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# Acceptance of the 2004 John Howland Award: Here's to Inefficiency!

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Polonius:
Therefore, since brevity is the soul of wit,
And tediousness the limbs and outward flourishes,
I will be brief; your noble son is mad:
Mad call I it; for, to define true madness,
What is't but to be nothing else but mad?
But let that go.

Queen:
More matter, with less art.
Hamlet, Act II, Scene II

I am deeply honored to be the recipient of this year's Howland Award. I am sure I share the feelings of previous Howland awardees. Since hearing of this honor, I've thought about the tradition of the recipients' providing a summary of their talk given at the Pediatric Academic Society meeting.

This is an opportunity to thank, publicly, my mentors and my family and friends for their help in making my career possible. It is a wonderful opportunity because I'm aware of all the people who have helped me along the way. It's also an opportunity to comment on some of my studies, which serve to illustrate my dependence on colleagues, at all levels, for their completion. In setting out to thank those who have helped, I came to realize quickly that many of them did not fall into the conventional definition of a "mentor."

The first person I want to recognize is my wife, Dr. Jane Donohue Battaglia (Fig. 1*A*). We were classmates together at Yale and have been married for 47 y. Throughout that time, she has been a wonderful companion but has also given me a fine example of scholarship in her own studies. After working in pediatric anesthesiology, she went off to get her master's degree in theology at the age of 56 and has been involved in the teaching of bioethics and humanities.

Mentors, in the traditional sense, began with my introduction to Prof. Donald Barron. The definition that I have used comes from Fowler and Levinson, who stress the evolutionary process in which both the mentor and the student are learning and changing from their interaction.

It was Dr. Daniel Darrow who introduced me to Dr. Barron, a native Midwesterner. Dr. Barron had left Sir Joseph Barcroft's lab at the time World War II started. He brought with him some of the wonderful influence of the British university and prized the importance of unstructured, leisurely discussions. These were held every day with all the fellows and students in his lab. He used this opportunity to emphasize the importance of carefully choosing the question you address, insisting that we should focus on having the *last* word in a field, not necessarily the first (Fig. 1*B*).

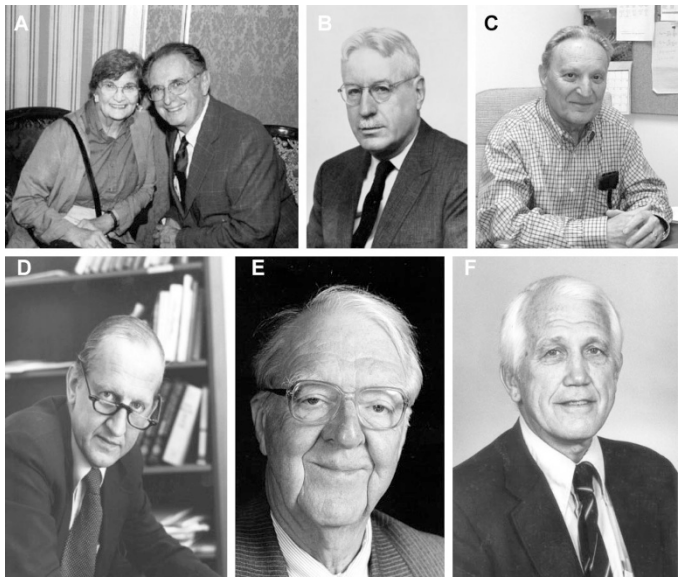


**Figure 1.** (*A*) Drs. Jane and Fred Battaglia. (*B*) Prof. Donald Barron. (*C*) Dr. Giacomo Meschia. (*D*) Dr. Andre Hellegers. (*E*) Sir Philip Randle. (*F*) Dr. Robert Cooke.

It was an exciting laboratory, and it was at this time, as a medical student, that I met two colleagues who were to play important roles in the development of my thinking. The first of these was Dr. Giacomo Meschia, M.D., Ph.D., a physiologist from Milan who had arrived in Dr. Barron's laboratory as a postdoctoral fellow from Dr. Margaria's laboratory (Fig. 1*C*).

The collaborative research begun at that time with Giacomo has continued for almost 50 y. It is actually a family affair since his marriage to my sister, Irene, and this has made it all the more special to me. At that time, Giacomo and Ivo Setnikar were the first to define and document the importance of reflection coefficients for determining osmotic gradients against an apparent chemical potential gradient. Their work in this area stemmed from a simple question Jane asked them when she was a medical student, which, again, emphasizes the impor-

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tance of informal exchange within a laboratory, unhampered by hierarchical considerations. A second colleague was Andre Hellegers, a Dutch obstetrician who came to Dr. Barron's laboratory from Nicholas Eastman's Department of OBGYN at Hopkins (Fig. 1*D*).

Andre and I continued to work together when we were both at Hopkins, he as faculty and I as a resident in pediatrics. Andre later established the Kennedy Center for Bioethics at Georgetown, where he remained as director until his untimely death in 1979. He was an incredible public speaker. Millie Stahlman put it most succinctly when, on the occasion of speaking right after Andre, she said, "My daddy always told me, 'Never follow the banjo player'" (Fig. 1*E*).

When I left Hopkins for a postdoctoral fellowship in England, Philip Randle, later to be Sir Philip, was my mentor in biochemistry. Sir Philip was Professor at Cambridge at the time, although later he retired as Professor at Oxford. It was an exciting time to be in Cambridge. Philip was working on the glucose and amino acid transport effects of insulin. During that year, Fred Sanger received the first of his two Nobel prizes for the sequencing of insulin. Again, the importance of unstructured leisure time was evident at Cambridge in the morning coffee meetings and afternoon teas, where all of the faculty, technicians, and fellows came together to chat. It was an environment low on resources but high on creative energy. I was impressed that Philip Randle still found time to round on special cases at Addenbrooke's Hospital and always invited me to join him.

At Yale, Jane and I were attracted to pediatrics through our contact with Dr. Morris Green, who was our attending, and Dr. Robert Cooke, who was our preceptor. I felt that if these men were examples of the people working in this field, then pediatrics must be a wonderful discipline in which to be. Dr. Cooke accepted both Jane and me as interns in pediatrics at Hopkins, where he was setting up what I believe was the first truly modern Department of Pediatrics (Fig. 1*F*).

It was an incredible blend of the "old tigers"—Lawson Wilkins, Helen Taussig, Harry Gordon, Harold Harrison, and Barton Childs—with the "new recruits"—Don Medearis, Bill Nyhan, Jerry Odell, Saul Brusilow, and many others. Cooke was an incredible mentor. It was only years later that I began to fully appreciate how busy he was, not only at Hopkins but nationally in pushing for an NICHD, for Kennedy Retardation Centers, and for the HeadStart program, to name just a few, yet he always gave me the feeling that he was excited by the research I was doing. He gave all of us the feeling that the science and the art and the ethics of medicine could and should be integrated. He provided a lab for me even during my residency years and later arranged with NINDB for me to work in primate research at the NINDB center in Puerto Rico. Both Andre Hellegers and Dick Behrman were colleagues throughout these studies, and Dick continued as a colleague, first in high-altitude studies in Colorado and later when he directed the primate studies in Oregon.

I left Hopkins and came to Colorado right after Andre and I had published an article on birth weight–gestational age distribution of infants. When I met Dr. Lula Lubchenco, who had also published a similar study at around the same time, we began to discuss how we could convince neonatologists and obstetricians to recognize the importance of gestational age information in the daily care of newborns. This led us to propose a simple classification of newborns that was widely adopted (Fig. 2*A*).

We used the descriptive term "small for gestational age" because it would encompass both infants with fetal growth restriction (FGR) and infants growing normally but small relative to a population standard. When ultrasound came into widespread use, intrauterine growth restriction was defined by biometric measurements made *in utero* many weeks before delivery and supplanted the need for such a classification, but at the time, it was useful and focused neonatologists on the importance of gestational age, not just birth weight alone. I do not believe these ideas would have fallen into place without the continual input from all of the people in the Colorado laboratory (Fig. 2*B*).

These fellows are shown in Figure 1. I owe each of them a great deal. In Colorado, Giacomo and I were centering our early studies on defining the composition of what we called "fetal milk," that is, the supply of nutrients from the placenta that the fetus used for growth and development (Table 1).

We initially simply tried to define the metabolic rate and the dietary supply of nutrients for the fetus, but a rather startling finding early in these studies was that fetal metabolic rate did not alter much with body size, both across gestational age for the same species and across species themselves. This simple observation went a long way in explaining fetal heart rate differences. It explained, for example, why the human fetus changes its heart rate as it grows far less than one would expect from allometric relationships well established in postnatal life. Also, it explained why despite enormous differences in size, fetal heart rate, as metabolic rate, remains fairly similar among species (Fig. 2*C*).

As a direct consequence of this, we could show that the fetal heart rate is actually less than the maternal in small mammals, where the pregnant uterus represents essentially a "cold spot" relative to the mother. Notice the prompt and striking increase in the heart rate of newborn small mammals upon birth.

My colleagues in this research would not qualify as "mentors" in the traditional sense because they were either my own age or much younger, but the interaction with colleagues who were senior technical staff and with postdoctoral fellows really provided the continuing learning environment we all need. The fellows shaped the research in many ways.

Jim Lemons, for example, recruited Cecilia Teng, the senior chemist who had developed all of the analytical techniques we used. She is still doing so and currently is developing techniques for studies of the nutritional import of trace sugars and polyols in early development. The first group of fellows were instrumental; not only did they contribute to the basic research program, but they also helped develop the idea of perinatal medical services, an idea that was reaching fruition in many medical centers and eventually led to the formation of the Perinatal Research Society.

I cannot emphasize too strongly how the informal discussions among faculty and fellows (Fig. 2*D*) led to the crystallization of most of the research ideas that came out of our

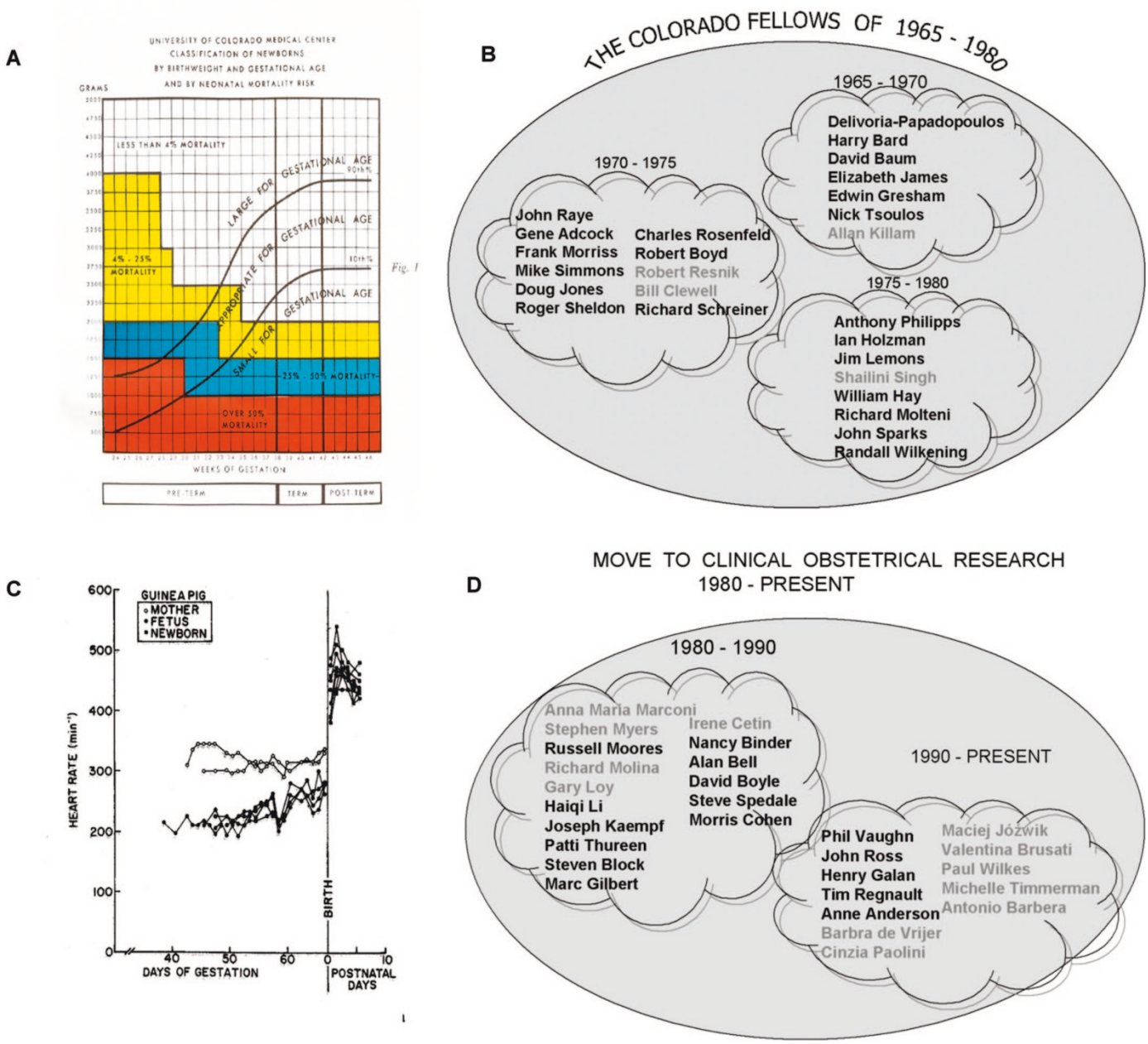


**Figure 2.** (*A*) Birth weight–gestational age distribution of infants (reprinted with permission from Battaglia et al., J Pediatr 71:159–163 © 1967 Mosby). (*B*) University of Colorado, Early Fellows 1965–1980. (*C*) Heart rate in guinea pig (reprinted with permission from Meier et al., Proc Soc Exp Biol Med 172:107–110 © 1983 by the Society for Experimental Biology and Medicine). (*D*) University of Colorado, Later Fellows 1980–present.

**Table 1.** *Oxygen consumption rates (ml/min·kg/body wt) of adults and fetuses in species of different size*

| Animal | Adult | Fetus |
|---|---|---|
| Horse | 2.0 | 7.0 |
| Cattle | 2.2 | 7.4 |
| Sheep | 4.0 | 6–9.4 |
| Rhesus monkey | 7.0 | 7.0 |
| Guinea Pig | 9.7 | 8.5 |

laboratory. It is primarily from their input that we moved on to examine the metabolic interactions between the placenta and fetal liver.

More recent fellows have extended studies of what has turned out to be a carefully integrated organ system. The most striking example of this is given by the interorgan exchange of glutamine and glutamate between the fetal liver. The studies also clarified one of the important roles served by the fetal hepatic release of glutamate, as it provided a means to shuttle carbon derived from amino acids to the placenta for oxidation. This is one of the functions served by hepatic glucose release in postnatal life (Fig. 3).

Our postdoctoral fellows that followed have explored the fetal hepatic-placental exchange of nutrients, and this, in turn, led to the development of stable isotopic techniques that we realized could be applied clinically. Recently, my research has focused on clinical studies in high-risk obstetrics.

Please note that more and more postdoctoral fellows were from obstetrics. Their influence in moving the laboratory to

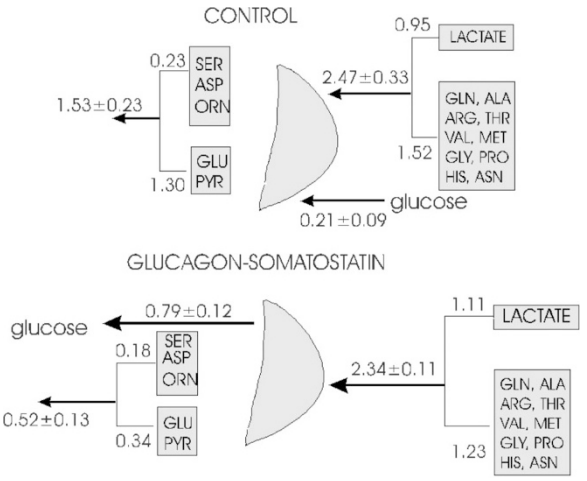


**Figure 3.** Glucagon effects.

clinical studies of high-risk pregnancies attests to the huge influence they have had on the directions of my own research. In many respects, clinical research is far more difficult than basic research, but it was becoming possible in human pregnancies to make fairly precise measurements of actual blood flow, not just as velocimetry (Fig. 4*A*). Combining such perfusion measurements with stable isotopic studies of nutrient transport opened up a whole new area of clinical obstetrical research. For example, we could measure the changes in umbilical blood flow in pregnancies complicated by FGR. We were impressed that even when flow was expressed per kilogram of fetal weight, these small fetuses had very significant reductions in umbilical blood flow, but Doppler technology was moving beyond this to measurements of blood flow in vessels as small as the ductus venosus (Fig. 4*B*). This was an example of human perinatal physiology moving into new areas.

**Table 2.** *Fetal Hepatic Blood Flow (umbilical flow—ductus venosus flow)*

| | NORMAL ($ml \cdot min^{-1}$) | FGR | P |
|---|---|---|---|
| LEFT | 62.3 ± 51.7 | 23 ± 31.4 | 0.01 |
| RIGHT | 51.5 ± 44.6 | 1.8 ± 37.7 | 0.001 |
| TOTAL | 13 | 25 | |

Here, you can see clearly that, in FGR pregnancies, the ductal shunt was significantly increased compared with normal pregnancies of the same gestational age. If umbilical flow is reduced and the shunt of umbilical blood away from the liver is increased, then it is no surprise that there is a striking reduction in blood flow to the fetal liver in some human pregnancies complicated by FGR (Table 2).

In all of this interactions with research staff and fellows, the key element of unstructured time for colleagues at all levels to discuss their research questions freely remains important and worthy of preservation.

So how do we do it in today's environment? Any faculty habits that block this informal exchange are probably counterproductive, and heading that list may be too much time spent in airports. We also need the confidence to avoid tightly controlled agendas.

Some time should be left without a fixed agenda, whether it is in department or division meetings or in departmental retreats. I think faculty would have much more to say, and some might even start attending again.

Obviously, there have been many changes in the practice of medicine that have placed more time constraints on young faculty than we fossilized faculty ever had to endure, but the new tools for communications and computing, while wonderful in themselves, are no substitute for communal thinking. So let's all toast whatever "waste and inefficiency" we can preserve in academics.

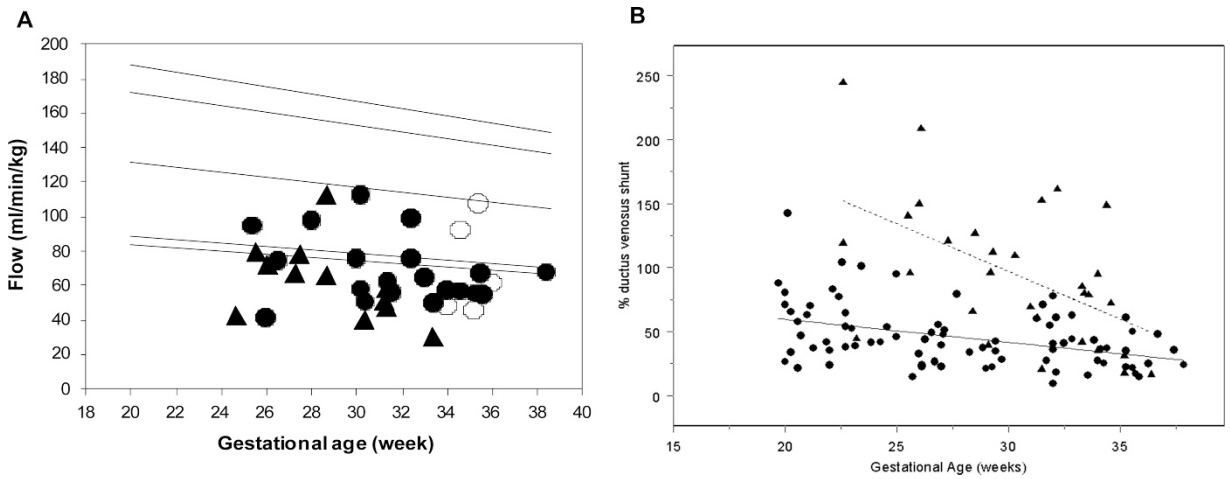


**Figure 4.** (*A*) Umbilical blood flow in pregnancies complicated by FGR. ○, group 1; ●, group 2; ▲, group 3 (reprinted with permission from Ferrazzi et al., Ultrasound Obstet Gynecol 16:432–438 © 2000 International Society of Ultrasound in Obstetrics and Gynecology). (*B*) Ductus shunt. ●, normal pregnancies; ▲, intrauterine growth-restricted pregnancies (reprinted with permission from Teng et al., Am J Physiol Endocrinol Metab 282:E542–E550 © 2002 by the American Physiologic Society).