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Obituary

Daniel A. K. Roncari, MD

Dr Daniel A. K. Roncari died peacefully on 28 May 1994 after a courageous battle with cancer. Dr Roncari had devoted his academic endeavours to the study of the fat cell, had demonstrated the intrinsic genetic differences of fat cells from lean and obese, and was an active member of the editoral board of *Obesity Surgery*. Born in Croatia and a Holocaust survivor, Dr Roncari emigrated to Canada from Italy when he was 14. He received his MD from Queen's University in Kingston in 1961 and his MSc in experimental medicine under Dr Charles H. Hollenberg at McGill University in Montreal in 1965. At Washington University in St Louis with Dr P. Roy Vagelos, he received his PhD in biological chemistry.

After becoming a member of the faculty of medicine at the University of Toronto, he went on to become the third director of the Institute of Medical Science from 1980 to 1983. He then moved to the University of Calgary to become the first Julie McFarlane Professor of Diabetes Research. Dr Roncari returned to Toronto in 1988 to become Physician-in-Chief at Sunnybrook Health Science Centre. Most recently he was Professor of Investigative Medicine at Sunnybrook.

He served on the editorial boards of several journals and on advisory committees of granting agencies, as well as serving an executive role with several scientific societies, including president of the Canadian Atherosclerosis Society.

Over his research career Dr Roncari investigated the cellular and molecular basis for the development of obesity. He was firstly interested in the elucidation of genetic, endocrine and trophic principles involved in preadipocyte replication, preadipocyte differentiation, and adipocyte 'de-differentiation'.[1] Among the first to demonstrate conclusively the existence of adipocyte precursors in adult adipose tissue,[2] Dr Roncari accumulated considerable evidence that indicated that adipose cells from massively obese individuals are intrinsically different from those obtained from lean individuals; he thereby demonstrated a strong genetic role in the development of obesity, which was later confirmed by others through epidemiological studies.

Preadipocytes isolated from massively obese persons were shown to have a greater capacity for replication than those obtained from lean individuals.[3] Subsequently, he and his co-workers demonstrated that the increased replicative capacity of preadipocytes from the obese was due to increased production and release of mitogenic proteins[4] (one of which was found to be related to basic fibroblast growth factor[5]) by these cells. Further, he showed that 17-beta-estradiol increases the production of some of these factors in genetically susceptible individuals, probably explaining the high prevalence of obesity in women.[6] In massively obese patients, moreover, preadipocyte clones were demonstrated to have a particular propensity for exaggerated differentiation and accumulation of triacylglycerol.[7] Thus, the coupling of excessive replication and differentiation would culminate in hyperplasia of mature, enlarged adipocytes, facilitating the development and progression of massive corpulence.

In examining adipocytes in culture, Dr Roncari demonstrated that these cells could become delipidated and resume division, thus challenging the notion of 'terminal differentiation' and the non-plasticity of the adult. Furthermore, 'de-differentiated' adipocytes from the obese retained the 'memory' of their preadipocyte origin, replicating to a greater degree than those from lean persons.[8] From these observations, Dr Roncari conceptualized that during prolonged adherence to appropriate eating and regular exercise (both caloric restriction, e.g. by bariatric surgery, and exercise have been shown to decrease preadipocyte replication *in vivo*), reversion of mature fat cells to earlier forms might be promoted even in the morbidly obese.[9] However, when this regime is halted and the genetically susceptible individual is again exposed to sufficient energy, inordinate proliferation of preadipocytes and of de-differentiated cells would recur. Coupled to excessive differentiation, each cycle of 'compliance and relapse' would result in an inexorably progressive increase in the complement of enlarged adipocytes, and thus, of the degree of adiposity.

Dr Roncari also considered a key mechanism in the

pathogenesis of obesity to involve fundamental abnormalities in bioenergetics which would result in an energy overload leading to excessive storage of chemical energy. In this regard, he formulated the following hypothesis: individual variation (under genetic control) in the large amounts of energy required for cellular biomechanical work accounts for the distribution of persons with potential for obesity.[10] Moreover, for each subject, there is a particular reciprocal relationship between the energy consumed for cytoskeletal functions and the remaining energy available for chemical storage, mainly as triglyceride in adipocytes.

Several avenues of investigation have provided support for the hypothesis. Studies with *Chlamydomonas reinhardtii* and *Drosophila melanogaster* mutants have shown that greater macromolecular stores accumulate when elements of the cytoskeleton or motor molecules are dysfunctional.[11] Furthermore, by means of video-enhanced contrast microscopy and analysis of impedance fluctuations due to nanometre movements, ongoing experiments were showing that human omental preadipocytes from obese subjects had depressed motions compared to cells from lean individuals. The increase in biomass of the mutants, as well as the greater dynamic action of lean individuals' cells supported an inverse relationship between chemical energy storage and energy utilization for cellular biomechanical functions.

Beyond discovering what nature chose to reveal, the ultimate aim of Daniel Roncari's work was the development of effective, preventive and therapeutic approaches to obesity. Prior to his untimely death at age 57, he was embarking on the study of the genes responsible for massive obesity in humans. A caring clinician, Dr Roncari will be sorely missed by his family, patients, and the bariatric surgical community.

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