weeks for example) of beam time and then had to get back in line. When Bell Laboratories researchers early on were granted priority access, because of their work in developing and building new instruments, there was what could charitably be called grumbling. Now, with Brookhaven's light source draining off the excess demand, says Arthur Bienenstock, the director of the Stanford laboratory, PRT's are being instituted. In fact, he adds, with a more even balance between supply and demand, PRT's even become necessary as a means of attracting a stable group of highly talented people.

Blume uses the example of wigglers and undulators to further illustrate that PRT's will not work in every situation. A wiggler is a special magnet that fits into one of the straight sections of a storage ring between the bending magnets. The wiggler bends the electrons into a sine wave–shaped path whose local radius of curvature is smaller than that of the smooth circular arc of the bending magnets. The resulting synchrotron radiation spectrum is enhanced in intensity and is shifted toward shorter wavelengths. With a wiggler, a low-energy storage ring that would not produce x-rays can be made to do so. An undulator is similar to a wiggler but has the effect of compressing the smooth synchrotron radiation spectrum into a few narrow peaks, thus greatly increasing the brightness of the light at these wavelengths. Some people think that in the future all synchrotron radiation will come from wigglers and undulators. In any case, Brookhaven has left room for four wigglers in its x-ray ring and so far has built one prototype magnet. Blume says that the demand for these few wigglers will be so great that the laboratory is reserving them for general user operation.

All in all, the National Synchrotron Light Source is a first-class facility. Together with the upgraded Stanford laboratory and Wisconsin's new source, it puts the United States on or above par with Europe. Nowadays that is no mean accomplishment.

—ARTHUR L. ROBINSON

Reevaluation of Cancer Data Eagerly Awaited

Cornell professor estimates it will take at least a year to repeat experiments in question

For the past year and a half, Efraim Racker's laboratory at Cornell University had a special air of excitement. A graduate student named Mark Spector was conducting seemingly spectacular experiments on a class of enzymes related to cell transformation. Spector's data brought research that others had been doing on RNA tumor viruses, growth factors, and the biochemistry of cancer cells together in a theory that Robert Weinberg of the Massachusetts Institute of Technology calls "as unifying and simplifying for studying the metabolic basis of cancer as Newton's work was for studying mechanics." Prominent scientists, including David Baltimore of MIT, Robert Gallo, George Todaro, and Edward Scolnick of the National Cancer Institute, and Tony Hunter of the Salk Institute were impressed by Spector's work and started to apply his results to their own research.

But now serious problems have come to light. Racker, convinced that at least part of Spector's work is not replicable, has retracted the papers the two coauthored in *Science* and *Cell*,* has withdrawn papers still in press, and is beginning the difficult and lengthy task of trying to repeat what Spector claims to have done. "I have to go back to square one. I will not believe anything that Mark did until I repeat it with my own hands," Racker told *Science* during an interview at his laboratory.

Spector, who has written a Ph.D. dissertation on his work in Racker's lab, was due to receive his degree this semester. But on 10 September, he withdrew his dissertation and withdrew from Cornell University at his family's urging. Spector maintains, nevertheless, that his research is legitimate and that his withdrawal is not an admission that he has any doubts about his data.

Spector was considered an extremely impressive student, brilliant and exceptionally talented technically. Racker, an eminent scientist on the verge of retirement, says he was grooming Spector as his own successor. As Volker Vogt, a Cornell University tumor virologist puts it, "Spector was a superstar."

Spector arrived at Racker's laboratory in January 1980 and began experiments related to Racker's long-held theory about the biochemistry of cancer cells. As Racker reports, Spector soon began getting interesting supportive data.

Tumor cells convert glucose to lactic acid much more rapidly than normal cells do. For years, Racker has wanted to know why. In 1973, Racker got a clue when he found that in Ehrlich ascites tumor cells in mice this conversion (glycolysis) depended on a high rate of activity of an enzyme in the cell membrane whose function it is to pump sodium out of the cell and potassium in. Energy for this enzyme, sodium-potassium ATPase, is supplied by the hydrolysis of ATP to ADP and inorganic phosphate, which are required for glycolysis. Racker hypothesized that the sodium-potassium ATPase is very active in tumor cells because it is inefficient and so must work overtime to maintain the proper sodium-potassium balance. Racker and Spector discussed their data and hypotheses in the *Science* article.

One of the first things Spector accomplished was the isolation of the sodium-potassium ATPase from mouse tumor cell membranes where, he demonstrated, it acts inefficiently. In contrast, he showed that a sodium-potassium ATPase isolated from the membranes of normal mouse brain cells is efficient as a pump.

Next, Spector reported that the reason the sodium-potassium ATPase is inefficient in tumor cells is because it is phosphorylated. When he removed a phosphate group from this ATPase, it became efficient. Moreover, he isolated an enzyme from the tumor cells, which he and Racker called PK_M (for phosphokinase) that added the phosphate group to the membrane pump. (A kinase is an enzyme that adds phosphate groups to a substrate—in this case to protein molecules.)

From then on, Spector's results be-

*_Science_, 17 July 1981, pp. 303–307, "Warburg effect revisited: Merger of biochemistry and molecular biology"; _Cell_, July 1981, pp. 9–21, "A mouse homolog to the avian sarcoma virus _src_ protein is a member of a protein kinase cascade"; _Science_ article retracted in _Science_, 18 September 1981, p. 1313; _Cell_ paper retracted in _Cell_, September 1981, p. 827.

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came more and more intriguing and more and more wide-ranging. The enzyme PK_M, Spector found, was only active if it itself was phosphorylated and it was phosphorylated by another enzyme, PK_S. PK_S in turn was active only if it was phosphorylated, and it was phosphorylated by another enzyme, PK_L. Similarly, PK_L was phosphorylated by PK_F. There also was a feedback loop. PK_S could phosphorylate PK_F. The result was what Racker called a "kinase cascade." Normally the four enzymes of the cascade are inactive. But in tumor cells they are turned on and, by phosphorylating the membrane pump, cause increased glycolysis. By phosphorylating other cellular proteins, these enzymes may cause other changes associated with cancer, such as changes in cell shape and loss of growth control.

The cascade enzymes, of course, must themselves be turned on in some way. Here Spector's work made molecular biologists sit up and take note. The kinases are turned on, Spector reported, only if they are phosphorylated at a tyrosine residue. The term "tyrosine phosphorylation" had become a catchword for the tumor virus community. All the kinases that have been isolated phosphorylate in the serine or threonine positions with the highly notable exceptions of nine different kinases coded by RNA tumor viruses and a kinase induced by epidermal growth factor that is involved in stimulating cell division. Tumor virologists found the hypothesis that tyrosine phosphorylation might be the key to malignant transformation an attractive one.

Next, Spector discovered that the transforming protein produced by Rous sarcoma virus turns on the kinase cascade by mimicking one of the cascade enzymes. At this point, quite a number of molecular biologists began wondering if the transforming proteins they were studying also fit into the cascade.

Spector began collaborating with tumor virologists including Baltimore, Scolnick, and Gallo and a major hypothesis began to take form. The emerging picture was that RNA tumor viruses produce proteins that either mimic the enzymes of the cascade or turn the cascade on. Then the cancerous process is set in motion. Cell transformation can be reversed by cyclic AMP which acts, according to Spector's work, by allowing a cyclic AMP–dependent enzyme to phosphorylate the cascade enzymes in serine positions. This serine phosphorylation, Spector claimed, turned off the cascade.

During this time, other laboratories had been unable to verify predictions that would follow if the theory were correct. And all along, Racker recalls, biochemists and molecular biologists privately told him they had some reservations about Spector's work. It was too good, the results came too quickly, they said. After all, Spector reportedly had isolated the four enzymes of the cascade—enzymes present only in minute quantities—had purified the enzymes, made antibodies to them, and showed they were activated when their tyrosines were phosphorylated and inactivated when their serines were phosphorylated.

The amount of work—and luck—all this entailed was staggering. But Racker knew how extremely hard Spector worked. "I have never seen anyone work so hard. He was here night and day. All the time," says Racker. Says fellow graduate student Robert B. Pepinsky, "The sizes of his experiments were orders of magnitude greater than anyone else's. He would run ten gels where others ran one."

But there were other indications, clearly apparent in hindsight, that Spector's work might not always be replicable. For example, says Vogt, whose tumor virus laboratory is one floor above Racker's lab, experiments would sometimes work and sometimes not. "We'd never get an experiment to work entirely on our own without Mark's involvement," Vogt says. But, he recalls, "we rationalized by saying Mark had golden hands."

There also were hitches in Spector's collaborations with Gallo and Scolnick. Spector's collaboration with Scolnick began last January when Spector reported indirect evidence that a protein made by Harvey murine sarcoma virus fit in the cascade by phosphorylating the sodium-potassium ATPase in cell membranes. This indicates that the viral protein might act like PK_M. Scolnick sent Spector reagents and Spector sent back pictures of gels from experiments demonstrating that the Harvey virus protein does indeed resemble PK_M and is precipitated by an antiserum to PK_M.

In March, Scolnick invited Spector to NCI to spend a week in his lab. For the first 2 days nothing worked. Then Spector called Racker and asked that new reagents be sent to him. With the new reagents, the experiments started working. Scolnick's lab was jubilant. After Spector left Scolnick's lab, Scolnick at first thought he could confirm predictions that would follow if the work he did with Spector were replicable. Later, he realized he could not confirm them.

Efraim Racker and Mark Spector

Cornell University

Gallo became involved with Spector because he is studying a simian sarcoma virus that transforms monkey cells. One of the viral genes codes for a protein that is the same size as the transforming protein produced by Harvey murine sarcoma virus. Last winter, just after Spector reported that the Harvey virus protein resembles PK_M, he proposed that the monkey virus protein might also resemble PK_M.

In February, Gallo sent some of the monkey protein to Spector who did experiments at Cornell. He found that the protein is precipitated by an antiserum to PK_M. "He got a fantastic precipitate. The gels were beautiful," says Gallo. Then Gallo asked Spector to send him the antiserum to PK_M so his postdoctoral fellow, Vittorio Manzari, could try and repeat the experiment. Spector sent the serum, but in Manzari's hands nothing worked, even though he tried 30 times to repeat Spector's experiments.

At this point, Gallo sent Manzari to Cornell with coded samples (Gallo says his lab often uses coded samples to eliminate bias in interpreting results). The experiments at Cornell worked. When Manzari returned to NIH, the experiments failed again. Gallo, who is convinced that the experiments Spector did with Manzari are not replicable, says he still is baffled by how Spector could have gotten the expected results with the coded samples. "Spector's got enormous ingenuity if he cheated," Gallo says.

After the experiments with the coded samples, Gallo was never able to get Spector to send him more antiserums. Other investigators who wanted to work with Spector's reagents also had difficulty obtaining them. During an interview at his home in Ithaca, Spector said he had not been anxious to share the reagents, which were difficult to prepare, because he had wanted some lead time to do his own experiments.

Racker had several reasons for his continued faith in Spector. "He's so brilliant. He is technically incredibly talented," Racker says. "And he always showed me the gels. I would sometimes suggest experiments and he [Spector] would get very excited, but the experiments did not always work. This fortified my confidence." Racker also had confidence because, in December of 1980, a postdoctoral fellow apparently verified that one of the cascade enzymes, PK_M, is active in phosphorylating sodium-potassium ATPase from a variety of species.

Then, early in July, Spector did something that, in light of emerging doubts about his research, made Racker, Vogt, and others at Cornell believe he was asking that his work be questioned. Spector made up an elaborate story about his mother being kidnapped from her Cincinnati home by a deranged neighbor. The episode contributed to Racker's concern.

At that point, Racker says, he began to check Spector's work even more carefully than he had been to see whether it was holding up. It was about this time that several tumor virologists were expressing doubt about Spector's work because they could not confirm its predictions. At a Cold Spring Harbor symposium in mid-July, Weinburg and others shared their concerns with Racker, who defended Spector's research because he had no definite proof that the work might not be replicable.

Then, later that month, Vogt decided to carefully check one of Spector's experiments. The experiment involved radioactive bands on a gel which, according to the protocol, should have consisted of a viral protein phosphorylated in the tyrosine position and the four enzymes of the cascade. The viral protein and cascade enzymes presumably were radioactively labeled with phosphorus-32. Vogt cut the bands out of the gel, intending to hydrolyze the proteins and see if indeed the tyrosines were phosphorylated. He then put the bands in a scintillation counter, which detects β particles such as are emitted by phosphorus-32. To Vogt's amazement, the scintillation counter registered no counts, indicating that the substance causing the protein's radioactivity was not phosphorus-32. Vogt found that the proteins were in fact labeled with iodine-125, a γ-ray emitter, demonstrating that whatever proteins were in the reaction were first iodinated and then put on the gel so that the experimental results would look like viral proteins phosphorylated with phosphorus-32. In short, it looked as if the experiment was a fake.

Spector agrees that there were iodinated proteins in the reaction, but he says that someone was trying to sabotage him, that he himself did not add the iodinated protein. Besides, he says, there was radioactive iodine all over the lab. Vogt agrees that iodine-125 was found in the lab—nine out of ten flasks of growth medium were contaminated with free iodine-125 for no apparent reason. Because Spector was one of only a few people who had access to the growth media room and because he was the only one of those who had access who worked regularly with iodine, Vogt says, "We think Mark did it."

Scolnick learned indirectly of Vogt's discovery and decided to check the gels left over from Spector's time in his lab at NCI. According to the protocol, the gels should have contained phosphorus-32–labeled proteins. Scolnick found them labeled with iodine-125. He is not sure how Spector could have used iodine-125 to falsify the results with the Harvey virus protein, if indeed he did so. Spector says he has no idea why there was iodine in Scolnick's gels.

As Racker's doubts about Spector grew, he investigated more carefully Spector's academic history. Spector's master's work was done at the University of Cincinnati under Douglas Winget who had once been a visiting professor in Racker's lab. While working for a master's degree (which he never received), Spector did experiments on in vitro photosynthesis which were of substantial interest to researchers in that field. Spector seemed to have purified a 65,000 molecular weight protein that allowed chloroplasts to oxidize water in the presence of light. Winget reports that because he has subsequently been unable "to get anywhere near the rates of oxygen evolution that Mark got," he is somewhat skeptical of the work. However, Winget does think that some extract from the protein can oxidize water (although it may not necessarily be the substance Spector claimed to have purified) and he has been pursuing the work.

It was on Monday 27 July that Racker confronted Spector with his doubts. He recalls saying to Spector, "I will give you 4 weeks to make the enzymes of the cascade and hand them over to me. I will check them for purity." Spector did so and Racker tested the enzymes. "In my hands, they were completely negative," he says.

Subsequently, Spector was able to produce a small quantity of partially purified PK_M, the first enzyme of the cascade, and Racker found it had some activity, although not as much as Spector had originally reported.

Spector told *Science* that the data he produced in Cincinnati, as well as the results he achieved at Cornell, were not in any way fabricated. "It's very easy for them to say that the experiments [at Cornell] were faked. It's very difficult for me to prepare all of the explanations of why they were not able to repeat my work," he observes. "I never claimed that they [the enzymes of the cascade] were absolutely stable. They gave me 1 month to reproduce an incredible amount of work." Reiterating his innocence, he says, "There's no way I did the things I've been accused of doing."

Racker says he is reserving judgment on all of Spector's work until he repeats it completely. Because of Spector's recent partial purification of PK_M, Racker believes this enzyme may exist. But he does not know whether the other enzymes of the cascade are real. He also has some faith in Spector's results with an activator that stimulates protein phosphorylation, as discussed in the retraction letter to *Science*. However, Racker thinks that the work with tumor virus proteins probably is wrong.

The data Spector presented fit perfectly with a theory that is inherently plausible. The fact that many knowledgeable people took it seriously lent it credibility. Now, only future experiments by those few investigators who are still entranced by the hypothesis will reveal whether it has substance or is just a house of cards.

—GINA BARI KOLATA

Racker says he is reserving judgment on all of Spector's work until he repeats it himself.