NCI Behavioral Research is Outside the Box

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- Arthritis patients using Palm Pilots to self-report their pain…
- A laboratory studying how people navigate the Internet…
- A web site to help others design "usable, useful and accessible" web sites…
- Methods developed to evaluate large federal research initiatives…
- An agenda to accelerate the testing, development and evaluation of health behavior theories…

This hardly reads like a laundry list of activities one would expect the National Cancer Institute to be interested in, but that's precisely what it is. All of these, and many other resource-building projects like them, are being funded by NCI through its three-year-old Behavioral Research Program (BRP), one of the most unusual programs in the U.S. government's science enterprise. Certainly the NIH hasn't seen its like before.

Robert Croyle, NCI's Associate Director for Behavioral Research, says that when he was recruited from the University of Utah in 1998, "my mission was to create a new and expanded behavioral research program that would greatly increase the quality and breadth of cancer-related behavioral science."

What BRP is looking for from the scientific community, Croyle says, are studies that apply conceptual and methodological innovations from psychological science to cancer-related issues and problems.

So what is he doing funding such projects as improved self-reporting for arthritis patients (see "Palm Pilots" below) and helping would-be webmeisters build better web sites? "We're trying to take on the very broad issues that have been neglected because they don't fit into any specific organizational box," Croyle explains.

Rimer

The BRP was launched in 1997 by APS Member Barbara Rimer, a health education specialist who had been recruited a year earlier by recently departed NCI Director Richard Klausner to direct a new Division of Cancer Control and Population Sciences (DCCPS), part of Klausner's major overhaul and expansion of NCI. (See Rimer interview, Page 15.)

Rimer brought Croyle to NCI the following year. By training an experimental social psychologist, Croyle had focused much of his research on how people respond to and interpret bad news – their reactions to negative medical test results. More recently he had zeroed in on the psychological aspects of genetic testing for cancer susceptibility.

"When I came to NCI three years ago," Croyle recalls, "there wasn't a lot of proactive, energetic activity going on. The position was new and unique, in that NCI, despite being the largest of the NIH

institutes, had traditionally supported only a few areas of psychological research.

“There was clearly a need to provide stronger support for basic psychological science and relevant fields that had been poorly supported by the NIH, like anthropology, communications, research methods, and new media technology. Oftentimes, there wasn’t a lot happening in behavioral science because there wasn’t the right leadership. Barbara Rimer changed that. She is incredibly proactive. She is constantly looking towards what’s the next new thing we should be doing.”

Under Croyle, BRP has expanded to five branches (see box, Page 14) and focuses on research that is transdisciplinary and collaborative.

“We strongly believe that collaboration is important not only for investigators, but for funders as well. We’ve devoted a lot of time and energy to creating major collaborative initiatives with other NIH institutes and private foundations. Most important, I’ve been given the resources to accomplish this. I’ve been given many new positions, and this has allowed me to recruit the very best scientists in all of the areas we work in.”

The expansion was rapid. In FY1998, BRP’s portfolio included 184 grants worth some $62.7 million; just two years later, it was responsible for 263 grants worth $110 million. In 1998 it had 28 employees; it now has 50 plus another 5 behavioral science personnel in other NCI offices.

(It should be noted that even these numbers don’t tell the full story of behavioral science at NCI. As Croyle points out, there are “lots of other sources of support for behavioral scientists throughout NCI, such as training and career awards, the Office of Cancer Survivorship, our clinical trials program, and work supported by the 60 NCI-funded cancer centers.”)

SUPPORT FOR BASIC RESEARCH

Croyle readily – even eagerly – acknowledges that “a lot of what we support we don’t see as limited to the cancer domain. We felt NCI should play a much more central role in supporting studies of basic psychological processes and developing resources that allow researchers to increase their efficiency and reduce redundancy. In my view, our most important role is identifying the barriers to rapid scientific progress and supporting strategies to overcome them. Barriers come in many forms, although the financial ones get the most attention. Sometimes a field simply needs leadership or a new research tool. I’ve found that just getting the right people in the right place is 90 percent of the battle.”

Croyle says he spends considerable time figuring out how to help scientists get unstuck. “Oftentimes researchers say, ‘Wouldn’t it be great if we had…?’ Fortunately, at NCI we are in a position many times where we can do something fairly quickly to fill those gaps. NCI’s size and internal resources are fairly substantial, so that allows us to do things a little more quickly. Also, the behavioral research program here is fairly large, so we have the staff to do more projects.”

For 2001, NCI identified three priorities in cancer research, two of them in BRP’s domain: tobacco and tobacco-related cancers, and health communications. The latter is receiving major emphasis, Croyle says, because even though much applied research relies on how risks and corrective measures are

communicated to the public, “historically there was very little support at NIH for investigating the basic processes underlying communications – information processing, decision-making, how people interact with new media technology.”

So BRP started a major initiative to launch up to six centers of excellence in cancer communications research in 2002; it created a “web-usability laboratory” to study how people use and navigate the Internet, how they read and process information on a web page, and difficulties they encounter looking for certain information; it launched a web site to help others build more effective health-communicating web sites. And now, it’s creating a website that will assemble various resources and tools on how to measure tobacco use.

At a meeting a few years ago, it was pointed out that no one had ever assembled an annotated bibliography of existing research on communicating health risks to the public. BRP stepped into that gap as well. Such a bibliography is now posted on its web site.

Other basic research tools BRP is developing include measures to evaluate large federal research initiatives, and, under the umbrella of its “Theories Project,” an agenda on what NCI can do to accelerate the testing, development and evaluation of health behavior theories.

CUTTING EDGES AND BOUNDARIES

“Certain kinds of scientific work, such as interdisciplinary collaboration and research synthesis, have not been adequately rewarded,” said Croyle. “We often target our support to those areas that show a lot of promise but may not fare well in the NIH review committee process because they are new, or they don’t fit into the traditional boxes.”

A case in point is BRP’s recent recruitment of several psychometricians to its staff to focus on measurement development and validation. The team includes a cognitive psychologist, a quantitative psychologist and a health economist. Its work cuts across boundaries to address fundamental issues of self-report measurements.

Lutgendorf

Not that BRP isn’t also looking at the bio-behavioral aspects of cancer. But even there, the program seeks the cutting edge. Susan Lutgendorf, of the University of Iowa, a clinical health psychologist who studies psychoneuroimmunology, works at that edge. She is investigating whether biobehavioral-immune mechanisms are involved in ovarian cancer. Her previous findings suggest that the way patients cope with stress may be associated with a cytokine, interleukin 6 (IL-6), that is involved in tumor progression. That got BRP’s attention.

“I like to think good work eventually finds a home,” says Michael Stefanek, chief of BRP’s Basic Biobehavioral Research Branch. “However, I also like to think that our assertive stance regarding our interest in psychoneuroimmunology (PNI) has helped investigators know there is a place that values

their area of science, and perhaps has added a bit to their sense of optimism and enthusiasm. In the past, PNI has had some difficulties finding a stable home, since PNI cuts across diseases, and the NIH Institutes are based upon specific diseases."

Lutgendorf says she has always been fascinated by mind-body interactions. Her interest in PNI and cancer date from the mid-1980s "when I started reading everything I could get hold of related to PNI, and took course-work in biochemistry and immunology so I could understand what I was reading." She did her graduate work at the University of Miami under a behavioral immunology training grant from the National Institute of Mental Health.

She credits Croyle and Stefanek with encouraging her to apply for a grant and, last summer, she and her team were awarded $125,000 a year to cover direct costs for two years. "It was a grant through their exploratory developmental mechanism," Lutgendorf says. "This is a terrific mechanism that lets you explore new ideas that are high-risk but also have a possibility of high payoff. This let our research team do something that had never been done before in humans."

Under the grant she and her collaborators are investigating relationships between stress, depression and social support and cellular immune function in women with ovarian cancer. A recent supplement is funding a small additional study that focuses specifically on IL-6, a cytokine that appears to support growth and metastatic spread of some cancers, including ovarian.

"We want to find out whether behavioral factors might contribute to immune vulnerabilities that are seen before a patient even begins treatment," she says. "We ask patients about life stress, depressive symptoms and levels of social support, all behavioral factors shown to have relationships with stress hormones and compromises to the immune response."

On the day of surgery, her team examines blood samples for activity by natural killer cells (cells that patrol for cancer metastases and can kill tumor cells) and the ability of T cells to produce cytokines that enhance their anti-tumor activity. What is unique in their work is that they are seeking immune response activity not only in peripheral blood, but also in the tumor itself and in the fluid around the tumor. "We want to see if the relationship between psychological and immune outcome factors are present in the area of the tumor, where these immune cells need to be doing their most important work. As far as I know, investigating PNI relationships at the site of the tumor has not previously been done."

Lutgendorf cautions that not all cancers are strongly controlled by the immune system. "We can't necessarily generalize from one cancer to another. However, in ovarian cancer, immune factors do appear to play an important part in the control of the disease. If we find biobehavioral immune relationships in ovarian cancer, behavioral interventions may prove to be helpful in this disease."

She says it is of major importance that BRP has so much interest in discovering how PNI relationships work. "There is a strong interest in the public at large about mind-body relationships," Lutgendorf says, "and a great deal of misunderstanding as well. It is only through the support of funding sources such as

NCI that we will ultimately come to understand how behavioral and hormonal influences may contribute to the growth and control of cancer, and the limitations of these influences."

THERE'S NEVER ENOUGH

With such an ambitious and far-reaching agenda, is BRP getting enough funding? There is never enough, Croyle says, but "support for behavioral and social science research at the NIH as a whole has been growing slowly but steadily. To a remarkable degree, the amount of activity during any given period depends on the particular institute's director. At some institutes, a small staff of behavioral scientists has struggled for years without support to get behavioral science on the map. At others, there is a critical mass of innovative thinkers with leadership support who are able to do a tremendous amount of good work for the field.

"My sense is that the downturn in the economy will put the brakes on growth for a while unless our advocates push even harder [for more]," says Rimer. "However, we continue to see strong Congressional support for behavioral research, and we are grateful for that."

Pledging to continue to push for behavioral science within the Institute, Croyle adds: "Simply nagging doesn't work. You've got to make a credible, clear, science-based case for behavioral science, and you need the right staff to do it. The ability to appreciate, understand and communicate with basic biomedical scientists is key. That's why recruiting energetic and creative scientists has been the key to our own success."

And that, he says, is because the most important gap BRP is trying to close is the human one between psychological science and the kind of public health research that NCI has traditionally funded. "I'm explicitly trying to bring the best of basic psychological science to the cancer domain, and at the same time I'm trying my damnedest to get cancer researchers to pay explicit attention to and incorporate the evidence and methods being generated by psychological science."

Palm Pilots and Patients

When patients or research subjects report how much pain they were in last week or how well they coped with stress, how reliable is their memory? It turns out it can be quite faulty.

A 1998 NIH study showed that even after two days, people cannot accurately remember how well they had coped with a stressful situation. Yet typical coping assessments involve considerably longer periods, and psychological science typically relates biological and genetic data to just such self-reports; if the self-report data are wrong, the research findings are undermined.

The need to measure the validity of self-reports by cancer patients and research subjects led the National Cancer Institute's Behavioral Research Program (BRP) to pay attention to arthritis patients. That's because of Arthur Stone, of State University of New York at Stony Brook, one of five editors of a recently published book of papers presented at a 1996 NIH conference, *The Science of Self Report: Implications for Research and Practice*.

“When recalling past experiences, people tend to remember peaks of intensity, or the most recent things, or are influenced by how they feel at the moment they’re making the ratings,” Stone says. In 1994, he and APS Fellow Saul Shiffman, at the University of Pittsburgh, had proposed that traditional self-report mechanisms be changed in two ways: they needed to ask people what they were feeling at that moment, and reports needed to take into account the respondents’ “ecology” by obtaining assessments in the participants’ environments as they went about everyday activities. Stone and Shiffman called it Ecological Momentary Assessment (EMA).

After a 1996 conference pointed out the glaring need for better measurement of the validity of self-reports, NIH advertised for applications to conduct such research. Stone proposed to collect EMA measures of pain and compare them to results from traditional questionnaires. NIH sent his proposal to NCI, which was interested. He received a five-year grant of $2.4 million in February 2000.

Traditionally, self-reporting is done using written questionnaires or booklets that subjects are asked to complete. There is no assurance that the responses are being written at the appointed time and not being put off until later in the day, relying on recall of how they felt earlier. Stone’s solution is to have subjects use Palm Pilots to record their answers. At six random times a day the arthritis patients and other pain sufferers are prompted by a pager to answer questions directly on a Palm Pilot screen, and the hand-held computers automatically record the time of the entry, eliminating recall bias.

Stone’s research is actually three distinct studies. The first, now completed, compared compliance of paper diaries with electronic diaries. Although he cannot yet reveal results, Stone says, “we think they are exciting.” A second study is paging subjects on different schedules to determine whether the burden of entering the data is itself influencing the results. The third, to start next year, will follow a hundred or so arthritis patients and match their Palm Pilot results and standard recall results to actual observations to see which match observed reality more closely. Multiple outcomes will be used to determine the meaning of the two types of assessments, traditional recall questionnaires versus aggregates of EMA reports.

“A lot of what has already been done (using traditional self-report methods) may be misleading,” Stone says. “Investigators may not be measuring what they believe they are measuring. Instead, they may be measuring the subjects’ personalities, or how they’d like to be coping, not how they are actually coping. If you’re developing a treatment package based on a construct that says it’s coping when it’s really not, you will be going after the wrong thing.”

Stone’s research has enormous implications. It could change how patients’ experiences are measured and assessed in a fundamental way, both for research and in clinical settings.

“It also suggests,” he says, “that we may have to go back and rethink what prior research has meant, how we interpret it. And we have to ask whether we can develop economically feasible measures to get at the actual constructs. I’m not advocating that people do EMA for everything. It’s far too expensive and difficult. But maybe there are other ways to get at this stuff. We need to know more about it, how big the problem is.”

Without NCI and BRP, it’s conceivable the research would not have been funded. NIH has no “Behavioral Medicine Institute” and no institute exists to study methodology. “These things tend to fall

through the cracks," Stone says. "So I have to hand it to NCI for recognizing its importance. I give them a lot of credit for grabbing it. They're not being parochial."