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Molecular cell biology and cancer metastasis

An interview with Garth Nicolson

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Professor Garth L. Nicolson is President, Chief Scientific Officer and Research Professor at the Institute for Molecular Medicine in Huntington Beach, California. He formerly held the David Bruton Jr. Chair in Cancer Research and was Chairman at the University of Texas M.D. Anderson Cancer Center in Houston. He was also Professor of Internal Medicine and of Pathology and Laboratory Medicine at the University of Texas Medical School at Houston and Professor of Comparative Pathology at Texas A & M University. Among the most cited scientists in the world, having published over 550 medical and scientific papers (including 3 *Current Contents* Citation Classics), Prof. Nicolson has edited 14 books and served on the Editorial Boards of 20 medical and scientific journals and is currently serving as Editor of two (*Clinical & Experimental Metastasis* and the *Journal of Cellular Biochemistry*). Professor Nicolson has received peer-reviewed research grants from the U.S. Army, National Cancer Institute, National Institutes of Health, American Cancer Society and the National Foundation for Cancer Research. Dr. Garth Nicolson has won many awards, such as the Burroughs Wellcome Medal of the Royal Society of Medicine, the Stephen Paget Award of the Metastasis Research Society and the National Cancer Institute Outstanding Investigator Award. He is also a Colonel (Honorary) of the U.S. Army Special Forces and a U.S. Navy SEAL (Honorary) [ed. "SEAL" represents *SEa Air Land;* it is a special forces unit of the U.S. Navy] for his work on Armed Forces and veterans' illnesses.

The publications and presentations of Garth Nicolson have continuously underscored the multiplicity of molecular networks implicated in cancer invasion and metastasis. He was, therefore, high on the list of the guest editors for the present Special Issue of *"The International Journal of Developmental Biology"*. The present e-mail interview took place from November 2003 to January 2004. Though we have not been engaged in experimental collaboration, I have followed Garth Nicolson's work very closely and it has clearly influenced some of the *in vivo* work performed in my laboratory. We had long and interesting discussions on both sides of the ocean during the Metastasis Research Society and many other scientific meetings. It gives me great satisfaction that Garth Nicolson readily accepted to be interviewed. We talked about his personal career, about biomedical science in general and, of course, about invasion and metastasis.

Before we chat about science in general, cancer, invasion and metastasis, there are a few interview classics which I would like to ask you about. Was your scientific career influenced by your familial background? Your education? Some of your teachers? When and why did you decide to embark on biology? Was any written paper or oral presentation decisive?

When I was growing up in Southern California in the 1940s and 1950s, I was always interested in science and engineering. My father was a mechanical engineer and my grandfather was a mining engineer, so it was probably in my genes! In school I was always torn between my love for athletics and my love for science. In fact, when I entered UCLA (University of California at Los Angeles) as a 15 year-old freshman (a student in the first year at a university or college) on a scholarship (provides financial support for students based on their excellence in academics or sports), I had to choose between athletics and engineering,

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Garth Nicolson during the period 1969-1972. (A) *Garth Nicolson as a graduate student at the University of California, San Diego, California in 1969.* **(B)** *Garth Nicolson (right) as an assistant professor with then post-doctoral fellow Kenneth Brunson (now a professor at North Texas State University School of Medicine) at the Salk Institute for Biological Studies, La Jolla, California in 1972.*

because it was impossible to do both. I chose science and engineering but that required that I give up my scholarship and get a job. Fortunately for me I had already spent some time as a SCUBA (self-contained underwater breathing apparatus) instructor, and with my certifications in diving I was able to land the perfect job as a professional diver working under a U.S. Air Force contract to test Air Force space capsule designs under simulated zero gravity under water in a very large tank not to far from UCLA. Although it took me longer to graduate, I look back fondly on those long hours underwater taking part in some very interesting aerospace experiments with talented Air Force and industry engineers. Along the way I decided to take a biochemistry class, and it changed my life forever. I decided that I must find a way to combine my love of the sea with my academic interests. But that was not to be. Again, I was at a crossroad in my life, and shortly after entering graduate school I had to make a decision. My decision came when I was working at the Scripps Institution of Oceanography at UCSD (University of California, San Diego) under Professor Andrew A. Benson, a world-famous biochemist for his discovery as a young scientist with Prof. Melvin Calvin (1961 Nobel Prize in Chemistry) of the Calvin-Benson Cycle in chloroplasts, describing the the fixation of CO2 into carbohydrate. I had been looking at what I felt were important areas of research, and I settled on biological membrane structure as an important new area because every living thing was separated from its environment by a cell membrane. Andrew Benson was very interested in membrane phosphoplipids, and he was working on membrane structure, which was at the time a major unsolved problem. I also had the privilege of working with Professor S. Jonathan Singer on this problem, and I was especially attracted to his knowledge of physical chemistry as applied to cell biology. With my background in the physical and chemical sciences, I was precisely in the right place at the right time to work on this marvelous problem under two of the most outstanding scientific minds of our time. Eventually I decided to move into Professor Singer's laboratory as his graduate student on the new upper campus at UCSD and spend my time working on membrane structure. Professor Singer's laboratory was quite diverse, going along with his nature and interests in science, and I was one of the few members of his group actually working on membrane structure. Part of the reason for this may have been my background in physics, chemistry and engineering. Without knowing, I had prepared myself well for this environment. It was an exciting time, and our work paved new ground in understanding biological membrane structure and its dynamics.

Permit me to go back to the 1972 publication by Singer and Nicolson about the fluid mosaic model of the plasma membrane. Peter Fisher's "Licht und Leben" (1985) reproduces the Science figure to illustrate Max Delbrück's interest in biological membranes as a new dimension in biology. This is but one illustration of the great influence this idea had and still has in molecular cell biology. I suppose the idea was developed during your stay in Singer's laboratory. What particular memories do you have from that time?

One of the important lessons of cracking the structure of biological membranes is that a multi-disciplinary approach was necessary. My role was to supply the data that supported our ideas on biological membrane structure, especially the thermodynamic theories that Professor Singer had already worked on. One of our arguments along the way concerned the dynamics of membrane structure, and this is probably why I eventually coauthored the seminal paper in Science in 1972 on the Fluid Mosaic Membrane Structure. I had also contributed data showing the lack of flip-flop of membrane glycoproteins and their ability to move laterally in the membrane, important supporting evidence for our theories.

Did this work on the plasma membrane bring you to cancer research?

I was extremely lucky to have my thesis work culminate in ten publications and an important review that became the most highly cited paper in all fields of science for the next decade. This allowed me opportunities that are rarely available to new graduates. After graduate school I decided to stay in San Diego and accepted a faculty position at the Salk Institute. In this new environment I was greatly influenced by Prof. Robert Holly, who had won the Nobel Prize for his work on tRNA. Dr. Holly had moved into cancer research. I had a brief

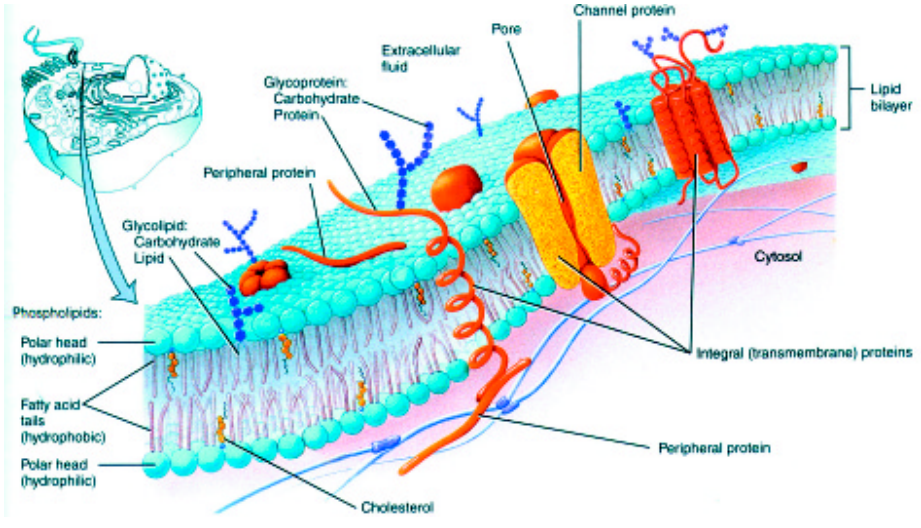
flirtation with cancer research as a graduate student from my interest in the dynamics of cancer cell membranes compared to normal cell membranes, and this seemed like an opportune direction for my new laboratory. I was also helped considerably by some private foundations that supported my research. At the time it would have been almost impossible for a recent graduate to obtain NIH funding, especially when I had just barely completed a NIH pre-doctoral fellowship. I will always wonder what those NIH reviewers must have thought of my applications for grant support written while I was still a graduate student!

May I take the opportunity of this interview to ask your opinion about the evolution during your career of certain aspects of science policy which are of great concern to young researchers, especially in the biomedical field? Is the competition for grants fair? The criteria in general and citation index (impact factor) in particular? What about the "publish or perish" pressure that lies on our Laboratories and especially on our PhD students? Will the peer review system survive the growing criticism of the scientific community?

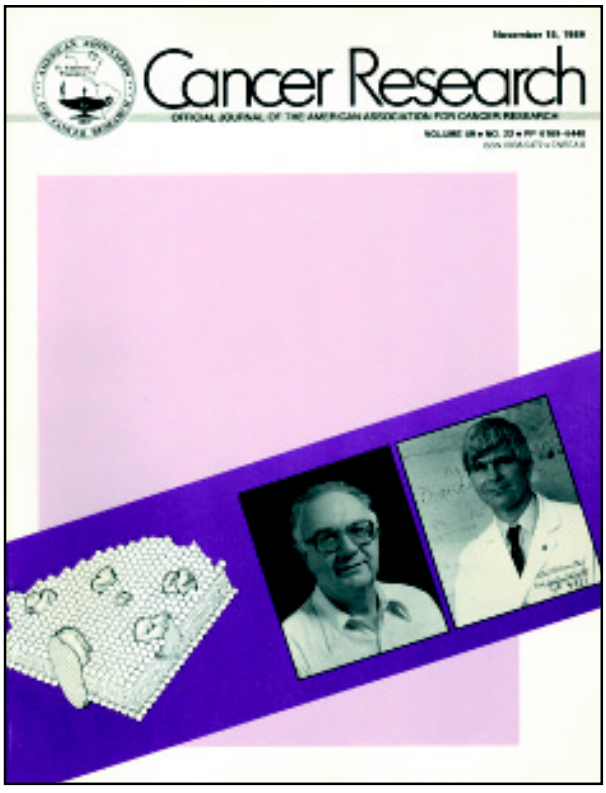
I have always had mixed emotions about the grant peer-review system. As a peer-reviewer on different national review committees, committee member and later chairman, I was always struck by the absolute fairness and objectiveness of some individuals and the narrow-mindedness and strict self-interest of others. In any competitive environment there will always be pressure to achieve, whether it is in sports or in the laboratory, but this type of environment can unfortunately also select for aggressive, self-promoting individuals who don't play by the rules. As a review committee chairman, I always tried to mix older, more statesman-like scientists with the less forgiving ego-driven people with the hope that fairness would prevail, and in most cases it did. But we obviously have a problem here with no simple answer in sight and with diminishing funds to do ever more expensive research. I don't have an answer to this dilemma, but I realize that there are some major problems with the way in which research funding is determined.

There is little doubt that advances in biomedical research have been enormous during the 20th century. There are of course many explanations for this. It is my impression that war had a big impact ("collateral benefit"). For example, the book by Soraya de Chadarevian (2002) highlights the influence of World War II on the development of molecular biology in Cambridge. What comes to mind is also the war gasses and chemotherapy; the atomic bomb (Hiroshima and Nagasaki, but also the scientists at Los Alamos) and carcinogenesis. You have been reflecting on this issue and we would greatly appreciate your thoughts.

I have been involved in seeking answers to war-related injuries, particularly those obtained during the recent Persian Gulf Wars but also the wars in South-East Asia. This started with a decorated family member who returned from the Gulf War and came down with an unusual illness that was being misdiagnosed as a stress-related problem. In this case we found an unusual mycoplasmal infection and also in ~40% of the ill veterans and more recently in their immediate family members, (Nicolson *et al.*, 2003b). Our work on the Gulf War veterans was later confirmed by others in a large study. Since we had studied the signs and symptoms in over a thousand Gulf War veterans, we were struck by the similarity of their illnesses to Chronic Fatigue Syndrome and Fibromyalgia Syndrome found in civilians. Studying these civilian illnesses we found similar chronic infections but in the case of civilians there were multiple infections (Nicolson *et al.*, 2003a). We have been working on new therapeutic approaches to treat these illnesses, and one of my recent efforts has been directed at repair of their intracellular membranes, which we have found are damaged and leaky in these illnesses. Interested readers can read a summary of this approach in a recent



The fluid mosaic model of the plasma membrane *(upper panel), as originally published by Singer and Nicolson (1972) served as a model for thousands of figures in later publications and textbooks, as exemplified in the lower panel taken from J. Tortora and S R Grabowski,* Principles of Anatomy and Physiology. *John Wiley & Sons, Inc. (2000).*



Cover of Cancer Research *showing S.J. Singer (left) and G.L. Nicolson (right) with the fluid mosaic model of the plasma membrane.*

publication (Nicolson, 2003). I find it amusing that I first worked on mitochondria as a beginning graduate student, and recently we have gone back to look at mitochrondrial damage in various chronic illnesses.

Students from different parts of the world have been working with you and you have visited many Institutes all over the world. Are their striking differences in (cancer) research between the US and Eastern Countries? Europe?

Science is an international effort, and I certainly find more similarities than differences in various countries. One of the differences, however, seems to me to be related to funding opportunities rather than differences in research approaches. Those countries that generously fund cancer and other biological research activities will find their scientists at the cutting edge. Those that don't will find their programs in secondary positions and their scientists will seek to leave for better opportunities. One of the most gratifying aspects of science has been working with students and post-doctorals from all over the world, and I don't have the space to list my colleagues here, but I have certainly learned as much if not more from them as they probably have learned from me.

How are genomics and proteomics, as they evolve today, going to influence our insight into the molecular biology of (cancer) cells?

I believe that we are going to focus more on regulation of gene expression and post-translational events rather than just genes and their structures, and this will be much more of a multi-disciplinary approach. This is already happening. I also believe that there will be much more integration of areas previously somewhat segregated, such as genetics, molecular biology, cell biology and physiology, protein, lipid and sugar chemistry, information science and the physics of macromolecular interactions, to name a few. Eventually this will have major impact on the way we approach and treat various diseases.

There is a rapid evolution in scientific communication due to electronic systems. On the other hand, the classical way of publication through printed journals has become progressively more expensive with more and more space limitation. How would you like to see further progress in this regard? Should biomedical results be published in more and more specialized journals? Concerning our own field of research, two specialized journals appeared: "Invasion & Metastasis" in 1981, and "Clinical & Experimental Metastasis" in 1983. Neither of them made it to the top and one of these had to be closed down because of lack of good manuscripts. This is in sharp contrast with the excellent papers about invasion and metastasis that do appear in top journals. Is this an argument against highly specialized journals?

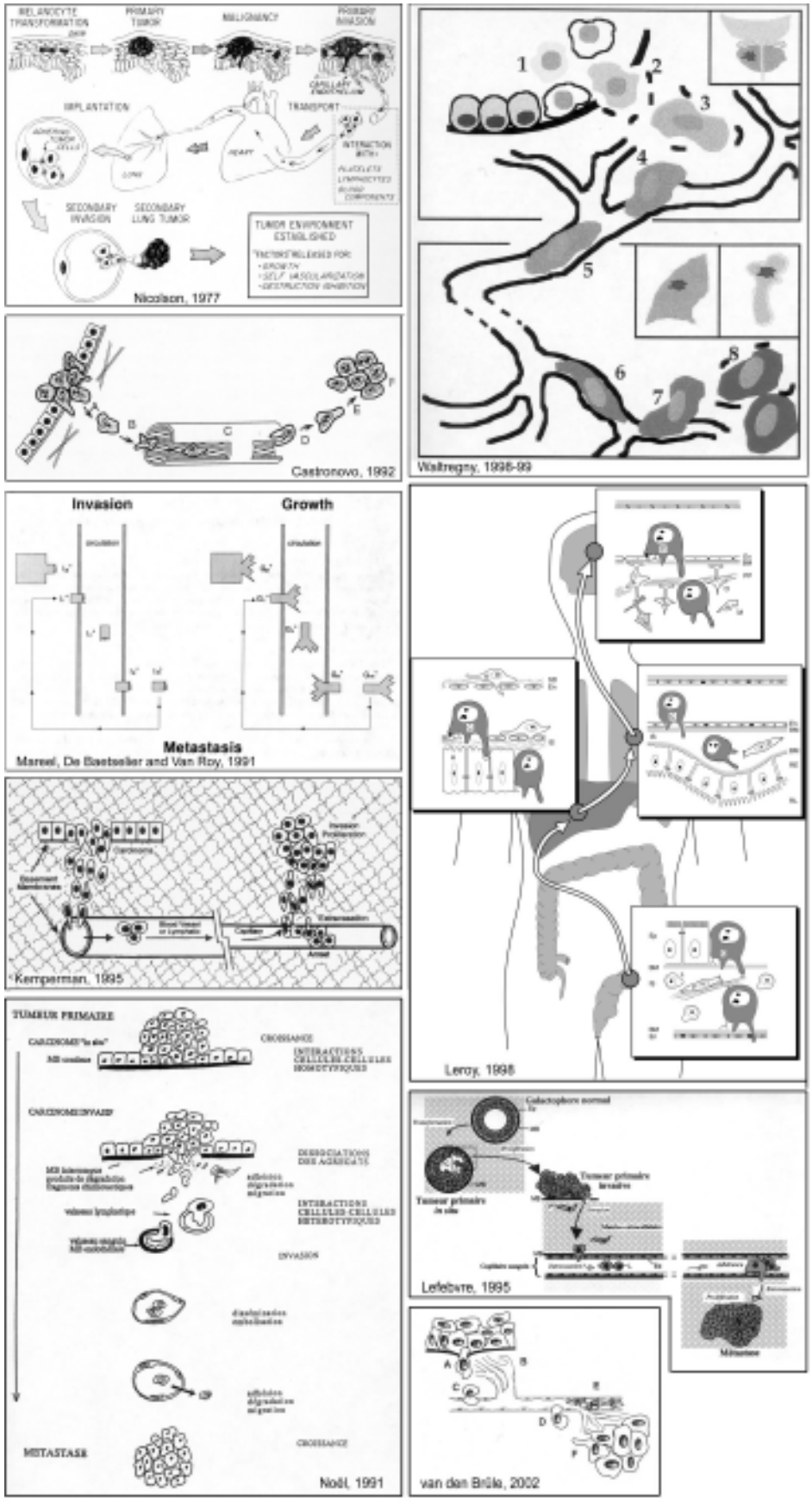
I believe that scientists will always try to publish their results in the most prestigious journals possible. However, few investigations may be worthy of publication in first ranked general journals, so we have seen a proliferation of secondary journals in specialty areas where authors can publish important but perhaps not earth-shattering papers. I don't find this bad or an argument against specialized journals. They play a necessary role in filling in the gaps left by break-through publications that may open new areas but rarely can fill in the information necessary for science to move ahead. I was always amused by comments from years ago by a young, aggressive scientist who only wanted to publish in Nature and Science and then move to new areas so that he could always be the first to publish earth-shattering data. I called this at the time "mountain hopping," because such individuals are not inclined to fill in the gaps left by their leap to another lofty scientific pinnacle. The attitude of this individual was that others could fill in the gaps; he couldn't be bothered. An unfortunate down side of this type of ego-driven approach is that rather large mistakes can also be made. I believe that there will always be a place for important, solid work, even if it is not earth-shattering.

Who has influenced your thinking about metastasis? What were the major steps? Why did Paget's "seed" and "soil" theory stand the test of time? Do names come to your mind of people who contributed greatly but how have been essentially forgotten?

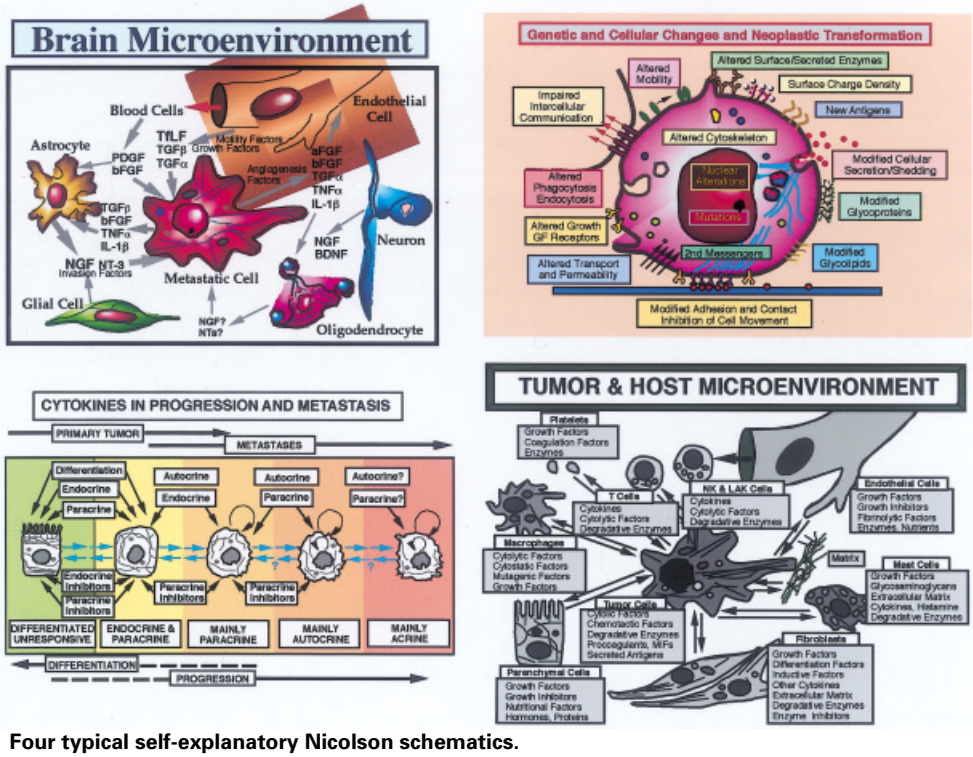
I am a believer that if one bothers to look at historical works, you will almost always find the seeds of our current scientific endeavors. These historical works may not be exactly accurate, but when you consider the available technology, they are very impressive. I would place Paget's (1889) "Seed and Soil" theory of metastasis at the foremost spot on my personal list, and it is certainly the most impressive theory for me in the area of metastasis research. Previously I had discussed this very topic with Lance Liotta, because he had such a personal interest in historical aspects of metastasis research. He wrote a historical piece on metastasis research in which the beginnings of this field are discussed.

Some concepts, schematically presented in many publications, have greatly influenced our thinking about metastasis. One example is Fig. 1 in Nicolson et al. (1977). Variations on this schematic have been shown hundreds of times in Meetings, in Reviews and in PhD theses (Fig. 4). Some of the cartoons that you presented were criticized for their complexity with too many molecules and too many arrows. As compared to actual schematics with protein complexes and networking between these complexes, your schematics now appear to underestimate the number of molecules participating in the cellular activities described by you. How should we handle these networks in our analysis of the molecular mechanisms of invasion and metastasis? What is the impact of new techniques such as micro-arrays?

In my reviews I always tried to be accurate for the information available at the time, and this is especially true of any composite figures presented in reviews,



Variations on the schematic (left hand top corner) published by Garth Nicolson in 1977 (Nicolson *et al.,* 1977) were taken from theses at which the interviewer participated as promoter or as member of the committee. *Alternatively, they are from Mareel* et al. *(1991). Theses by: Frédéric van den Brûle, Contribution à l'étude des galectine-1 et galectine-3 au cours des processus d'invasion physiologique et pathologique. Université de Liège, Belgique (2002); Vincent Castronovo, Interactions entre cellules cancéreuses et laminine au cours de l'invasion tumorale et de la dissémination métastatique, Université de Liège, Belgique (1992); Hans Kemperman, Integrins and mucins in liver metastasis of carcinomas. University Nijmegen, The Netherlands (1995); Agnès Noël, Interactions entre les cellules d'adénocarcinome mammaire, la matrice extracellulaire et les cellules des tissues hôtes? Université de Liège, Belgique (1991); Ancy Leroy, Cellular and molecular mechanisms of invasion of Entamoeba histolytica trophozoites. University of Ghent (1998); Olivier Lefebvre, La stromélysine-3 et ps2: deux genes surexprimés dans le cancer du sein. Etudes de leur rôle physiologique chez le souris. Université Louis Pasteur, Illkirch-Graffenstaden (1995); David Waltregny, Contribution à l'évaluation pronostique des lesions cancéreuses prostatiques chez l'homme: intérêt de la detection de la protéine RL67 et de la sialoprotéine osseuse. Université de Liège (1998-1999).*



Four typical self-explanatory Nicolson schematics.

which were mainly educational tools for students and those outside the field to help them assimilate a lot of information. As time goes on and more information is available, such figures are obviously not as accurate as when they were originally produced, but what is important are the concepts that they render, such as the synthesis of immense amounts of data into some general framework that can help us conceptualize events at a higher level. As we begin to know more about gene expression and its role in cancer progression and metastasis, one is struck with the complexity of the cellular phenotype and the multiple gene products that seem to be involved as well as the multiple ways in which complex malignant phenotypes can evolve. Once we have a better idea of these complex relationships, new concepts of cancer progression and malignancy will ultimately emerge, just as they have in previous decades. However, in the near future we will probably be more and more dependent on computers to sort and organize the information that previously we could manage on our own.

I am sure you remember the long discussions about assays for invasion and metastasis which took place at almost every one of our Meetings. Would you agree that we have learned from most of these assays, from their similarities and also from their differences compared to the natural situation? Today, leading journals hardly publish any one's data unless they include *in vivo* work with transgenic animals. Is that *the* Model? What about *Xenopus* (Vleminckx *et al.*, 1997), *Drosophila* (Pagliarini and Xu, 2003), flying and crawling into the metastasis field?

I have always believed that studying normal events in nature can provide us with important insight and information on the mechanisms of aberrant behavior, such as cancer invasion and metastasis. My belief is that the aberrant behavior that we study as pathology has some normal counterpart, and that it is important to study normal cellular behavior to help us understand pathological behavior. The details of Xenopus may not exactly extrapolate to mammals, but some of the basics are bound to be the same. So I believe that the study of life in all in its forms will yield information that is useful to science as a whole.

Starting with the B16 melanoma cell family (for example Nicolson and Custead, 1982), you have used various cell lines throughout your work. Recent publications by Masters *et al.* (2001) have cautioned about half of the cell lines not being what they are supposed to be. Do you think this comment jeopardizes to a considerable extent the conclusions drawn by many of us from work with cell lines? Should we stop working with these old cell lines all together?

I have always cautioned researchers that tumor cell lines are not static. They change with time, and we have always stressed that their biological properties must be checked before embarking on time-consuming research that might not relate to the properties of the cells that they used. This cautionary comment is also true about the systems used for testing. I recall one incident where a researcher was using one of our selected cell lines in animals but used aged animals instead of young animals and found a different result. He also found a different result in animals with a slight genetic variation from the strain that we originally used. When researchers ask me for cell lines that we used in the 1970s and 1980s and have remained frozen since that time, I tell them that they should only use more recent isolates that are constantly being tested for their biological properties. In fact, due to a massive freezer accident, I no longer even have any of these ancient cell lines, and so I can't provide them to researchers. But in retrospect, it is just as well, because an important aspect of this field is making sure of the properties of your materials. Too often researchers were provided cell lines and mishandled these cells to varying degrees out of ignorance or impatience, and the research that resulted from their studies is of questionable importance.

Invasion as compared to metastasis. Garth Nicolson's work is more on metastasis than on invasion; more on secondary than on primary tumors. Is that so?

I believe that some of the same principals that govern primary invasion are also applicable for secondary invasion, with some differences related to the secondary as apposed to the primary tumor environment. For example, the secretion of degradative enzymes, in general, is a requirement for both invasion at the primary and secondary sites; however, there may be specific activities that are necessary to penetrate

Members of Garth Nicolson's championship vollyball team. *Dr. Nicolson at the back row holding the trophy, is Team Captain (1995, Houston, Texas).*

particular structures, such as the blood brain barrier, that are not necessary for primary invasion. I have reviewed this on occasion (Nicolson, 1993; Nicolson *et al.*, 1994; Nicolson *et al.*, 1996).

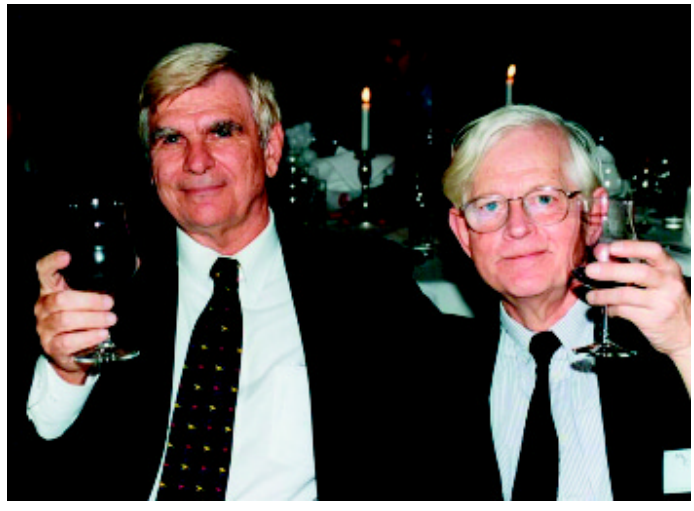
I recall your experiments *in vitro*, demonstrating the organ-specific homing of metastatic cancer cells, interacting with organ-specific molecules on endothelial cells (Nicolson and Dulski, 1986; Nicolson, 1987). Where are we today? Do cancer cells spread to most organs and grow specifically where the soil is favourable? Do they home specifically and grow wherever they arrive?

As with most biological questions, you can find examples of both if you look hard enough. We have examples of tumor cells that are released into the circulation as multi-cell clumps that mechanically arrest in the first capillary bed encountered and thus form secondary tumors at that site, and we have examples of tumor cells that are fully capable of passing through the first capillary bed, re-circulating and specifically arresting and invading at only certain organ sites. We also have examples of tumor cells that start out as organ-specific or at least organ-preferential but with time they change (tumor progression?) to more general colonization properties and are capable of colonizing multiple organ and tissue sites. All of this probably mirrors the clinical situation where examples of all of the above can be found.

You were one of the first to draw our attention to the existence of genes, the activation or inactivation of which participated in metastasis. At the beginning we thought that alterations of such genes were specific, implicated in metastasis but not in transformation and growth of the primary tumor. Now there is a debate about this specificity as well as about the (in)activation of metastasis genes early, as compared to late, during cancer progression. What is your opinion? Recently published reviews mention 12 to 13 metastasis suppressor genes (Steeg, 2003). If one would like to examine the data very stringently, what are the postulates to be applied for a metastasis gene?

I was never convinced that there are specific genes for metastasis. I have always called them metastasis-related or -associated genes because it is extremely unlikely that genes evolved to encode molecules for the metastatic process. Genes that encode molecules that are involved in the metastatic process also have completely normal uses that have nothing to do with metastasis. Metastasis-associated events such as cell adhesion, cell growth, cell invasion, etc. have counterparts in normal development. Thus the metastasis-associated genes are for the most part completely normal genes that are inappropriately regulated during the metastatic process. Exceptions may be genes that are altered by mutation, rearrangement, etc. and now have new activities. But because the metastatic phenotype is often an unstable phenotype, we need to focus on alterations in gene regulation rather than gene structural alterations as the most logical explanation for tumor cells acquiring the metastatic phenotype. I also have never believed that genes that are consistently over- or under-expressed during the metastatic process have nothing to do with metastasis. These expression events that are related to metastatic properties must occur for a reason, and it is thus likely that there is some relationship, but it does not have to be a direct relationship. In fact, it will probably turn out that most of the metastasis-associated genes have only an indirect effect on metastasis. For example, they could be allowing expression of normally suppressed gene families that are important in early developmental processes where some completely normal cells have invasive and colonization properties that are not present at later stages of development.

Which of the genes launched by Garth Nicolson had most impact on others' work? *Mta1* is an interesting example, put forward as a promoter of metastasis on the basis of experiments with the 13762NF rat mammary adenocarcinoma system (Toh *et al.*, 1994; Nicolson *et al.*, 2003c). Interestingly



Profs. Garth Nicolson (left) and Keld Danø (right) *at the International Conference on Staging of Cancer in Munich, Germany, December 6, 2001. Prof. Nicolson was the conference Keynote Speaker.*

the Mta1 protein turned out to be a repressor of estrogen receptor-mediated transcription through recruitment of histone desacetylase (Mazumdar *et al.*, 2001). In the latter paper the authors state that *"However, direct evidence to link enhanced Mta expression with metastasis is currently lacking".* Coming back to postulates, what is the direct evidence that is lacking?

There are a number of examples, but as an example the *mta1* gene was found as a differentially expressed gene in highly metastatic rodent cells. When we (Toh, Nawa and others) began our studies on *mta1* expression in rodent tumors and *MTA1* expression in human cancers we found good correlations with over-expression in epithelial cancers (lung, breast, ovary, colon, rectum and other gastrointestinal and oesophageal cancers) but not others (melanoma, endothelioma, fibrosarcoma). We also found that inhibiting *mta1* expression in metastatic cells by use of antisense inhibited their invasive and growth properties, and more recently that transfection of the *mta1* gene into poorly metastatic cells increased their metastatic potential. I would like to clearly state, however, that it is extremely unlikely that the *mta1* gene in rodents or *MTA1* gene in humans or similar genes are *the* determinant of metastasis. This is an example of only one of many genes that can *affect* the metastatic process by providing (or reducing) molecules that can change gene expression programs important in invasion and metastasis or can alter growth properties.

Your last metastasis paper (Haier *et al.*, 1999) focused on the role of integrins in cancer cell adhesion and uses a flow chamber rather than static cultures. Do you think this is a crucial step in metastasis? Would it be a putative target for therapy? What kind of therapy? Are circulating cancer cells present and if so, do they present a threat to patients at the moment they come for therapy?

With Jorg Haier we sought to develop new procedures that more closely mimic the actual events of tumor cell blood-borne implantation. This is a dynamic event that occurs under flow conditions, and this is why Dr. Haier and others are determined to examine the role of adhesion molecules and eventually invasion molecules under flow conditions similar to those encountered in the microcirculation. Although it is much too soon to consider if we will find anything useful for therapy, most consider these events probably not useful for therapy since by the time most metastases are discovered, they have already undergone implantation and secondary invasion. The only possible therapeutic use of anything that we might find would be in limiting the further spread of cancer cells, such as during surgical removal of a primary tumor that has invaded into the circulation or limiting the further spread of existing metastases. Whether this would be of any therapeutic benefit for cancer patients remains to be determined.

Thank you, Garth. The readers of our Special Issue will most certainly learn from your experience.

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