Basic Research in Nephrology: Are We in Decline?

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There is a specter haunting nephrologic research today, the specter of decline. Perhaps I am simply parroting a recent spate of books arguing that everything is in a state of decline: countries, the United States in particular, Western civilization, quality of life, and manners. Declinism, made popular a hundred years ago by Spengler in his Decline of the West, seems to be back in the news, although a brief search of books published in the past shows this notion has never gone out of fashion.

I have been having these ruminations toward the end of my role as an editor, first of the Journal of Clinical Investigation and then of Kidney International. In these capacities, I was closer to the pulse of the field given that I had to deal with a large number of studies by my colleagues and got to know more of their work than I usually did. Although this Spenglerian mood may reflect intellectual fashions in other fields, we console ourselves that at least in science, we can perform a study to test whether we are actually in decline or not.

However, the first question in this study would be the following: Yes, you may think we are in decline but compared with what or to whom? Is there an absolute metric that shows basic renal research is not what it used to be? Furthermore, no one can write about decline without assigning blame and identifying who is letting the barbarians through the gate. Contemporary political declinists have it easy; it is China, of course, again 200 years after Napoleon’s fear of waking the sleeping giant, or the incredibly clever treatise by Clive James arguing a decline of Western civilization for the disappearance of remarkably great thinkers and essayists.

For us scientists, it is not going to be possible to define an absolute parameter by which all fields of science can be judged. Indeed, as I mention below, the technical level of research in our field is much higher now than say 30 years ago. However, one can ask a more modest, although answerable, question. Are we doing as well as we were? It is pretty clear that at least in science, we can perform a study to test whether we are actually in decline or not.

First, I would like to state that although the numbers of physicians and scientists entering our field may have been decreasing, I do not think this is a prime reason our discipline is tipping toward decline. It is rare that a renal investigator like me gets the privilege of observing the mechanics of publishing the best basic renal research at close hand. Over the past 10 years, I was the lucky recipient of this honor through two well-placed journals. During this period, I observed a remarkable array of papers go through the process of submission, revision, and acceptance. For the first time in my career, I had firsthand knowledge of the state of research of basic science as it relates to the kidney. The results have often been exhilarating; editors get great pleasure from presenting exciting papers to their critical colleagues on an editorial board. It is pretty clear that we as a field have come a long way from the old days. Modern work uses exciting state-of-the-art methods to uncover new mechanisms in physiology and pathophysiology. The vitality of research in podocytes and the identification of the many mutations of podocyte proteins that cause human proteinuric diseases, for example, provide molecular insights into many of the disease processes plaguing patients with kidney dysfunction.

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Similarly, identification of the genes involved in a variety of human or animal models of cystic kidney disease has participated in the growth of knowledge of a cellular organelle, the cilia, with a myriad of functions associated with a variety of puzzling disorders.

Even in the classic domain of renal physiology, long the jewel in the crown of our basic research, the introduction of genetics has reinvigorated this field by providing us with new mechanisms and new explanations for many hypertensive and hypotensive syndromes, confirming the conviction of most nephrologists that the kidney is near the center of causation of hypertension, perhaps the world’s most common disease. These developments are certainly a cause for celebration and pride of achievement for our field.

This gratifying state of affairs resulted from the insights taken from cell biology, molecular genetics, and developmental biology, utilizing them to explain critical phenomena in kidney function. Advances in these fields over the past 20 years have been like a tide that lifted the boats of research in all applied areas such as ours as well as cardiology and gastroenterology.

Although there is no doubt about our benefit from this rising tide, I slowly started to get the impression that our share of publications in the front-line journals of biomedical research compared with other organ-based fields was not commensurate with the advances I described above. Now that I am no longer an editor, I have more time to perform a little research into this issue and I am afraid that compared with our sister disciplines, we are actually in decline, at least in terms of losing bandwidth, a nicer term than market share. A smaller market share is a dangerous thing to have, as most businesses would quickly tell you. The idea that our field is smaller means we have less visibility for recruitment of the next generation of investigators. What is the reason that our visibility has shrunk over the past few decades? Are there more systemic reasons for such a finding? Here I present the findings of my research into these issues and propose a hypothesis that might be a plausible source of these findings.

ARE WE LOSING BANDWIDTH?

Comparisons are useful but they need to be buttressed by some sort of control data and I choose here historical controls of the share that our field obtained from among the recent past. The scientific basis of the disciplines of internal medicine, the specialties of nephrology, gastroenterology, and cardiology, all began at approximately the same time, immediately after World War II. These disciplines were stimulated by the developments and availability of a variety of measuring instruments that allowed a more quantitative approach to observations on individual patients or experimental animals. The best research that these early endeavors generated was published in the *Journal of Clinical Investigation*, a journal that remains prestigious even though it is no longer the only one in its class. I performed an analysis of the papers published in this journal from its inception in 1924 until today. I simply counted all papers and measured the fraction of these papers that had some relevance to renal issues or other areas of science. The results are shown in Figure 1. They show that our share of published papers rose to 14% in the late 1970s and 1980s but has been declining over the past 2 decades in almost a linear manner. If one extrapolates the line, we might find there will be very few, if any, renal publications by 2020! A random look at the first few issues of the *Journal of Clinical Investigation* in 2012 show no more than two papers in 3 months. Note that the fraction of papers of clinical renal interest in the *New England Journal of Medicine* is very low but has been stable, but others have speculated about the reason for this low number.

One trivial explanation is that subspecialty research is pyramidal and as the base in some disciplines expand (ours has not), all things being equal, so does the top when it comes to publishing in high-profile journals. Nephrology is a small field and we have been publishing the same number of excellent papers every year for the past 50 years, but other fields have been growing more and thus are publishing more; hence, the renal fraction is decreasing as the total number of papers in the *Journal of Clinical Investigation* is increasing. However, that is not the case. Table 1 shows that nephrologists published 243 papers in the *Journal of Clinical Investigation* during the peak 5-year period, whereas only 96 papers were published in the latest 5-year period. This leaves us with the obvious conclusion that perhaps the editorial board of this journal is not interested in renal research. Yet every editorial board, which changes at 5-year intervals, has one or more senior nephrologists...
on it (myself included in 2000–2005) and a recent editor in chief, Larry Turka, was a nephrologist.

Hence, it is not likely we were not defending our turf. Could it be that we are not a field that supports each other? I actually believe so from my observations of how reviewers who are nephrologists treat each other compared with other fields, and during my tenure on certain study sections at the National Institutes of Health where grants from many specialties were simultaneously evaluated. However, I do not think this is the explanation for the particular issue I raise here, because the decline began in 1980 and hence there have been more than six different editorial boards that included leading nephrologists, at least some of whom might have felt they needed to support their colleagues. Regardless of the psychology or paranoia that many of us have regarding rejection and acceptance of our manuscripts in this particular journal (and there is plenty of it having had one of my papers rejected recently after 3 revisions), I can assure readers that no renal editor of the Journal of Clinical Investigation can harbor these negative feelings. The editorial board of the journal has a weekly meeting in which the decision to accept or reject papers is done as a group and the only pleasure one gets from being an editor at the Journal of Clinical Investigation is when one is presenting an exciting paper to one’s distinguished colleagues. The closest description of one’s feeling is that of bragging; you brag about the interesting complexity of the argument and the directness of the evidence in an area that is familiar to you but esoteric to your colleagues. Most of the other editorial work is actually pretty unrewarding.

Another possible explanation is that, since the 1980s, nephrologists did not send their best papers to the Journal of Clinical Investigation; rather, they sent them to other prestigious journals such as Cell, Nature, and Science or the new journals, Nature Medicine and Nature Genetics. However, an analysis of Nature Medicine or Nature Genetics shows that over their life history of almost 20 years, they have each published at best four papers a year with renal interest, a number that has not changed with time (Table 2). I will not show the number of recent papers in our field published in Nature, Cell, or Science for fear of inducing terminal depression in the reader.

These findings need to be compared with those in two sister fields, cardiology and gastroenterology, which are more similar to ours in history. As shown in Figure 2, papers in the Journal of Clinical Investigation that deal with the heart have maintained a steady presence, being about 8% of all papers. Note, however, what happened in gastroenterology, including hepatology. They have had an upward trajectory that will certainly equal or exceed the renal rate in our heyday. Similarly, Table 2 shows these two fields certainly best us in Nature Genetics and Nature Medicine. We account for only 1% of the papers in Nature Medicine and 2% in Nature Genetics, whereas gastroenterology had 4.8% and 5.1%, respectively. Furthermore, over the past few years, Nature itself, arguably the leading journal of science, has published many supplements in which a field of investigation is highlighted. Admittedly, some of these are supported by industry; regardless, senior investigators are asked to review various aspects of a field. None of these supplements had anything to do with the kidney. Yet just in the past year there were supplements on cardiovascular biology,6 the intestinal microbiome,7 and hepatitis C.8

Is our field shrinking? I am not so sure; the number of journals in nephrology is pretty significant at 69, including urology. In gastroenterology and hepatology, the number is 72, including surgical journals. The number of attendees at the national meeting of the American Society of Nephrology is pretty substantial, with about 13,000 in 2011. The American Gastroenterological Association and American Heart Association meetings have somewhat higher numbers of attendees, with 16,000 and 18,000, respectively. It is difficult to draw any conclusions from this because one must dissect out from these the number of papers presented that are in basic research, the subject of my commentary. Nevertheless, I suspect we are, perhaps, publishing fractional stories across multiple publications, rather than putting one great story together that justly deserves printing in one or more high-profile journals.

A POSSIBLE MECHANISM OF DECLINE

First, let me mention that the more vigorous areas of renal research require use of several basic disciplines. For example, the

Table 1. Papers published in the Journal of Clinical Investigation arranged by discipline

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Total</th>
<th>Renal</th>
<th>Heart</th>
<th>Gastrointestinal and Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1925–1929</td>
<td>300</td>
<td>6 (2)</td>
<td>21 (7)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>1930–1934</td>
<td>419</td>
<td>19 (4.5)</td>
<td>39 (9.3)</td>
<td>13 (3.1)</td>
</tr>
<tr>
<td>1935–1939</td>
<td>434</td>
<td>21 (4.8)</td>
<td>12 (2.7)</td>
<td>30 (6.9)</td>
</tr>
<tr>
<td>1940–1944</td>
<td>501</td>
<td>30 (6)</td>
<td>6 (1.2)</td>
<td>23 (4.6)</td>
</tr>
<tr>
<td>1945–1949</td>
<td>1664</td>
<td>106 (6.4)</td>
<td>37 (2.2)</td>
<td>68 (4.1)</td>
</tr>
<tr>
<td>1950–1954</td>
<td>833</td>
<td>84 (10.1)</td>
<td>68 (8.1)</td>
<td>98 (12)</td>
</tr>
<tr>
<td>1955–1959</td>
<td>977</td>
<td>82 (8.4)</td>
<td>48 (4.9)</td>
<td>68 (7)</td>
</tr>
<tr>
<td>1960–1964</td>
<td>1083</td>
<td>96 (8.9)</td>
<td>72 (6.6)</td>
<td>117 (10.8)</td>
</tr>
<tr>
<td>1965–1969</td>
<td>1135</td>
<td>147 (13)</td>
<td>86 (7.4)</td>
<td>188 (16.6)</td>
</tr>
<tr>
<td>1970–1974</td>
<td>1772</td>
<td>243 (13.7)</td>
<td>123 (6.9)</td>
<td>301 (17)</td>
</tr>
<tr>
<td>1975–1979</td>
<td>1750</td>
<td>193 (11)</td>
<td>109 (6.2)</td>
<td>276 (16)</td>
</tr>
<tr>
<td>1980–1984</td>
<td>2267</td>
<td>226 (10)</td>
<td>117 (5.2)</td>
<td>325 (14.3)</td>
</tr>
<tr>
<td>1985–1989</td>
<td>2695</td>
<td>226 (8.4)</td>
<td>220 (8.2)</td>
<td>413 (15.3)</td>
</tr>
<tr>
<td>1990–1994</td>
<td>3420</td>
<td>249 (7.3)</td>
<td>241 (7)</td>
<td>412 (12)</td>
</tr>
<tr>
<td>1995–1999</td>
<td>2991</td>
<td>208 (6.9)</td>
<td>329 (11)</td>
<td>457 (15.3)</td>
</tr>
<tr>
<td>2000–2004</td>
<td>2309</td>
<td>114 (4.9)</td>
<td>185 (8)</td>
<td>282 (12.2)</td>
</tr>
<tr>
<td>2005–2009</td>
<td>2178</td>
<td>95 (4.3)</td>
<td>204 (9.3)</td>
<td>286 (12)</td>
</tr>
</tbody>
</table>

Data are n (%).

Table 2. Papers published in Nature Medicine and Nature Genetics arranged by discipline

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Renal</th>
<th>Heart</th>
<th>Gastrointestinal and Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature Medicine</td>
<td>7240</td>
<td>73 (1)</td>
<td>271 (3.7)</td>
<td>350 (4.8)</td>
</tr>
<tr>
<td>Nature Genetics</td>
<td>5966</td>
<td>120 (2)</td>
<td>192 (3.2)</td>
<td>302 (5.1)</td>
</tr>
</tbody>
</table>

Data are n (%).
most obvious examples are human genetics and developmental biology, which turned their attention to kidney research in the last decade. In human genetics, a discipline anchored in clinical medicine, we simply waited for the right person to do kidney-related research. The consequence of the efforts of these pioneers was the appearance of new fields of renal research, podocyte biology, ciliopathies, and cystic diseases, as well as the role of the kidney in BP regulation. In developmental biology, we had the dumb luck of having the kidney as a large organ; hence, when knockout methods became available, the absence of the kidneys in certain mutations could not have been missed. Our luck continued into this in the sense that the investigators then turned their attention to kidney development, a now thriving and exciting area of research.

We need to determine the mechanism by which our sister fields succeeded. In the same way that these new fields participated in and invigorated kidney research, we need to find additional areas that we might want to jump into, this time not depending on luck. But first we need to modify our behavior regarding other fields of basic science whose relevance to renal research has been ignored by nephrologists.

To propose a mechanism for this decline, I use a metaphor that might be helpful in visualizing what has been happening to us. At one time, organogenesis or tissue specification was thought to begin when a group of cells became similar or identical to each other and began to associate with each other. This sorting hypothesis was fairly dominant in the field and led to the discovery of cell adhesion molecules as the mechanism for sorting. In this way, cells recognize others as being part of their tribe and importantly exclude (sort out) others that do not belong to this phenotype. Although this is an important idea, it is not sufficient to explain the development of organs. Today we think of organogenesis as requiring a diversity of cell types, each of which contributes a significant input to the formation of other parts of the organ. For instance, in the kidney, we need at least three cell types: ureteric bud, metanephric mesenchyme, and stromal cells. Each pair of these compartments participates in reciprocal induction to form the adult kidney. And I am not including the endothelial, vascular smooth muscle, or nerve cells necessary to make the whole kidney. Although the above might strike some of you as an irrelevant or inappropriate metaphor, let me present some examples of where our “sorting out” model has prevented us from expansion while it’s absence has helped other fields gain the upper hand in strength and vigor.

When was the last time you saw a nephrologist (and I mean that in the broadest sense of the word) study cancer, whether of the kidney, bladder, or prostate? Is there a paper on clear cell carcinoma or prostate cancer published in our journals? Prostate cancer is arguably the most common cancer in the United States (240,000 new cases a year). Oncology has undergone a revolution in the profundity of its insights, many of which become translated into exciting discoveries in cell signaling as well as growth regulation and determination of the size of cells and number of cells. All of these are critical components with great relevance to kidney development and I am sure to a variety of renal diseases, not to mention the importance of clear cell carcinoma itself, a fairly common malignancy (60,000 new cases a year) for which we could have easily developed earlier diagnostic methods and better treatments. I am sure that it will come as a surprise to many readers that gastroenterologists are very interested in their malignancies. The chief of gastroenterology in my department is a successful scientist who is an oncologist but can give lectures on gastroesophageal reflux disease like the expert he is. Many of the most highly quoted papers in gastroenterology are due to major discoveries in gastrointestinal malignancy.

Another field that I suspect we actively sorted out is hypertension. There is barely a session on the basic science of hypertension at our national meetings and we have essentially left the field even though I am sure most of us believe that hypertension is fundamentally a renal disease. Yet the cardiologists have many sessions in their annual meetings on hypertension. I also believe that leaving the field has been detrimental not only to us but also to research in hypertension. Bragging aside, our kind of research always emphasizes pathophysiology and causation, whereas a brief scan of the papers and lectures in the annual hypertension meetings shows that hypertension...
has been downgraded to a risk factor, hence merely a statistical entity devoid of biologic meaning. The consequence of this is the domination of the pharmaceutical industry that, in its current troubled state, is only interested in me-too drugs and hence the paucity of emerging new pathways. We should bear some responsibility for this.

A third subject sorted out of our field is kidney stone disease. Here is a condition clearly due to the kidney and affects the kidney, yet I do not know of many divisions of nephrology that have active research programs in this very common condition said to occur in 1% of the population. By that I mean research into the chemistry, pathophysiology, or genetics of stone disease, not merely the mining of existing data and drawing correlations.

A fourth subject is infection of the urinary tract. A major field with immense clinical relevance has been left out of our research portfolio. Again, we neither have sessions on this fertile field nor do we encourage research in it. Consider the role of the microbiome in the gastrointestinal tract. It is hard to think of a more exciting recent discovery in medical biology than the role of the microbiome in health and disease. Yet just in random conversations with other nephrologists, everyone seems to think that the urine is sterile without considering the fact that sterility is based on culture methods that are designed for growth of pathogenic organisms. We need studies on commensal bacteria in the urinary tract and their role in immunity.

In essence, I feel our field has emphasized the core disciplines of kidney research such as renal physiology, renal immunology, renal progression, and, more recently, development and human genetics. What we have missed is expansion into other fields of biomedical research that would expand our horizons, introducing completely new areas of research that are directly applicable to our favorite organ.

This inward-directed approach to basic research in nephrology compared with other clinical disciplines is somewhat dispiriting. One gets the impression that we have become like one of these religious sects in which there is emphasis on purity of doctrine and where the growth of the sect depends only on conversion. Well, we know that conversion to our faith has been difficult. Diversity is necessary in everything, even if one looks at the growth of a religion. Diversity is the source of power, especially in biomedical research.

**WHAT IS TO BE DONE?**

The research enterprise of our field is very long and winding and hence no drastic changes can be made rapidly. At any rate, I feel we have to be prepared to make changes that have long-term consequences. Because individuals perform all research, we need to train a new cadre of young scientists in areas that will expand our discipline. Cancer, infections, stones, and the microbiome need to be brought into our areas, and many others that the readers may want to add. This requires some selfless sacrifice by the leadership of the field.

There is a lesson to be learned from arguably the most exciting area in renal research today, human genetics, which led into a flourishing of research into podocyte biology. We need to direct young scientists entering the field into a field that is much bigger than nephrology, such as oncology, which would then yield immense benefits to the core areas of renal research. The goal is to make a renal scientist a binational citizen who is engaged in a major wide-ranging basic discipline as well as the research into the kidney. If we remain focused on only our own parochial interests, we will atrophy.

How to do this requires that all of us be part of this decision. It is hopeless to think that the National Institutes of Health or the American Society of Nephrology can do this. The pressure that they are under from a variety of special interest groups makes any forward-thinking efforts pretty unlikely. Large amounts of resources are also wasted on centers of research that simply preach to the choir, or construction of common resources, such as atlases, that few, if any, scientists use, and many other quixotic programs that copy what is being done elsewhere without a feeling for what is actually missing in the field.

As always, it will require the leadership of individuals who can put the future of a field ahead of their own; that unfortunately is the most difficult of all positions to be in. But one or very few individuals produced many of the great successes I discussed above; hence, the situation is not hopeless. We just need a few more great young thinkers to jog us away from derivative paths toward a road not taken.

**CONCISE METHODS**

I searched the above-mentioned journals for articles that have the word "renal" in the manuscript rather than "kidney" because it turned out that when I used "kidney," too many papers were identified that on closer examination turned out to use HEK 293 cells (where the "K" is kidney). I confirmed the fact that the search was adequate by examining all papers in the *Journal of Clinical Investigation* in 1976 and found that although the concordance was not perfect, the search underestimated the number of papers by about 13%. I found 63 papers of renal interest, whereas the search strategy identified 55. Amusingly, the reason for the underestimate is that the work reported in many papers that year was performed in toad and turtle bladders and none of the authors (myself included) mentioned the word renal in the text. A repeat study for 2006 showed that the strategy identified 15 papers, whereas a search of all papers during that year identified 15. Similar results were obtained for searches in cardiovascular and gastroenterologic papers with slight underestimation of the actual abundance of the papers in both categories.

**DISCLOSURES**

None.

**REFERENCES**