a thin membrane filter, and this allows re-dissection of the components and their separate analysis by modern technology. In addition, the isolated, uncommitted mesenchyme has become a useful target tissue when various candidate molecules for signal substances are tested. Grobstein himself used the model-system in the latter part of the fifties to explore in detail the transmission characteristics of the inductive signals, and he was the first to foresee the decisive role of compounds in the extracellular matrix (Grobstein, 1961). In 1967 his vast experimental results and a profound knowledge of the literature were summarized in an excellent review (Grobstein, 1967). The time was not yet ripe for direct molecular approaches, but here Grobstein could foresee the development of the field, and he offered a model, ending in the following statement: *"Materials (associated with cell surfaces) can interact at interfaces between unlike tissues to produce new macromolecular complexes whose properties are jointly determined by the synthetic activities of the cells on the two sides."* This view, expressed more than 30 years ago and based on non-molecular biological experimentation, is not far from our present concepts of tissue interactions mediated by extracellular growth factors with restricted mobility acting via surface-associated receptors. Grobstein's doctrine and its experimental basis re-opened the entire field of embryonic induction and provided new model-systems for its exploration and for the ongoing molecular analysis of cell and tissue interactions.

Gradually, Clifford Grobstein became increasingly interested in the applications of our knowledge on embryogenesis to human problems, such as *in vitro* fertilization, abortion embryo transfer and human cloning. In one of these, "Science and the Unborn", Grobstein meticulously ponders the beginning of human life and our rights to interfere with the developing embryo. He distinguishes between four stages in embryogenesis: preembryo, embryo, fetus and neonate, and discusses in detail the characterization of these stages with special emphasis on the development of the central nervous system and the brain. The discussion of our attitudes towards the human being at these stages reflects the author's strong moral code combined with a profound understanding of embryonic development. The book, like the previous ones, is an honest scientific attempt to approach one of the central ethical problems in today's medicine. *"The unborn should be valued not only as offspring but as ancestors to generations-to-be. Policy decisions about them must therefore enlist the highest standards of human concern and wisdom"* (Grobstein, 1988). Clifford Grobstein himself was a man of science-based wisdom with exceptional human concern.

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