will touch and then drift apart again. But if there is something deeper in the connection between the two fields, sparks may fly.

Now that two proofs have been reported, combinatorial mathematicians feel that they are gaining insight into the theoretical underpinnings of their field. Erdös, however, has made a still stronger conjecture. He proposes that if the sums of the reciprocals of the integers in a subset diverge (that is, if the reciprocals are added up and, as more and more terms are added, the sum grows larger and larger without bounds) the subset will contain arithmetic progressions of arbitrary length.

If true, Erdös' latest conjecture would imply his original conjecture and would also solve a long-standing problem about the distribution of prime numbers. It would indicate that arbitrarily long arithmetic progressions of primes exist. So far, because the primes are so sparsely distributed among the rest of the integers, only short progressions of less than about length 16 have been found. Neither Erdös nor anyone else has any idea of how to prove or disprove this most recent conjecture. For the solution to this problem, Erdös is offering a $3000 reward. If the size of Erdös' reward indicates the relative difficulty of proving his new conjecture, nothing short of Revelation may allow the reward to be claimed.—GINA BARI KOLATA

Multiple Sclerosis: Two or More Viruses May Be Involved

Until recently, the strongest evidence that multiple sclerosis (MS) might be caused by a virus was epidemiological. The pattern of occurrence of the disease suggests that MS is very likely caused by a viral infection early in life. But there has been only indirect immunological evidence to support such a possibility. No one has ever isolated a virus that, when injected into animals, produces MS. Until 5 years ago, no one had even isolated from MS patients a virus that might be associated with the disease.

In the past 5 years, though, much more direct evidence has been obtained. Many investigators have found traces of the measles virus at different sites in the bodies of MS patients, and one group recently identified a persistent measles infection in MS patients. Another group has isolated from MS patients a virus that is serologically related to measles virus. And two other groups have identified a second, unrelated virus, that they think is associated with MS. Some of the results conflict with each other, and some are controversial. Nonetheless, these findings promise that a firm identification of the causative agent of MS may be made in the foreseeable future and that steps can be taken to prevent future infections.

Measles (rubeola) virus has been a prime suspect in MS at least since 1962, when John M. Adams and David T. Imagawa of the University of California School of Medicine at Los Angeles identified antibody to the measles virus in the blood and cerebrospinal fluid of MS patients. Other investigators, including Martin Panelius and Aimo A. Salmi of the University of Turku in Finland, Kenneth B. Fraser and his associates at the Queen's University of Belfast, and Jacob A. Brody and John L. Sever of the National Institute of Neurological Diseases and Stroke (NINDS), have subsequently confirmed that higher than normal concentrations of antibodies to measles virus occur in the blood of most MS patients and that the antibodies are present in cerebrospinal fluid from many MS patients. Panelius and Salmi and D. Carleton Gajdusek of NINDS have shown that antibodies to measles virus can also be isolated from the brains of some patients who died from MS.

These results are considered significant because viral antibodies are not generally found in the brain or cerebrospinal fluid. They thus suggest not only that a large number of MS patients had a measles infection, but also that the virus proliferates in the bodies of MS patients at one or more sites at which it does not proliferate in healthy individuals.

Antibodies to Many Viruses

The significance of these findings is clouded somewhat by the discovery of other antiviral antibodies in cerebrospinal fluids from MS patients. C. Henry Kempe and his associates at the University of Colorado School of Medicine, for example, found high concentrations of antibodies to vaccinia virus (which is used to vaccinate against smallpox) in cerebrospinal fluid from about half the patients they studied. And Natalie E. Cremer of the California State Department of Health has observed antibodies against many viruses, including measles, rubella, vaccinia, and herpes simplex. It has thus been reasoned that MS patients have an inborn defect in their immune systems that allows viruses to proliferate in the central nervous system.

Even though MS patients produce larger than normal quantities of antibody against measles and other viruses, they may have a deficient cellular immunity—that is, the virus-sensitized leukocytes that would normally abolish a viral infection may be produced in insufficient quantities or may not respond to an infection properly. John B. Zabriskie of Rockefeller University and Virginia Utermohlen of Cornell University have found, for instance, that leukocytes from MS patients do not respond to measles virus as effectively as leukocytes from healthy individuals. This impairment was not observed for any other virus tested. A similar defect in cellular immunity has been observed by Caspar Jersild, Torben Fog, and their associates at the Copenhagen University Hospital. Jersild and Fog, however, also observed a deficient response to other paramyxoviruses, members of the same family of viruses as measles.

Zabriskie and Utermohlen's results have been confirmed by William Sheremata of the Montreal Neurological Institute, but other investigators have not been successful in reproducing the results. Why different investigators have obtained different results is still unknown. Zabriskie's results suggest that the cellular immune system of MS patients has a specific defect which prevents it from responding adequately to an infection by measles virus. The results of other investigators suggest that there is a more general defect in the cellular immune system, and that the reduced response to measles virus is a particularly sensitive indicator of that defect.

That the latter possibility might be correct is indicated by experiments with transfer factor, a substance that is thought to provide a way to transfer cellular immunity. (Transfer factor is, itself, a controversial subject, and many scientists believe that there is no firm evidence to support its existence.) Transfer factor is thought to be a small nucleo-

protein that prompts leukocytes to recognize specific viruses or other antigens. Transfer factor prepared from leukocytes that have been sensitized to the measles virus, for example, should stimulate the production of measles-specific leukocytes when injected into an MS patient. If the MS disease process is maintained by a measles infection that persists because of a specific defect in cellular immunity, then injection of measles-specific transfer factor should abolish the infection.

Zabriskie and Fog have both tried treating MS patients with measles-specific transfer factor and each initially reported favorable results, raising a great deal of hope among MS patients. But subsequent studies performed with double blind controls, Zabriskie says, do not show the improvement. It may be that transfer factor is not a real entity, or it may simply not be an effective way to fight diseases such as MS. It may be that measles does not play a role in MS. Or it may be that there is no defect in cellular immunity, but that some other factor is interfering with it.

Blocking Factor in Blood

Joseph A. Bellanti and his associates at the Georgetown University School of Medicine have found that the blood of MS patients contains a substance, known as blocking factor, that prevents leukocytes from destroying cells infected with measles virus. The blocking factor does not affect the ability of leukocytes to attack cells infected with other viruses. It is not observed in the blood of healthy individuals, but it is found in the blood of patients with subacute sclerosing panencephalitis (SSPE), another persistent disease that is thought to be caused by measles virus.

Bellanti finds that leukocytes from MS patients can attack measles-infected cells in the presence of serum from healthy individuals. The blocking factor thus appears to be a specific response to the infection. The factor is associated with the immunoglobulin G or antibody fraction of blood serum, suggesting that it might be either a viral antigen or a combination of antigen and antibody. It is known that excessive production of antibody to a viral agent can suppress cellular immunity toward that agent. It is thus possible that the virus might release a great amount of antibody to provoke an enhanced antibody response. It is also possible that the MS patient might have an inborn defect that causes him to produce excessive amounts of antibody.

One further piece of indirect evidence that supports the measles virus theory should be mentioned, both because it illustrates some of the contradictions in the experimental results and because of the possibility that it can provide a test for the clinical identification of MS. A definitive diagnosis of MS is notoriously difficult, particularly when the disease is in its early stages. Many investigators have thus sought biochemical tests for diagnosis, but none has yet proved entirely successful. Nelson L. Levy and his associates at the Duke University Medical Center have found, however, that leukocytes from MS patients adhere to measles-infected human epithelial cells (in the absence of blood serum) much more strongly than do leukocytes from healthy individuals or from patients with other diseases. This is exactly the opposite of what Zabriskie has found.

The source of the conflict between Levy's and Zabriskie's results is not known, but Levy says his results are highly reproducible. The effect is observed regardless of the severity or duration of the disease, and is observed even when the patient is in remission. Levy argues that this phenomenon may eventually provide a definite test for early identification of MS.

Despite all this indirect evidence implicating viruses in MS, it has been very difficult to provide direct evidence. One approach has been to look for viruses visually. Many electron microscopists have examined autopsy tissues from MS patients and occasionally sighted objects that could be viruses. John Prineas of the New Jersey Medical School, for instance, in 1972 reported that tissues from MS lesions contain a filamentous material that closely resembles the core of paramyxoviruses. Many investigators have since reported similar findings. The significance of these results has come into question recently, though, because similar material has been observed in tissues from patients with other illnesses. Only a few investigators now believe that the particles are actually viruses.

Another approach has been adopted by Albert W. Cook, Louis Pertschuk, and Jack Gupta of the Long Island College Hospital. Spurred by the reports of some MS patients that a gluten-free diet seemed to ease their symptoms, Cook and his associates set out to study gluten sensitivity in the intestine, an organ that has received little attention in MS. They immediately observed that biopsy specimens from the intestines of MS patients contain large depositions of complement, a substance that is involved in immune reactions.

The specimens were further examined with immunofluorescent antibody techniques and, in each of 36 patients studied, the investigators found evidence of the presence of measles antigen. There was no evidence for the presence of any other virus. There was also no evidence of complement deposition or viral infection in the intestines of healthy individuals or of patients with other neurological diseases such as Parkinson's disease and Huntington's chorea.

Since there are similar complement deposits in the central nervous system of MS patients, Cook argues that the deposits may represent an immune reaction set off by a persistent antigenic stimulation elsewhere in the body. That evidence of the virus should be found in the gastrointestinal tract is not surprising, he adds. The measles virus appears to have a certain affinity for the intestines and may frequently cause diarrhea and other intestinal problems in young children after an infection. Their success occurred, he says, simply because no one had ever looked for viruses in the intestines of MS patients before.

First Time Measles Identified

The results of Cook and his associates represent the first time that the measles virus has been firmly identified in MS patients. Its presence in every one of the patients examined is strong evidence that it may be involved in the etiology of the disease. But the situation is complicated by the fact that two other viruses have been isolated from MS patients. One of the viruses is a parainfluenza virus that is serologically related to the measles virus. The second virus is much more closely related to viruses that have been isolated from animals with slow virus diseases. Research on these viruses has proved to be exceptionally difficult, and there is a great deal of controversy about the significance of their isolation. Nonetheless, the scientists who have isolated the viruses have great confidence that the viruses they are studying are related to MS.

The parainfluenza virus was isolated by Hilary Koprowski, Volker ter Meulen, and their associates at the Wistar Institute and the University of Wurzburg in Germany, respectively. They isolated the virus by fusing brain cells from MS patients with kidney cells from African green monkeys, a process that frequently causes latent viruses to replicate. The isolation of this virus, which they call 6/94 virus, was very difficult and occurred only with specimens from two patients. Neither they nor other in-

vestigators have been able to isolate it again.

Although the 6/94 virus is similar to the measles virus, it is most similar to another paramyxovirus known as the Sendai hemagglutinating virus of Japan. Koprowski and ter Meulen found that the two viruses cross-react immunologically, that they have similar numbers and types of proteins, and that there are extensive homologies between the RNA sequences of their genomes.

The 6/94 virus will infect and persist in cultured human brain and other mammalian cells. But like the Sendai virus—and unlike most other viruses—it cannot be passed to a second culture of such cells. Interestingly, the virus from the mammalian cells will infect macrophages (a type of leukocyte) and, after being grown in the macrophages, will once again infect mammalian cells. Koprowski attributes this phenomenon to the activity of proteases (enzymes that degrade protein) within the macrophage and, in fact, treatment of the cultured 6/94 virus with trypsin will accomplish the same thing. It is possible that this response in the presence of mammalian cells is a protective mechanism that, in effect, enables the virus to maintain a low profile and avoid an all-out immune response that would abolish the infection. Intriguingly, Fraser and other investigators have reported that a flare-up of MS after a period of remission is accompanied by an increase in the concentration of proteases in the blood and in tissues around the sclerotic plaques.

Inoculation of the 6/94 virus into the brains of adult mice produces a chronic neurological disease that is very little like MS. Its principal characteristics include an infiltration of immune leukocytes into certain areas of the brain and degeneration of the brain's white matter. Antigens specific for the 6/94 virus persist in certain areas of the brains of diseased mice for 14 days after infection, but Koprowski and his associates have never been able to isolate the virus from the mice.

Koprowski and his associates also injected the 6/94 virus into newborn chimpanzees. Inoculation of the virus into the noses of the chimpanzees produced a respiratory disease similar to influenza. Some of the animals inoculated this way died of pneumonia and autopsies showed brain damage, although the damage was not like that of MS. The virus was inoculated directly into the brains of three other animals. One died of pneumonia, but the other two developed recurrent seizures about 14 months after the inoculation.

Autopsy of the brain of one of these two chimpanzees showed substantial tissue damage, although this damage was also different from MS. But there are some striking similarities between the experimental disease and MS, Koprowski says. Most significant is the fact that the animals showed no symptoms for almost 14 months after inoculation, suggesting that the disease is an experimentally induced slow virus disease. Furthermore, the neurological symptoms appeared intermittently and the onset of symptoms was frequently preceded by respiratory infections. This pattern is observed in human MS, and suggests that the two diseases have a similar etiology.

Two aspects of the 6/94 infection in mice may also shed some light on human MS. The disintegration of brain white matter occurs even when the virus is

Speaking of Science

Social Anthropologists Learn to Be Scientific

Many social anthropologists traditionally have not considered themselves scientists so much as humanists. They often applied for research grants to sources other than the National Science Foundation (NSF), which usually did not favor their humanistic bent. In recent years, however, as more and more social anthropologists began to compete for funds, they have increasingly turned to the NSF.

Nancie Gonzalez, who is in the middle of a 2-year stint as Program Director for Anthropology at the NSF, thinks that social anthropologists have rarely fared well there because many of them are not trained to think like scientists. She is trying, with some success, to help these investigators present their ideas in such a way as to make their proposals competitive for NSF funds.

Gonzalez says she was shocked when she first saw some of the "mushy" grant proposals submitted by social anthropologists to the NSF. A number of these proposals were accepted but many more were not. Authors of some proposals would write that they wanted to study a particular group simply because it is disappearing or because no one had ever described it before. In contrast, Gonzalez says, grant proposals from archeologists, who tend to do better at the NSF, more often state a specific problem that the investigators wish to solve and tell why that problem is important and interesting.

According to Gonzalez, social anthropologists on NSF panels, who advise the foundation on which proposals should be funded, recognize bad proposals and recommend rejections. In fact, social anthropologists tend to be harder on their peers than other kinds of anthropologists are.

As a social anthropologist, Gonzalez was concerned about this situation and sought to remedy it. She wrote a description of what a good research proposal should be and sent it to applicants. She visited about 60 universities in the past year and lectured at meetings to try to explain, among other things, why proposals from social anthropologists are so often turned down. And when a promising research proposal is rejected because of the way it is written, Gonzalez writes the applicant a personal letter and suggests that the proposal be rewritten and submitted again to the NSF.

The results of this effort have been encouraging. In the past year, grant proposals from social anthropologists have been considerably more sophisticated, and the resubmitted proposals, which now constitute as many as one-third of all proposals being considered, often fare well.

It now appears that in order to get more money from the NSF, social anthropologists will have to think more like scientists. Although there will always be a humanistic contingent who should not look to the NSF, Gonzalez believes that there is now a large group of social anthropologists who should be able to compete for funds at the NSF. It's all a matter of learning the language and the ways of the scientific world.—G.B.K.

inactivated by ultraviolet light before inoculation. Furthermore, the virus produces no effect when it is injected into congenitally athymic mice, which have no cell-mediated immunity. These results suggest that it is not replication of the virus that produces damage to the brain, but rather that it is the body's immune reaction to the virus.

Koprowski speculates that the proteins of the 6/94 virus may contain some amino acid sequences (and thus some antigens) that are similar to those of proteins in the central nervous system. When the cellular immune system attacks the viral proteins, therefore, it may also inadvertently attack components of the central nervous system. If the original infection is transient, the damage to nervous tissue might be minimal. But if the infection persists for long periods, the damage might accumulate until pathological symptoms develop. It is possible, perhaps even probable, that more than one virus contains antigens that are similar to those of the central nervous system. MS might thus be the result of multiple infections—although one agent, such as the measles virus or the 6/94 virus, might be the major precipitating agent.

Many investigators now agree that a sequence of events of this sort could explain the development of MS. But other factors must also be involved. Genetic susceptibility to the effects of the virus is apparently necessary for development of the disease. A second virus has also been isolated from MS patients, and its participation through a different mechanism may also be required. But work with this virus has proceeded even more slowly than work with the 6/94 virus, and even the fact of its existence is still heatedly debated.

The second virus, which has been dubbed the MS-associated agent (MSAA), was first identified in 1972 by Richard I. Carp and his associates at the New York State Institute for Research in Mental Retardation. They injected mice with extracts from the brain, spleen, blood, or cerebrospinal fluid of MS patients. Within 16 to 48 hours after the injection, the mice showed a decrease in the number of polymorphonuclear neutrophils (PMN's) in their blood; PMN's are a special kind of leukocyte, and a decrease in their number may signify a viral infection of some sort. Carp found that the effect persists for at least 16 months, during which time the mice are otherwise normal. The effect is not seen when the mice are given extracts from healthy individuals.

The agent that causes the depression in PMN count can be transmitted to other mice by inoculation with blood or brain homogenates from the first mice, and in this fashion transmitted through several generations of mice. Because of the dilution involved in this process, continued transmission indicates that the agent is replicating in the mice. The agent is removed from the blood by passage through a 25-nm filter but not by passage through a 50-nm filter. The small size and the fact that the agent replicates suggest that MSAA is a virus.

Carp has had great difficulty reproducing his results and most other investigators have been unable to do so. The PMN assay, Carp says, is very difficult to work with. In particular, various infections of the mice reduce the PMN count so that infection by MSAA does not produce an observable effect. Carp says that most of the mice received in his laboratory during the past few years already had infections, and thus were not usable for the assay. He assumes other investigators have had the same problem. But because of this difficulty, many virologists have dismissed his results as artifacts.

MSAA Results Confirmed

Last year, however, Werner Henle and his associates at the Children's Hospital of Philadelphia reported that they had not only reproduced Carp's work, but also extended it. They observed the depressed PMN count in the original strain of mice used by Carp, in other strains of mice, and in other animals, indicating that the effect does not depend on the mice themselves. Like Carp, they found that MSAA was not recoverable from every MS sample; it can be recovered most frequently from patients in whom the disease is most active, and least frequently from those in whom the disease is quiescent. Most important, Henle found that the effect of MSAA on PMN's can be blocked by blood serum from patients with MS. This neutralizing factor is associated with the immunoglobulin G fraction of the blood.

The neutralizing activity was not found in the blood of healthy Americans or Americans with other viral infections. It was found occasionally, however, in the blood of relatives of MS patients and in the blood of medical personnel who are in frequent contact with MS patients. Intriguingly, very high concentrations of the neutralizing agent were found in blood serum from healthy individuals in East Africa, where MS is virtually unknown. This supports the epidemiological evidence that exposure to a presumed MS virus early in life confers lifelong "immunity" to the disease.

Henle agrees with Carp that the PMN test is exceptionally difficult to use, and both groups have had great difficulty getting consistent results with it. They are thus searching for alternative ways to grow and isolate the virus. Carp has developed a test that involves cultured mouse cells. This test is also difficult, but it has the great advantage of being based on a tissue culture system, and it could provide the means for a detailed analysis of the virus. It may, however, be necessary to develop still better techniques before other investigators will be able to work with the virus and before they will accept Carp and Henle's findings.

The role of MSAA in MS is still unknown, but Carp and Henle think that it is significant in the development of the disease. It is possible that MSAA may act in conjunction with the measles virus or the 6/94 virus. Carp points to experiments performed by him and other investigators with scrapie, a neurological disease of sheep and goats that is known to be caused by a slow virus. Mice inoculated with extracts from scrapie tissue show a decline in PMN count. The agent responsible for this effect is also between 25 and 50 nm in diameter and replicates in mice. Perhaps most important, it has been shown that this scrapie PMN agent is different from the scrapie disease-producing agent.

Carp has demonstrated that the scrapie PMN agent is not the same as MSAA, but it seems likely that they are closely related. It thus seems possible, Carp says, that the scrapie PMN agent and MSAA each acts in conjunction with the appropriate disease-producing agent either to cause the primary infection to persist or to render the immune response to the primary infection aberrant.

It is clear that MS is a very complicated disease. But there no longer seems to be much doubt that a virus is involved in the causation of MS. And the recognition of that fact should be a spur to further efforts toward identification of the agent or agents and implementation of steps to prevent future infections.

—THOMAS H. MAUGH II

This is the second of three articles.