Brain Injury Rehabs Under Fire

Little noticed as yet by the press, a major new health-care scandal is percolating into view. It involves a widespread, costly, but poorly regulated area of care that many people still know little about: proprietary (for-profit) residential rehab facilities for patients who suffered traumatic brain injury (TBI) in car crashes or other violent events.

Two million Americans suffer TBI annually, according to psychologist George Zitnay, Ph.D., chief of the nonprofit National Head Injury Foundation (NHIF) in Washington, D.C. He said their care costs $25 billion per annum.

These patients first are treated at acute care hospitals, stabilized, and then sent by their families to what often are far distant TBI rehab places—the “providers” as they are called in this industry’s jargon. They provide long-term convalescent care.

The proprietary providers include both individual facilities and chains of several or more such places. The industry and some providers have become the targets of complaints by “survivors” — as TBI patients designate themselves — and their families. Criticism also is coming from professional rehabilitationists who have worked at, or learned about the cost, and the care delivered by following patients they have referred to these facilities. These complaints currently are being looked into by state and federal agencies, Congress, accrediting bodies, and a few journalists.

Complaints Are Made

The principal charges: Poor and unnecessary care. Denial of freedom — the right to leave — and other civil rights. Conflict between professional decisions and business considerations. Price gouging, which thus far is being paid for by Medicaid, insurers, and families who often cannot afford it — but who cannot afford, either, to abandon rehab they are told offers “hope” for a loved one’s recovery.

Specific charges that have been made include:

- Patients may be admitted to facilities largely on the basis of a “wallet biopsy” — an assessment of their ability to pay — and are kept, and rehabilitated just so long as the money lasts.
- Patients are confined in locked buildings against their will, without legal justification — or recourse.
- Patients are sent to out-of-state facilities — even though community re-entry is a staple of TBI rehab — because federal Medicaid legislation allows providers to charge more for services that are not available in one’s home state.
- At Christmas and other holiday times, providers encourage home leaves to keep censuses — and revenues — high.
- Unproven and controversial rehab methods are used.
- Business considerations, meaning profits, often prevail over professional judgments about what patients need.

There now are 800 TBI rehab facilities in the U.S., according to NHIF’s Zitnay. Many — possibly the majority — are proprietary, but there are no accurate counts, NHIF and other rehab sources say.

Problem’s Scope Unclear

“If the bottom line is to make money,” said Zitnay, in a phone interview, “then the patient — the consumer — is never the major concern.”

Fortunately, he added, only “a handful” of providers operate in this way. Some of his NHIF colleagues, and others, believe, however, that the problems are widespread:

“‘It’s all the companies,’” according to Mrs. Phebe Whitehead, of Baltimore, who is director of the Maryland Head Injury Foundation, and a member of the NHIF national board. The NHIF Survivors Council chairwoman, Mrs. Sherry Watson, of Las Cruces, NM, said, by phone:

“In my opinion, it’s the whole industry we’re looking at,” not just one provider.

One focus of current complaints is an industry leader, the New Medico Head Injury Systems, of Lynn, Mass. It employs 8,000 people, at 36 facilities in 15 states, and has 200 sales reps “to drive up business,” according to science reporter Peter Wehrwein, in the Albany, N.Y. Times Union (May 19).

A New Medico spokeswoman, Kathleen Rowe, confirmed by phone that the company has 36 facilities in the U.S., that specialize in brain injury rehab.

A physiatrist (medical rehab specialist), Thomas P. Anderson, M.D., who was New Medico’s medical director between 1985 and 1988, said in a phone interview that he quit there and went to Harvard, because of business office interference in his professional decision-making.

“The problem was that I wasn’t really over-seeing the service,” said Dr. Anderson, “A lot of the decisions [that] were made by administrative people should have been strictly professional, or cooperative — not one sided.”

Dr. Anderson said that some of the rehab methods used in New Medico facilities — such as comstim, or coma stimulation, in which therapists read the newspaper and other material to

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comatose patients — are “controversial.” Dr. Anderson added:
“I think New Medico is guilty of abuse. They kept patients for
quite a long time when there was little evidence of progress.”

Judgments Are Mixed

Professional assessments of New Medico’s care vary sharply.
“They usually have excellent clinical staff for most of their
programs,” said a speech therapist and rehab administrator who
was program director at a New Medico facility in the South in
the late 1980’s, and now works for a nearby non-profit facility.
The problem, said this professional — who asked not to be
named — was in the business administration:
“If you don’t do what they ask you to do, you don’t stay very
long.”

This ex-New Medico administrator explained, in a telephone
interview, that she had quit to preserve her professional reputa-
tion, because she was being pressured to do things “that were not
in patients’ best interests.”

She and other rehab professionals stressed, that in some
facilities, and on some services within individual facilities, the
care is excellent.

A much more critical assessment comes from physiatrist
Kenneth K. Hoelscher M.D., of Syracuse, N.Y., who worked at
a nearby New Medico facility for 15 months before leaving
recently under pressure. The rehabilitation care was “terrible”
he says, but the nursing care was “good.”

Can The Brain Be Taught?

He said the wide range of therapies used at New Medico for
“so-called cognitive remediation” of the brain have not been
shown to be effective in the published medical literature.

“The whole thing was based on the supposition that they sold
the public on, that you can intervene much more than you can
in brain damage.”

Rather, Dr. Hoelscher said, the best way is to take care of the
patient’s body, and wait — and hope — that the brain recovers.
This can be done for a few hundred dollars a day at a nursing
home, he says, and doesn’t require rehab routines that may cost
two or three times as much.

Other physiatrists said, however, in interviews that cognitive
remediation can help, if given in a comprehensive rehab setting.

A “power tactic” to bring in clients was described to reporter
Wehrwein by Phil Barry, a psychologist, who was program
director of a New Medico facility in Cortland, N.Y. for four
years, until he resigned last year. He told the Albany reporter
that the company pressured families, “telling them there was
one bed available when there were 12 beds.”

Asked to comment on charges of poor care and business-
office pressure on professional workers, and on other
complaints, New Medico PR woman Rowe said she was instructed
not to do so by New Medico’s lawyer. The reason, she explained,
was “because they touch on issues that are already, or may be
in the future, the subject of litigation brought by New Medico.”

Another ex-New Medico administrator, whom Wehrwein
reports was fired, has written critically of the TBI rehab industry
in general. Rehab counselor Brian MacMahon, Ph.D., of the
University of Wisconsin-Milwaukee, writes in his new technical

“Due to the incorporation of rehabilitation as a business
enterprise and . . . overlapping trends, the modern day rehab setting
has too often been transformed into an environment where hate,
power, envy, and greed are observed in business policies, prac-
tices and everyday operations.”

He cites, as one example, business office pressures to discour-
age patients from having home leaves during the Thanksgiving-
to-Christmas holiday season:

“It is eventually decided that it is in the therapeutic best
interest of all TBI clients to remain in the facility during major
holidays so that ‘continuity of care’ would be maintained,” he
writes. “This is a classic case of creating a false conflict by
compromising one rehab tenet (normalization) in the alleged
interest of another (continuity of care).”

Escape Described

One of New Medico’s and the proprietary rehab industry’s
sharpest critics is a survivor, writer Lucy Gwin, of Rochester,
N.Y. She was an inpatient at New Medico’s Community Re-
She has sued New Medico, charging “negligence, negligent
supervision, assault, battery, violation of [her] constitutional
rights to privacy, negligent infliction of emotional harm, and
false imprisonment . . .

“Incidents include a physical assault, being confined against
her will, and witnessing assaults on other patients,” she charges.

In an elaboration of her experiences that she says she sent to
congressional panels and state and federal agencies, Gwin writes:

“I saw people who tried to escape (from the mansions where
we were housed) knocked to the ground and dragged back . . . I
saw one fellow kicked in the head . . . Thus, I knew better than
to try to escape . . .

“Friends who came to see me had been persuaded by the
docctors’ that I would not be well enough to go home for many
months. That I was dangerous to myself and to others . . .

Later, she says, a friend came to get her.

“As we were loading my belongings in his truck, he was
summoned inside to take a call from the corporation’s Boston
lawyers. He was told that I was dangerous, that he would be
responsible for damage I did to anyone . . . He was made to sign

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a form accepting responsibility for me and any damage I might do for the rest of my life. When the phone rang again, he was told that the police would be called, and I would be committed to a mental hospital, he to a jail.

"We split quickly." In a phone interview, the friend, Frank Palumbo, of Rochester, said of Gwin's account:

"That's accurate."

Asked if they were aware of instances in which patients were held in rehab facilities against their wishes, both Dr. Anderson, the former New Medico medical director, and NHIF director Zitnay denied any specific knowledge of such incidents.

"I don't know — I can't comment on that specifically," Zitnay said.

"The NHIF is in the process of developing very stringent quality [standards]," Zitnay said. "We're looking into those issues now."

Some NHIF officials, unlike Zitnay, said they are aware of abuses of patients' personal freedom in the TBI rehab industry.

Imprisonments Claimed

"Facilities confine survivors to locked units or seclusion rooms without legal authority to do so," according to Sherry Watson, the Survivors Council chairwoman, in a printed statement distributed for a recent NHIF conference. In a phone interview from Los Cruces, she said:

"People are put into locked-door facilities, and they are told, 'You can't get out because of your inappropriate behavior.'"

The neurobehavioral centers are "the most expensive" proprietary TBI facilities, Watson said. They bill medical insurers or families that can afford them $30,000 per month, or more.

Other survivors and professionals describe rates in TBI rehab facilities that range from a few hundred dollars a day, up to $1700 a day, depending on the type of facility, care given, and form of payment available.

Medical and psychiatric inpatient facilities have legally mandated procedures for patients who wish to leave against medical advice, explained neuropsychologist James Lamott, Ph.D., who works in a community TBI rehab facility in Rockville, MD. But no such regulations are in place for TBI rehabs that inhabit the "grey area" between nursing homes and school-like facilities.

"I have been involved with patients who have not been allowed to leave, to call their families, to call their lawyer," Lamott said by phone. "They've been placed on all sorts of restrictions, allegedly for their own good, but with no court supervision at all."

In Lamott's view, these practices are widespread and illegal.

Rehab Goes On and On

"As long as your funding lasts, you'll be in a facility," explains Sherry Watson of NHIF. Several other survivors and professionals who were interviewed agreed.

Patients "quite often" are kept until the money runs out, says social worker and disability specialist Janet Williams, M.S.W., of the University of Kansas in Lawrence, who previously worked for NHIF, as well as for one of the proprietary chains (not New Medico). This "absolutely" is a pattern in the field, she said by phone. She said costs can run from $500 to $1000 per day.

"People say that the number of beds has risen because of the need," Williams added. "But, really, it's because of the amount of money available."

The chain facilities perform a "wallet biopsy" on prospective clients, explained pediatric physiatrist Vikki A. Stefans, M.D., of Arkansas Children's Hospital, who sees patients before they go to TBI rehab facilities, and then follows their cases while they are there. Once patients are admitted, she and several other rehab professionals said, the staff may pressure the family to keep the patient in the facility, when inpatient care no longer is helpful, or needed, because there still is insurance money or state funds left upon which to draw.

She described one of her patients, a 13-year-old girl, who had done well at a New Medico facility.

Toilet Training Could Cost $40,000

"They tried to extend her stay unnecessarily, for trivial goals that the family really was invested in," Dr. Stefans said. Specifically, the facility was "pushing" to keep the child an additional 60 days, at $700 a day, so they could change her toilet-training schedule from once every two hours to once every three hours.

"Reading the [case] notes, it was clear that everything else had maxed out," Stefans said. The toilet-training change was the only thing that could be cited to keep the child in.

"It was time for that kid to go home!"

At the opposite extreme, in terms of disability, surgical nurse Donna Whitam, R.N., who is neurosurgery coordinator at New York University Medical Center, in Manhattan, describes a case she is familiar with in which a man in a "persistent vegetative state" — a coma — has been kept for many months in distant rehab facilities, far from his home, at a cost of a quarter million dollars. Whitam declined to identify the providers.

"There's no hope," she says. "The family's been destroyed."

This patient should have been moved to a far-less-costly nursing home, near his family, rather than be kept far away in an expensive TBI rehab, Whitam said. But the wife disagrees because she feels guilty.

Whitam adds: "There's a feeling in rehab it goes on and on — until there just is no more money!"

Complaints Stir Interest

Currently, two House subcommittees, one chaired by Rep. Ron Wyden (D-Ore.), the other by Rep. Ted Weiss (D-NY), are looking into the TBI rehab industry. A U.S. attorney's office, in Boston, also is looking into TBI rehabs, according to a congressional source and other sources.

NBC television news spent eight months and $100,000 making a nine-minute segment for "Expose" that focused on New Medico, the producer, Richard Berman, who has since left NBC, said by phone. Though it was finished last spring, Berman said NBC told him that scheduling problems have kept the piece from airing.

"Expose" was cancelled last month. But it is due to be combined with another show this month, and the TBI piece may appear then, an NBC news executive said by phone.

December 1, 1991
What's Right — and What's Wrong —

In October, this reporter was accepted into a two-week fellowship program for science reporters, on the topic of the brain. It was conducted by the Knight Center for Specialized Journalism of the University of Maryland College of Journalism, at College Park. Stories on these two pages derive from this fellowship — for which we are grateful. — D.R.Z.

Neuroscience is a vast and productive research enterprise, which is all the more remarkable because it hardly existed — at least by that name — a few decades ago.

At the recent annual meeting of the Society for Neuroscience, in New Orleans, neuroscientists presented some ten thousand research reports. This mind-boggling output surely will advance understanding of, and healing options for the brain and the spinal cord — neuroscience’s target organs.

Neuroscience’s achievement is particularly impressive because unlike, say molecular biology, it is not yet a conceptually organized discipline; it lacks a central dogma — though it may be approaching one (See Box, below).

Neuroscience is, rather, an interacting collection of old and new disciplines — including neurobiology, genetics, experimental psychology and psychopharmacology — brought under one roof in part for administrative convenience and political clout, including fund raising. Research money is needed — badly — and current “Decade of the Brain” promotions may help snare it.

This reporter and 20 colleagues recently were taken on an extensive intellectual tour of current neuroscience research by scientists and administrators in the Washington area. Presenters ranged downward from the directors of NIH and lesser federal agencies that deal with the brain to bench scientists, clinicians, to eager “post-docs” and fellows in various neuro-specialties. The briefing provided as clear a précis of this huge scientific endeavor as a reporter is likely to get. A few highlights stand out:

- Three-D mapping to identify precisely which brain areas mediate which human activities — the 19th century phrenologists’ failed dream — rapidly is being realized by dramatic imaging methods (PET and MRI) and micro-electrical recording from arrays of sensors set, temporarily, inside patients’ skulls — and even deep within their brains.
- The electrical, chemical and structural bases of cell-to-cell communication are being identified, and the complex neural networks of these cells, whose function is called life, are being discovered.
- Clear correlates are emerging between diseases — epilepsy, depression, and most recently schizophrenia — and brain structure and function, opening some significant new treatment options, and promising many others.

Superlatives cannot capture the elegance and power of these advances!

Is there, then, also a flaw? We think so — a significant one!

It is the assumption, implicit in many of the researchers’ talks, and explicitly stated in a few of them, that human life can be understood, by science, wholly in terms of brain, and its functions as mind and behavior. More rudimentarily, this view has it that life is to be construed as molecular biology, since molecular changes are the substrate of all mental activity.

Mind as its Molecules

This “materialistic” view was stated most forcefully by keynoter Jon Franklin, our science-writer colleague, who now teaches journalism at the University of Oregon. Jon has interviewed dozens if not hundreds of neuroscientists, and distilled their views into a book, Molecules of the Mind (Atheneum), in which he describes “a grand chemical symphony that seems to explain us so well.”

We are “gizmos,” he says, not “spiritual creatures,” and our mental illnesses “are as physical as cancer,” and “as

Ten Postulates Proposed for Neuroscience

Neuroscience is advancing toward a basic understanding of the nervous system that is not likely to be falsified by new discoveries, researcher Dominick Purpura believes. These are the 10 “principles” that he calls the “foundations for the brain’s new science” — in a mixture of his words and ours:

1. The nerve impulse is the basic currency of the nervous system.
2. Communication between nerve cells, and with other cells occurs at the synapses.
3. Sensory information arises from sense-specific peripheral receptors (touch, taste, pain, etc.) linked to particular pathways into the spinal cord and brain.
4. Physical movement results from motor-sensor programs located in the brain and spinal column.
5. Homeostatic and adaptive mechanisms for self and species survival are organized in the one-square centimeter of brain tissue called the hypothalamus.
6. Emotion is a behavioral state that reflects cognitive and involuntary processes integrated through limbic and midbrain systems.
7. Learning and memory result from temporary or permanent changes in the strength and efficacy of appropriately stimulated synaptic connections.
8. The cerebral cortex is regionally specialized, and it is organized for parallel processing of both input and output signals.
9. The primate brain evolved through enormous elaboration of its visual and auditory recording systems and central processing systems.
10. Brain development and maturation result from programmed interactions of temporally overlapping genetic and extrinsic events.
With the New Science of the Brain

curable as pneumonia.''

Closing the briefing on a similar note, two weeks later, Washington, D.C. neurologist Richard M. Restak, M.D., derivatively dismissed Christian and Cartesian dualism —the doctrine that mind and body are separate — by declaring:

“Everything that has to do with mental illness has to do with the brain.”

“Mind,” he added, “is the functioning of the brain.”

Only one of the fifty speakers took sharp exception to these views. Neuroscientist Dominick P. Purpura, M.D., who is dean of the Albert Einstein College of Medicine, in New York, immediately followed Franklin to the podium and pointedly declared:

“I would challenge the idea that by understanding every molecule you can understand the mind!”

We concur, but would go a step further. We were dismayed (but not surprised) by the words and concepts that we did not hear in the talks by neuroscientists. Except from Dr. Purpura, we do not recall hearing the word personality. The word psyche, which denotes to us an individual integration of thought and feeling, went similarly unsaid. So were ego, id, and most other words that stand wholly or in part for the wellspring and dynamic organization of human experience. The unconscious was absent. Even consciousness was ignored, perhaps because, as one scientist admitted, “We don’t even know how to define it.”

And yet, undoubtedly, it is there.

Empiricism Has Risks

We understand and agree that science is a reductionist effort. One has to find and look first at the tiniest parts in order to infer a whole. But, we see here, too, an exclusionary empiricism that skitters over the physical attributes of the brain, but leaves the deeper, darker recesses of the psyche, or dare one say soul, unattended.

Neuroscience thus seems to have a hidden agenda: the dehumanization of the science of the “mind.” It seems to strive to be squeaky clean, liberated from the darker realms, described by Freud and many others, of passions and instincts and motives — the unconscious drivers of human behavior.

From the clinical point of view, this is a disaster. It eliminates the individual as a sufferer, whom mental health professionals are sworn to treat.

No ‘Magic Bullets’

No matter how much is learned of the biology of schizophrenia or depression, we think it naive to believe that a “magic bullet” neuroleptic or other drug will one day bind up and heal all psychic wounds. Earlier, it was naive to believe that insulin was the panacea for diabetics. But people did.

Scientifically and philosophically, of course, a neuroscience that excludes the individual as he (or she) can best be defined at the time, is empty and dry. Since individuals, with their quirks, are empirically as well as intuitively quite real, a human science that denies or ignores them is, ultimately, fatally flawed. It cannot help us understand ourselves as individuals or as familial and social beings.

By these exclusions, neuroscience cedes the human subject back to the old, irrational orders — religion, authority, tradition — from which we were liberated by the Enlightenment and the existential philosophies of the 19th and 20th centuries. The agenda of these older forces — now returning to the fore — always has been to curb free-thinking and free spirits.

Valley Center

I will have to give up my doctor soon.
In two more months.
She graduates to private practice and
I will stay at the Community Mental Health Center with Dr. Smith.
I’ll have to start all over again.
I’ve learned to trust without dependency.
It was so lucky that she was at Building Sixteen when I arrived.
I will be on the medication for life.
Unless they decide that schizophrenia is caused
by your Mother having eaten peanut chews.
I don’t know — having alcoholism and mental illness —
it’s a heavy trip.
I find release in poetry.
There are few answers.

— Martha B. West

Valley Center

Two-Way Synapse Found

BETHESDA, MD

The conventional view in neurobiology — based on the available evidence — has been that each neuron (nerve cell) performs only a single function: It releases one of several neurotransmitters from its axon. This messenger either stimulates or inhibits the activity of the next cell(s) down the line in a neural pathway.

Now, neurobiologist Daniel L. Alkon, M.D., and co-workers at the National Institute of Neurological Disorders and Stroke, here, say they have discovered a dual-purpose neuron in the leaming area of a snail’s brain, where the animal’s visual and vestibular pathways meet. It apparently can be changed from an inhibitor to a stimulator.

This neuron secretes two variants of a neurotransmitter called GABA. Initially, one variant predominates, and it inhibits adjacent neurons. But after the snail has been subjected to “training” maneuvers by the researchers, the GABA output shifts toward the alternate form, Dr. Alkon says. The same axon sites now stimulate rather than inhibit adjacent neurons.
What Controversial 'Cell' Report Says

Waltham, Mass.

A federal grand jury in Baltimore has listened to incriminating testimony from the Secret Service, and soon may indict Boston immunologist Thereza Imanishi-Kari, Ph.D., for submitting fraudulent data to the National Institutes of Health (NIH) and Congress about a research paper published five years ago in the journal Cell.

The paper itself has been called fraudulent by Imanishi-Kari’s former post-doctoral research fellow, Boston biologist Margot O’Toole, Ph.D., who now is at the Genetics Institute, in Cambridge, Mass. This judgement was affirmed by a preliminary — but now discredited — investigation by the NIH Office of Scientific Integrity (OSI) that relied heavily on O’Toole’s input.

Meanwhile, however, evidence is emerging that the disputed paper was and is scientifically valid — as Imanishi-Kari continues to insist. Her co-author, Nobelist David Baltimore, Ph.D., now president of Rockefeller University in Manhattan, retracted the paper last spring. But he recently wrote a letter to the editor of Nature (Sept. 5) to say that other researchers have confirmed the paper’s key findings.

Careers Are Jeopardized

This continuing — and, unfortunately, confusing — chain of events has major consequences for the careers, reputations and lives of Imanishi-Kari and other participants. It has far broader ramifications for science, and for all scientists, academics and others who value free inquiry and believe it should be protected from governmental and congressional attack. The current investigation of Imanishi-Kari, who now is at Tufts University Medical School, is being pushed by Rep. John T. Dingell (D-Mich.), head of the House subcommittee on oversight and investigations.

Dingell’s aim, we believe, is to mobilize widespread popular discontent against science and the rationality and often disquieting creativity that underpin it. The Cell paper and the sprawling Imanishi-Kari “case” thus have become critical focal points in this conflict.

To resolve the controversy in their own minds, taxpayers, like NIH officials, government probes and the grand jurors, need to decide: Is this paper good science, as Imanishi-Kari insists, or fraudulently bad science, as her accusers say?

Paper Is Very Technical

This judgement has been frustrated, we believe, because the paper is poorly written; Imanishi-Kari, a Brazilian woman of Japanese descent, obtained her scientific training in Europe — and is not wholly fluent in English. Much more important, her research arena is arcane and abstruse. It is difficult even for other biologists to penetrate, and is nigh unto opaque to nonscientists — including this reader — for whom, of course, it was not originally intended.

We are not aware of any clear, popular exposition of the Cell paper and its scientific context. So we have set out to provide one here. We do so for its intrinsic interest and, more importantly, as a basis for PROBE readers to begin to decide for themselves if Imanishi-Kari fulfilled her scientific obligation, or, rather, is a cheat.

To accomplish this, we sought help from Brandeis University immunologist Joan Press, Ph.D., who works on similar scientific problems. Press is a colleague and public defender of Imanishi-Kari, and also her friend. We have worked very closely with Press — whose help we here acknowledge.

# # #

The genetic inheritance that is carried in the chromosomes of mice and human reflects the contributions of genes — sequences of chromosomal DNA — from each parent. The offspring has two forms, alleles, of each gene, one allele contributed by the father, the other by the mother.

Each gene produces a single substance, a protein, that is responsible for a single physical trait. Usually, both alleles of a gene are expressed: the offspring produces a paternal and maternal form of each protein.

Immune System Differs

This is not the case, however, for the genes that make protective proteins for the immune system called antibodies, which specifically recognize and neutralize dangerous non-self substances such as viruses and bacteria, which are called antigens.

Each antibody contains a heavy chain protein made from only one of the two sets of parental alleles; which parent’s allele is used is random. This biological phenomenon, in which the matching allele from the other parent is not used or expressed, is called allelic exclusion. It is a mystery.

“We don’t know how it happens,” says Press. The Imanishi-Kari experiments were intended in part to find out how allelic exclusion occurs.

One explanation for why this may occur is to protect the individual from autoimmune reactions. If a specialized cell that produces antibody were not allelically excluded, it could produce two antibodies, each with a different specificity. One antibody might react with a dangerous bacterium A, but the other might be directed against an antigen — call it protein B — that the human or mouse inherited from a parent. This would make the immune response non-specific: The cell triggered by bacterium A also would make antibody to the self protein B. A dangerous, self-destructive autoimmune reaction could ensue.

Imanishi-Kari and others have used genetically engineered rodents, called transgenic mice, to study allelic exclusion. The gene for the heavy chain protein is removed from a mouse cell that is making antibody. This heavy chain gene is injected into the fertilized egg, or zygote, from a mouse of a different strain, and so now is called a transgene, as in transplant. The transgene and the zygote differ in their alleles for the heavy chain gene.

Several zygotes containing the transgene are implanted in the uterus of a female mouse, which delivers a litter several weeks later. Most of the offspring will carry the transgene, as well as the endogenous genes that originally were present in the zygote.

Earlier experiments from Baltimore’s
lab had shown that the heavy chain transgene sometimes, but not always stops the endogenous heavy chain genes from being used. It does not wholly exclude them. The experiments in the controversial Cell paper were based on this earlier observation. If some of the endogenous heavy chain genes were being expressed, then the question was, Did the traits of the transgene influence the endogenous genes that were used and thus the antibodies that would be produced?

"In this paper," Imanishi-Kari, Baltimore, and their co-workers wrote, "we explore whether the types of endogenous genes expressed are modified by the presence of the transgene and its products."

**Segments Recombine**

Their answer to this question derives from the fact that the heavy chain gene is made by a recombination of three different gene segments, called VH, D, and J. Each parental chromosome contains many different VH genes, many different D genes, and many different J genes. In the mouse, there are at least several hundred different VH genes; these can be grouped into 13 VH gene families, based on their relatedness to each other (by DNA sequence). If one assumes the genes are like beads strung onto a string with two ends, then genes in some of these VH gene families cluster together; certain families are found at one end of the string, while other VH gene families are found at the other end, which is close to the D and J genes.

In the creation of a heavy chain gene by DNA recombination, one VH, one D and one J gene segment are brought together on the one parental chromosome that will be used by the offspring. This VDJ rearrangement forms the heavy chain "variable" region, and it programs the part of the heavy chain protein that is responsible for a specific antigen.

**Diversity Is Protective**

The other, constant region of the heavy chain protein is made by gene segments, called C genes, that sit next to the VDJ rearrangement on the chromosome. There are several different C genes, and the one that is used determines whether the antibody that is made is immunoglobulin G, or, rather, immunoglobulin A, M or E. These differences, however, do not influence the antibody's specific recognition of an antigen.

Because any VH gene segment can recombine with any D gene segment which can recombine with any J gene segment, an enormous number of different heavy chains can be made. This antibody diversity is an important component of the immune system because it means that a comparably high number of different antibodies can be recognized — and resisted.

The transgene used in the Imanishi-Kari experiments consisted of a particular VDJ gene rearrangement and a constant region made of one of the two possible alleles from the C gene that makes immunoglobulin M. The transgene was put into a mouse that carried the alternative C gene for immunoglobulin M.

Imanishi-Kari isolated individual antibody-producing cells from the transgenic mice, and analyzed their antibodies to determine whether they used the transgene or endogenous genes for their heavy chains. Many of the cells used only the endogenous genes; the transgene was turned "off" in these cells, Press says.

This now has been confirmed by researcher Luciana Forni, at the Basel Immunology Institute. She reported that "only a proportion of plasma cells producing endogenous immunoglobulins co-express the transgenic product." (European Journal of Immunology 20:983, 1990).

Dr. Imanishi-Kari made two other observations that Press says were "curious and intriguing":

First, one of the antibody-producing cells made an antibody whose VDJ region was very similar — but not identical — to the transgene, by several criteria: the antibody used the same D and J gene segments as the transgene; the VH gene was from the same VH gene family used by the transgene; and the DNA sequence at the recombination sites between V-D and D-J that formed the VDJ rearrangement were the same for this antibody and that of the transgene.

However, the C gene used by the antibody was not from the transgene, which stipulates immunoglobulin M. It rather was immunoglobulin G, which had to have come from the endogenous gene. If it was possible, Imanishi-Kari wrote, that this antibody represented some form of recombination between the transgene and an endogenous gene — which would be very interesting, Press says. But, Press says, Imanishi-Kari "did not make a big deal of this since, as she noted in her paper, she couldn't rule out the possibility that this was only an endogenous gene that was very similar to the transgene."

**Results Confirmed**

Since then, molecular biologists in two other labs — Erik Selsing's, at Tufts, and Tasuku Honjo's at Kyoto University, in Japan — have shown that a transgene can be recombinated with an endogenous gene, possibly by two different genetic mechanisms (Gerstein et al., Cell 63:537, 1990; Shimizu et al., Journal of Experimental Medicine 173:185, 1991).

Press says:

"It is highly likely that one impetus for these other scientists' work was Imanishi-Kari's findings in the Cell paper."

The second curious finding, which was the focus of the Discussion in the Cell paper, was that many of the antibodies made from the endogenous genes mimicked or resembled the transgene in certain traits. Yet these endogenous antibodies could not come from the transgene; nor could they reflect recombination events between the transgene and the endogenous genes: These antibodies were not immunoglobulin M (the transgene could only make immunoglobulin M antibody), and they did not use VH genes from the same VH family used by the transgene. They were completely different at the "molecular" level (DNA), yet they were similar in other traits (called idiotyp). Imanishi-Kari and her co-authors concluded in the paper that "the expression of endogenous genes mimicking... the transgene suggests that a rearranged gene

"It is highly likely that one impetus for these other scientists' work was Imanishi-Kari's feelings..."

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introduced into the germ line can activate powerful cellular regulatory influences."

Excitement Provoked

This finding was reported at the time by science journalists. The Cell paper also generated excitement in the scientific community, because, according to Press, "it supported an existing theory which said that antibodies naturally connect to each other, and cells connect to each other much as surfaces would interact if they were each other's mirror images." Imanishi-Kari showed that these "transgene-like" antibodies used endogenous genes from certain VH gene families that are close to the D and J gene segments at the 3' end of the chromosome.

Press says "this is not surprising. Many investigators now shown that VH genes from these 3' VH gene rearranged preferentially during early B cell develop normal mice. The idiotypic relatedness between these at and the transgene is more difficult — but not impossible — to explain."

Critics Balk at Findings

It is these results that have caused the most controversy. Critics have charged that they were fraudulently obtained.

Press says that Imanishi-Kari has since confirmed this finding. She adds that she is not aware of any other researcher who has tried to replicate it as yet.

While "strange," Press adds, these observations "are explicable by several mechanisms — and shouldn't give people lumps in their throats."

Thus, in the five years since the Cell paper was published, some of its key observations have been confirmed by other scientists. David Baltimore, having "withdrawn" the paper — thereby reducing the pressure he was facing, and, very possibly, saving his job and career — nevertheless courageously returned to the fray, in his letter to Nature (Sept. 5).

"The traditional test of science," he wrote, is: "Have the data proved reliable?"

He continues:

"For the [Cell] paper, the data have proved more durable than the data in most papers. No experiments of which I am aware have appeared in the literature that contradict the [Cell] paper. In fact, there is much published evidence, and more coming, that support the paper's results in remarkable detail."

According to Press, some of the papers cited by Baltimore support various findings of the Cell paper. Others give possible scenarios that could account for the "idiotypic relatedness" of the transgene and endogenous antibodies Imanishi-Kari analyzed in the Cell study.

The disputed Cell paper that may lead — imminently — to Imanishi-Kari's indictment and arrest thus appears to have met the test of science. It has confirmed — and been confirmed by — researchers, using both similar and dissimilar approaches. It makes it highly unlikely, in our view, that the paper was fraudulent. If it were, how could such findings be confirmed scientifically by others?

It seems to us that Margot O'Toole and others who find fraudulence in the Cell paper need to answer this question.

The Tougher Test

Biologist Press suggests one additional test of whether a paper is not just science, but good science: Does it stimulate discussion and new ideas and experiments? She says the Cell paper meets this test:

"This paper is really great because all of the papers that were before it, and all that came after form a consistent thought pattern."

"A lot of the stuff in it has been confirmed, either directly or indirectly, and it's got a lot of important possibilities in it. But the problem is that all the crap that has become involved with it has really destroyed its ability to be talked about in a useful way."