

A Preliminary Report

June 8, 2011

Submitted for Publication:

Biological Trace Element research

The Cause, natural history, prevention and cure for muscular dystrophy (myopathies - MD) - long thought to be a genetically transmitted disease in the "horse and buggy" Amish populations of Adams, Allen and Switzerland Counties of Indiana, has been determined to be a preventable and reversible collection of diseases,

the origins of which have been identified as a combination of nutritional deficiencies and a mal-absorption syndrome!!

The team leader, Dr. Joel D. Wallach, whose landmark research (The Center for the Biology of Natural Systems: Washington University, St. Louis, MO., The St. Louis Zoological Gardens, The Shaw's Botanical Gardens - Funded by The National Institute of Health) comparing causes of death in hundreds of species of zoo

animals with causes of death in humans (The Diseases of Exotic Animals: W. B. Saunders Publishing Co., Philadelphia. 1983) is listed by the Smithsonian Institute as a "National Treasure" has identified various forms of muscular dystrophy (myopathies - MD) in the Amish communities of Adams, Allen and Switzerland Counties, Indiana as a combination of a classic well documented mineral deficiency (less than 0.1 ppm soil Se levels - Purdue University Schools of Agriculture and Veterinary Medicine)

and that is intensified by a common mal-absorption syndrome (celiac disease).



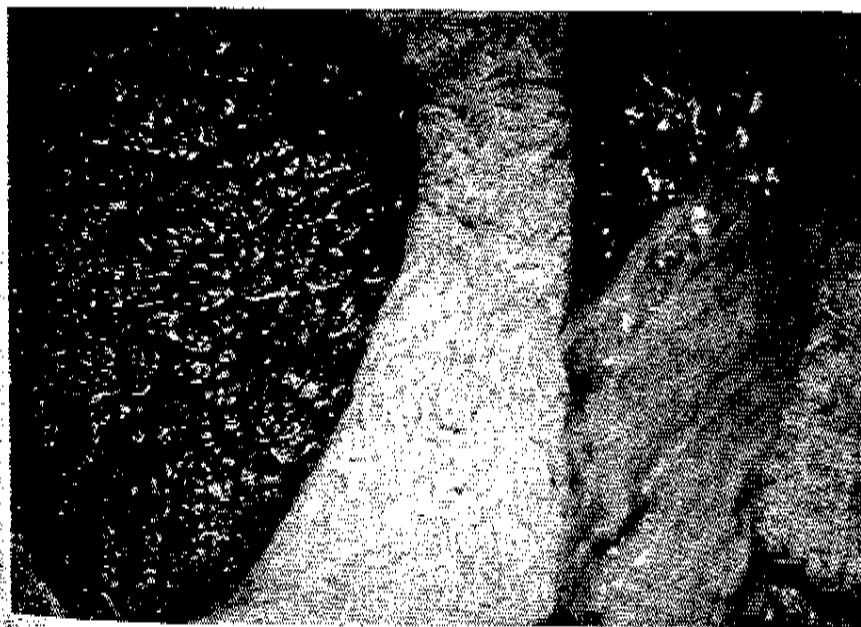
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Muscular dystrophy in a boy (note enlarged calves).



D

Muscular dystrophy in a boy (note enlarged calves).

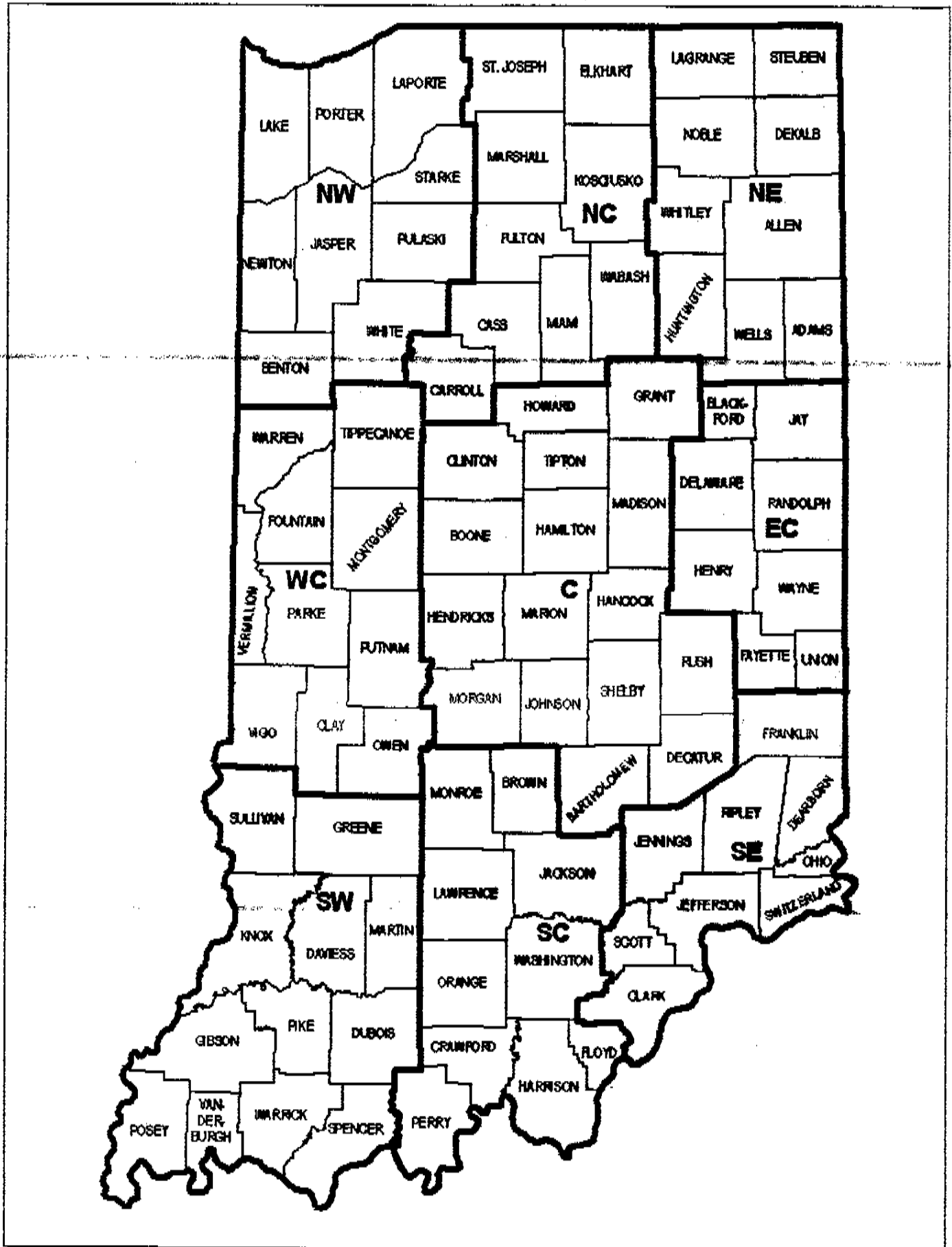


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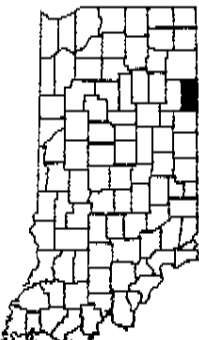
Normal muscle (left) and MD muscle (right)

(continued)

INDIANA AGRICULTURAL STATISTICS DISTRICTS



COUNTY HIGHLIGHTS



Adams County

		RANK				RANK					
2007 Census Population	33,762	45	2008 Cash Receipts	\$214,414,000	14						
2007 Total Land Area (acres)	216,979	71	Crop Receipts	\$79,127,000	44						
2007 Number of Farms	1,315	4	Livestock Receipts	\$135,287,000	8						
2007 Land in Farms (acres)	182,490	34	2008 Other Income	\$9,816,000	23						
2007 Average Size of Farm (acres)	139	80	Government Payments	\$3,880,000	41						
2007 Value of Land & Bldgs (avg/acre)	\$4,339	7	Imputed Income	\$5,936,000	20						
2007 Cropland (acres)	165,835	31	2008 Total Income	\$151,078,000	15						
2007 Harvested Cropland (acres)	158,853	32	Less: Expenses	\$122,304,000	15						
2007 Pastureland, all types (acres)	6,712	61	Realized Net Income	\$28,774,000	14						
2007 Woodland (acres)	7,435	61									
2009 CROPS		PLTD	HARV	YLD	UNIT	PROD	RANK	LIVESTOCK	NUMBER	HEAD	RANK
Corn	64,800	61,400	167	Bu	10,230,000	41	Jan 2010 All Cattle	19,100	9		
Soybeans	84,000	83,900	50.0	Bu	4,189,200	20	Beef Cows	*	*		
Wheat	12,900	12,700	76.5	Bu	973,700	5	Milk Cows	8,200	5		
Alfalfa Hay	---	7,300	3.80	Ton	27,900	8	2007 All Hogs	152,980	4		
Other Hay	---	1,700	2.20	Ton	3,700	44	2007 All Sheep	1,093	10		
Popcorn	---	253	---	Lbs	751,918	15	2007 Chickens	1,834,850	2		
							2007 Turkeys	45	19		



Allen County

		RANK				RANK					
2007 Census Population	348,761	3	2008 Cash Receipts	\$141,063,000	32						
2007 Total Land Area (acres)	420,594	1	Crop Receipts	\$107,002,000	23						
2007 Number of Farms	1,649	1	Livestock Receipts	\$34,061,000	33						
2007 Land in Farms (acres)	254,136	8	2008 Other Income	\$10,455,000	19						
2007 Average Size of Farm (acres)	154	75	Government Payments	\$4,955,000	19						
2007 Value of Land & Bldgs (avg/acre)	\$4,024	16	Imputed Income	\$5,500,000	23						
2007 Cropland (acres)	230,416	8	2008 Total Income	\$139,832,000	19						
2007 Harvested Cropland (acres)	215,595	8	Less: Expenses	\$115,308,000	18						
2007 Pastureland, all types (acres)	10,849	33	Realized Net Income	\$24,524,000	24						
2007 Woodland (acres)	9,882	46									
2009 CROPS		PLTD	HARV	YLD	UNIT	PROD	RANK	LIVESTOCK	NUMBER	HEAD	RANK
Corn	73,700	71,500	177	Bu	12,680,000	32	Jan 2010 All Cattle	11,600	23		
Soybeans	103,500	103,300	53.5	Bu	5,528,500	4	Beef Cows	900	73		
Wheat	20,400	20,300	70.5	Bu	1,428,800	3	Milk Cows	2,200	17		
Alfalfa Hay	---	7,600	3.80	Ton	28,900	7	2007 All Hogs	46,094	28		
Other Hay	---	2,100	2.50	Ton	5,300	32	2007 All Sheep	560	38		
Popcorn	---	---	---	Lbs	---	---	2007 Chickens	*	*		
							2007 Turkeys	79	15		

		RANK				RANK					
2007 Census Population	9,667	88	2008 Cash Receipts	\$11,191,000	88						
2007 Total Land Area (acres)	141,348	86	Crop Receipts	\$7,797,000	88						
2007 Number of Farms	374	81	Livestock Receipts	\$3,394,000	83						
2007 Land in Farms (acres)	47,461	87	2008 Other Income	\$3,922,000	79						
2007 Average Size of Farm (acres)	127	84	Government Payments	\$1,174,000	82						
2007 Value of Land & Bldgs (avg/acre)	\$3,521	49	Imputed Income	\$2,748,000	61						
2007 Cropland (acres)	25,402	87	2008 Total Income	\$10,849,000	88						
2007 Harvested Cropland (acres)	20,030	87	Less: Expenses	\$10,809,000	88						
2007 Pastureland, all types (acres)	15,489	17	Realized Net Income	\$40,000	90						
2007 Woodland (acres)	9,853	47									
2009 CROPS		PLTD	HARV	YLD	UNIT	PROD	RANK	LIVESTOCK	NUMBER	HEAD	RANK
Corn	5,700	5,300	153	Bu	810,000	88	Jan 2010 All Cattle	5,700	60		
Soybeans	8,300	8,200	44.0	Bu	359,300	86	Beef Cows	2,800	28		
Wheat	*	*	*	Bu	*	*	Milk Cows	500	36		
Alfalfa Hay	---	*	*	Ton	*	*	2007 All Hogs	*	*		
Other Hay	---	4,800	1.50	Ton	7,200	25	2007 All Sheep	71	88		
Popcorn	---	---	---	Lbs	---	---	2007 Chickens	751	43		
							2007 Turkeys	*	*		



Switzerland County

A Preliminary Communication: Muscular Dystrophy (Myopathies, MD): the genesis, natural history, prevention and cure.

Joel D. Wallach, B.S., D.V.M., Post Doc. Comp. Path., N.D.

Ma Lan, M.D., M.S., Steve Wallach, Marvin Ropp, B.S.,

Richard M. Lambright, Peter Glidden, B.S., N.D. and

Charmaine Murphy

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(Keshan Disease - China; Amish; athletes - i.e. Walter Payton - 1985, Reggie Lewis -1994; Wes Leonard - 2011) has been proven to be the cause of hypertrophic cardiomyopathy, muscular dystrophy, cystic fibrosis and liver necrosis (acute liver necrosis, primary sclerosing cholangitis, liver cirrhosis, etc.).

In addition to suffering from diseases produced by selenium deficiency, the subsistence farmers of Keshan County, China are subject to numerous congenital and acquired diseases directly related to deficiencies of iodine, calcium, boron, etc. (Keshin -Beck Disease); the Amish subsistence farmers of Adams, Allen and Switzerland Counties of Indiana, in addition to high rates of muscular dystrophy (myopathies - MD), suffer from deficiencies of zinc (Down's Syndrome, cerebral palsy, spina bifida, cleft palate/lip, etc.), manganese (congenital deafness), folic acid deficiency (spina bifida, etc.).

The 1977 discovery by Wallach that cystic fibrosis was a congenital deficiency of selenium was confirmed by experts in the pathology and pathophysiology of cystic fibrosis - despite the support of experts from outside agencies, Wallach was summarily terminated and his work was dismissed by the Yerkes' staff as trash science, however, the discovery was ultimately acknowledged in an article (Morton, W. A. and Swindler, K.: Serendipitous Insights Involving nonhuman Primates. *ILAR Journal*. The National Academy of Sciences. 46: 4 pp 346 - 351. 2005) in the *International Laboratory Animal Research Journal* (the official journal of The National Academy of Sciences) as an example of unexpected beneficial discoveries gleaned from basic research:

Serendipitous Insights Involving Nonhuman Primates.

William R. Morton and Kathryn Swindler

Serendipity Among Primates

Within the sphere of research involving laboratory animals, the nonhuman primate affords researchers a unique and valuable opportunity because humans, monkeys and apes share many physiological, biochemical and behavioral traits. These similarities reflect close genetic relationships and make the nonhuman primate an ideal animal model for many human diseases (Rand 2003). This special relationship also presents fertile ground for the serendipitous discovery. Most of the serendipitous occasions described below present such events in the course of nonhuman primate animal studies. Some are apocryphal. In particular cases, the nonhuman primate is involved in a chance find only in the testing phase after a serendipitous occurrence with human subjects (e.g., the case of minoxidil, a drug developed to control high blood pressure).

The examples of serendipity that appear below demonstrate the classic serendipitous condition - the coupling of insight with unplanned events (Wallach 1978; Fine and Deegan 1996). The following examples are briefly described and range from gross observations to fine endocrine detail: infant behavior, birth periodicity, leprosy, cystic fibrosis, environmental enrichment, founding of a primate center, endocrinology, and drug development.

Cystic Fibrosis

Emory University (1978) reported that "a classic textbook case" of cystic fibrosis as found in humans had been identified (in animals for the first time) in a nonhuman primate, an animal in which the disease had not been described previously. An assistant veterinary pathologist, (Joel D. Wallach, B.S., D.V.M., Post Doc. Fellow, Comp. Path.), unexpectedly, discovered the disease during the routine autopsy of a 6-mo-old male rhesus monkey that died of unknown causes. The diagnosis was confirmed by Dr. Victor Nassar, an Emory pediatric pathologist at Atlanta's Grady Memorial Hospital and by Dr. John Easterly, a pathologist at the Chicago Lying-In Hospital and national authority on cystic fibrosis. The monkey, one of a group (of NASA monkey's) being studied for the space program, instead provided the first (reproducible animal and) nonhuman primate model of cystic fibrosis. Yerkes (Regional Primate Research) Center veterinary pathologist said, "We are very fortunate that the rhesus monkey is the animal model that was found by (Wallach) because more is known about this animal than about any other nonhuman primate. They are also available for research in fairly large quantities."

In 1990 Wallach and Ma published the results of a joint pathology project in Keshan County, China that showed that 32 percent of Keshan Disease patients, a universally agreed upon (WHO) selenium deficiency disease, were also afflicted with the pancreatic, heart, liver and lung lesions typical of classic cystic fibrosis - again lending additional support for the original 1977 report by Wallach that cystic fibrosis was in fact a manifestation of a congenital selenium deficiency:





Information Services
Emory University
Atlanta, Georgia 30322

News Copy From EMORY UNIVERSITY

John Rozier, Director
(Code 404) 329-6

RELEASE DATE: Sunday AM's - March 5, 1978

March 3, 1978

SUBJECT: First Case of Cystic Fibrosis
Discovered in Nonhuman



Scientists at the Yerkes Regional Primate Research Center of Emory University have discovered cystic fibrosis in a young rhesus monkey at autopsy--the first nonhuman case of this disease known to medical science.

"This appears to be the first animal model of cystic fibrosis, and we're excited about its implications," said Drs. Joel Wallach and Harold McClure, veterinary pathologists at the Yerkes Center.

Since cystic fibrosis is thought to be a genetic disease, there is a possibility that the parents or relatives of the affected monkey can have additional offspring with cystic fibrosis.

An animal model of cystic fibrosis will permit investigators to learn a great deal about the basic causes of the disease and how it might be treated, the Yerkes scientists explained. At present, the basic defect of the disease is not known.

Cystic fibrosis is a disease of children, adolescents, and young adults which is characterized by abnormal mucus secretions and fibrous scarring in various organs such as the pancreas, liver, lungs, and reproductive and digestive systems. Many of its victims die in early life of complications such as malabsorption and pneumonia.

More than 25,000 white people in the United States have the disease, but a much larger number--five percent of the white population--are thought to be carriers of the recessive gene of cystic

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A private, gift supported institution with 7,500 students and 38,500 alumni, Emory University has served the South and the nation since 1836 as a center of teaching, research and community activity. College, Graduate School, Schools of Medicine, Law, Theology, Dentistry, Nursing, Business Administration.



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Cystic Fibrosis

fibrosis. It is rarely seen in the black population or in people of Asiatic origin.

The discovery came as Dr. Wallach, assistant veterinary pathologist at the Yerkes Center, was performing a routine autopsy on a six-month old male rhesus monkey that had died of unknown causes. He noticed pancreatic disease and bronchial mucus production; evaluation of the tissue later under the microscope revealed "a classic textbook case" of cystic fibrosis as pictured in human medical literature, the Yerkes scientist said.

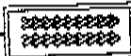
Studies of tissue from other organs confirmed that the monkey was indeed a victim of cystic fibrosis, Dr. Wallach said. Dr. Wallach's diagnosis was confirmed by Dr. Victor Nassar, an Emory pediatric pathologist at Atlanta's Grady Memorial Hospital and by Dr. John Easterly, pathologist at the Chicago Lying-In Hospital, who is a national authority on cystic fibrosis.

A report on the discovery was made yesterday (Saturday, March 4, 1978) at a Primate Pathology Workshop held in Atlanta. Drs. Wallach and McClure gave the presentation at Emory's Glenn Memorial Building near Grady Hospital.

They said the affected animal was bred in a colony of rhesus monkeys supported by the National Aeronautics and Space Administration for studies pertaining to the U.S. space program.

"We have here a classic example of serendipity," said Dr. Wallach and McClure. "These animals were being studied for the space program but are now also providing us clues in a different area altogether."

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Cystic Fibrosis

Dr. Nelly Golarz de Bourne, histologist at the Yerkes Center, is conducting NASA studies on the monkey colony in collaboration with Dr. Geoffrey H. Bourne, Yerkes Center director. Their records go back at least 10 years, and include information pertaining to breeding and diseases of the animals.

"We can now go back and look at slides of animals that died to see whether any of them might have had any of the more subtle changes of cystic fibrosis," Dr. McClure explained.

"This discovery has made us aware that these animals can have the disease, so we can make an all-out search for new cases, both in the past and future. If we can breed a supply of animals with cystic fibrosis, using the parents, siblings, or other relatives of the one that had the disease, this will be a great boon to researchers."

Up to now, research efforts toward understanding and curing cystic fibrosis have been severely hampered by lack of an animal model.

"We are very fortunate that the rhesus monkey is the animal model that was found by Dr. Wallach, because more is known about this animal than about any other nonhuman primate," Dr. McClure said. "They are also available for research in fairly large quantities."

Dr. James A. Peters, medical director of the Cystic Fibrosis Foundation, which has its headquarters in Atlanta, commented: "We eagerly await the results of Dr. Wallach's studies because of the importance of an animal model to both basic and clinical research on cystic fibrosis."

He noted that Dr. Wallach will participate in a May 25-26 workshop in Bethesda, Md., on the animal model for the study of cystic fibrosis which will be jointly sponsored by the U.S. National Institute of Arthritis, Metabolism, and Digestive Disease and the Cystic Fibrosis Foundation.

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From: Tom Sellers, Science Ed.

Fig. 7-6 C)

Lancet article, November 1985 supporting authors work
(congenital selenium deficiency as cause of cystic fibrosis).

THE LANCET, NOVEMBER 30, 1985

1238

Activity	Average time (min/day)		
	Pregnant (n=31)	Lactating (n=31)	NPNL (n=53)
Personal	969	918	678
Domestic	294	198	307
Child care	23	172	35
Social	55	62	195
Field work	51	77	161
Animal care	32	13	37
Travel	2	..	19
Leisure	7	..	8
Other occupation	7
Business

NPNL = non-pregnant, non-lactating (age 20-59).

and 2010 (NPNL) kcal. This suggests that changes in activity pattern alone could account for a reduction in energy expenditure of about 16% between non-pregnant and pregnant states in these women. The predictions of daily energy expenditure are supported by our estimates of energy intake in the same women, also by 24 h recall, which were 1606±83 (pregnant) and 1997±88 (NPNL) kcal (mean±SEM).

Durnin et al speculate that the scope for changes in physical activity may vary from one population to another. We believe that in rural south India, where the normal level of physical activity is high, significant changes in activity occur in pregnancy and lactation. These may occur to such an extent that the energy intake and energy expenditure of pregnant women may be 15-20% below that of non-pregnant non-lactating women.

Department of Human Nutrition,
London School of Hygiene
and Tropical Medicine,
London WC1E 7HT

G. MCNEILL
P. R. PAYNE

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SELENIUM DEFICIENCY, CYSTIC FIBROSIS, AND PANCREATIC CANCER

SIR,—In 1979 Wallach¹ advanced his environmental selenium deficiency theory of cystic fibrosis (CF), based on observations in a primate, questionnaires to 120 families with at least one affected child, and an understanding of the complex interactions between nutritional factors that promote or retard lipid peroxidation.² He concluded that CF could be "an acquired environmental disease that can be produced by a deficiency of selenium, zinc, and riboflavin and exacerbated by diets also low in vitamin E and rich in polyunsaturated fatty acids". This unorthodox view was dismissed³ and concern was expressed about the recommendation of supplementary doses of selenium, since there was "lack of any evidence as to selenium deficiency" in CF children⁴ (indeed, the implication was that selenium supplements with 25 µg selenium yeast daily had contributed to the deaths of two children). Dr Stead and colleagues (Oct 19, p 862) now provide clear evidence of selenium, with or without vitamin E, deficiency in young adults with the disease and raise the spectre of cancer (pancreatic and extrapancreatic) if the deficiencies are uncorrected.

The dilemma would be resolved if, instead of focusing on antioxidants alone, attention was also directed towards factors that increase the demand on tissue antioxidant stores—for example, increased production of oxygen and other chemical radicals via cytochromes P450. Our studies in patients with chronic pancreatitis illustrate this principle^{5,6} and strongly suggest that this disease is a

casualty of heightened, but unmitigated, "oxidative detoxification reactions". A modified concept in CF, with inappropriately high cytochrome P450 activities as the basic genetic defect—but which could be compounded by environmental factors—provides a framework within which published observations can be rationalised.⁷

(1) In patients with CF, as in chronic pancreatitis, theophylline clearance is raised,^{8,9} indicating increased activities of hydrocarbon-inducible forms of cytochromes P450. The overlap between inherited and acquired exocrine pancreatic disease is further evidenced in the report of a family in which two members had CF and three had calcifying chronic pancreatitis.⁹

(2) Lesions resembling CF macroscopically and/or microscopically (tubular complexes) can be produced in animals by injecting carbon tetrachloride,¹⁰ implanting benzo(a)pyrene,¹¹ or rendering the animals deficient in selenium.¹ These dissimilar methods share the ability to drive the mono-oxygenase/antioxidant axis in the direction of lipid peroxidation—by generating reactive drug intermediates, inducing cytochromes P450 and thereby increasing production of oxygen radicals, or depleting radical quenchers, respectively.

(3) Tissues affected in CF are just those which retain cytochromes P450 activities after birth.¹²

(4) Mucus secretion, so characteristic a feature in CF, subserves a role in antioxidant protection.¹³

(5) The reported increases in lactoferrin and lysosomal enzymes in the serum and lipofuscin in tissues of CF patients are explicable—the first retards lipid peroxidation, the second reflects the vulnerability of lysosomes to oxygen radicals, and the third is a manifestation of excessive lipid peroxidation.

(6) Inducibility of some forms of cytochrome P450 is genetically determined; the placenta is generously endowed with mono-oxygenases; some environmental pollutants linger within the body long enough to cause placental enzyme induction in subsequent conceptions;¹⁴ and prenatal induction of the mono-oxygenases can persist into adulthood. All these facts—and many others—allow the flexibility that is needed for any concept in the context of CF.⁷

To return to the question of antioxidant supplementation in CF, our evolving concepts suggest the need to titrate dosage to demand: this can be achieved only if all three components of the axis are considered (ie, inducers, promoters of induction, and antioxidants). The corollary is that "normal" serum levels of antioxidants are no guarantee that tissue levels are optimum in the face of chronically increased demand.

University Department of Gastroenterology,
Manchester Royal Infirmary,
Manchester M13 9WL

JOAN M. BRAGANZA

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Genesis

A series of interviews, autopsies and laboratory investigations have provided a plausible explanation of the genesis of human muscular dystrophy (myopathies - MD) and its variable presentations (miscarriages, cardiomyopathy heart disease, spinal muscular atrophy (SMA), liver necrosis, cystic fibrosis, fibromyalgia, etc.).

Muscular dystrophy (myopathies, MD) in select populations of American Amish in Adams, Allen and Switzerland Counties and Keshan cardiomyopathy in Keshan County northeastern China occur in extraordinarily high rates. Conventional medical theories view human muscular dystrophy (myopathies - MD) as a genetically transmitted disease and view Keshan disease (cardiomyopathy) as a disease of a mycotoxin (aflatoxin) contamination of stored grains or a viral myocarditis.

A comparison of the environment (soil and food levels of selenium), diets and lifestyle of the residents of Keshan County, China and Adams, Allen and Switzerland Counties, Indiana, USA reveals a remarkably similar pattern.

In both the Keshan County population and the Indiana Counties populations there are two very different demographic groups - the larger parts of the populations are the "modern" and "sophisticated" urban dwellers who primarily use diverse outside sources of food purchased from large national grocery chains; the smaller populations in both counties are

subsistence farmers (Chinese minorities and Amish farmers) who live primarily off of the land with either none or minimal outside sources of food.

In both Keshan County (Qiqihar University) and Adams, Allen and Switzerland Counties (Purdue University) there is a well documented extreme deficiency of the trace mineral selenium in the local soil (less than 0.1 ppm selenium levels). As a result of the universally recognized pathological consequences of selenium deficient soils, all animal feeds must be supplemented with preventative and therapeutic levels of selenium to prevent losses from muscular dystrophy (myopathies, MD), yet humans living on foods grown in the very same deficient soil are proactively encouraged by the medical community to "eat well and to not waste money" by supplementing with vitamins and minerals.

Both the peoples of Keshan County - China and Adams, Allen and Switzerland Counties, Indiana, USA grow wheat, barley, rye and oats, consume a significant portion of their calories as whole grain breads, noodles and cereals and also use wheat flour in fried food batter, gravies, sauces, meat balls and beer.

The daily consumption of whole grains (wheat, barley, rye and oats) produces a high rate of gluten intolerance (celiac disease, leaky gut syndrome, colitis, irritable bowel syndrome, inflammatory bowel disease, ulcerative colitis, Crohn's Disease, diverticulitis, appendicitis, etc.) and the attendant mal-absorption syndrome exacerbates the trace mineral deficiencies in the soil (less than 0.1 ppm of selenium) and therefore the food and contributes to extraordinary rates of miscarriage (as many as 3 to 12 per mother of MD children) and deficiency diseases such as muscular dystrophy, myopathies, cystic fibrosis, Keshan Disease (cardiomyopathy), spinal muscular atrophy (SMA), Down's Syndrome, congenital deafness, cerebral palsy, cleft palate, cleft lip, hypothyroidism (cretinism), etc.

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Serendipitous Insights Involving Nonhuman Primates

William R. Morton and Kathryn Swindler

William R. Morton, V.M.D., is Director of Paris NHP, Edmonds, Washington. At the time of manuscript preparation, Dr. Morton was a Professor of Comparative Medicine at the University of Washington and Director of the Washington National Primate Research Center (WNPRC), Seattle, Washington. Kathryn Swindler is a Technical Specialist at the WNPRC.

Abstract

Serendipity is discussed as a form of controlled chaos, a phenomenon in a class with synchronicity and other actions affecting research in terms of theory versus observation (e.g., "optional stopping"). Serendipity is a fundamental aspect of basic research, a profitable and normal outcome in the context of "informed observation." The serendipitous finding fits into the following pattern: it is unanticipated, anomalous, and strategic. All observations that have meaning must fit into some context in the observer's mind or suggest a revolutionary new context. It is critically important to maintain access to the resources provided by established primate centers and similar laboratories to capitalize in a timely way on serendipitous findings and to benefit from valuable discoveries made in more directly targeted development investments. Examples are given of serendipitous insights gained in experimentation and observation relative to nonhuman primate research, including both broad and narrow topics. Genomics, which uses comparison-based strategies and capitalizes on the DNA sequences of genetic information, presents what might seem the basis for endless serendipity because nonhuman primates are likely to share most genes present in the human genome. Other topics discussed include infant behavior, birth periodicity, leprosy, cystic fibrosis, environmental enrichment, endocrinology, drug development, and the rapidly expanding study of infectious diseases and pathogen-based bioterrorism.

Key Words: nonhuman primate; observation; research; serendipity; synchronicity

Serendipity or Informed Observation?

One does not need to look very far in the annals of science and scientific laboratory research to find examples of serendipity or the related concept of synchronicity. An early citation of both phenomena centers on the Augustinian monk Gregor Mendel, whose order encouraged him to learn. He set out to do so, as instructed, in the monastery gardens, and from this work arose the foundations for modern genetics (Luria et al. 1981). This scenario has been cited as serendipity: Why not Brother Abbot? Why not the library or vivarium? Perhaps the monastery fathers had an inkling of what kind of mind

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the monastery gardens, and from this work arose the foundations for modern genetics (Luria et al. 1981). This scenario has been cited as serendipity: Why not Brother Abbot? Why not the library or vivarium? Perhaps the monastery fathers had an inkling of what kind of mind they were dealing with. Perhaps the pairing of Mendel and the garden may indeed have resulted purely from chance and the results from serendipity. Mendel himself might consider the eventual development of a prenatal test for Tay-Sachs disease (Direen 2000) a serendipitous result of his studies, although it also may be the predictive result of a cumulative store of vast amounts of research and knowledge and a defined line of inquiry.

That no one recognized Mendel's achievement in the mid-1850s certainly is not serendipitous. However, the simultaneous rediscovery in 1900 of Mendel's rules of heredity by three scientists, Erich Tschesnak von Scysenegg, Karl Correns, and Hugo De Vries (Luria et al. 1981), may be cited as an example of synchronicity, certainly as accurately as the synchronicity of the theories of Darwin and Wallace. Serendipity and synchronicity are quite different occurrences but, as pointed out by Dr. Campbell in the Introduction to this issue (Campbell 2005), both occurrences rely on the breadth of knowledge and the quality of discipline in the researcher, and both may occur as a result of investigations that have yet more to discover.

Steven Shapin (2004), in his review of Robert K. Merton's book *The Travels and Adventures of Serendipity: A Study in Sociological Semantics and the Sociology of Science*, regards the ideal scientific position for encouraging discovery as somewhere between the extremes of inductive and deductive reasoning. Shapin proposes that one have a reasonable expectation of what is being sought so that both expected and surprise results will be recognized, yet at the same time be ignorant enough of what one may find (or open enough) to consider alternative outcomes (Shapin 2004). The term "serendipity" is frequently used to identify advantageous discoveries revealed in the search for something else. Yet whether or not an event is serendipitous may be in the eye of the beholder. Gary Fine and James Deegan assert that theory itself does not develop out of thin air, but instead comes from an amalgam of trends of thinking in favor at the time in the context of the researcher's own experience (Fine and Deegan 1996). Furthermore, it is also possible that observations may be discounted because they fit into one of the following categories: they are not in sufficient agreement with the theory advanced, hence pre-

William R. Morton, V.M.D., is Director of Paris NHP, Edmonds, Washington. At the time of manuscript preparation, Dr. Morton was a Professor of Comparative Medicine at the University of Washington and Director of the Washington National Primate Research Center (WNPRC), Seattle, Washington. Kathryn Swindler is a Technical Specialist at the WNPRC.

scouting the observer with an opportunity missed; or they are somehow flawed and rightly dismissed. Lewontin (2004) has noted that "the problem of how to cull observations honestly is a constant preoccupation." There is also the possibility that some experiments end as a result of "optional stopping," in which a researcher believes the theory to have been proven at an arbitrary point and so stops (Lewontin 2004). Author Lewontin notes that Mendel's results were possibly too close to the 3:1 ratio he expected and may represent a case of optional stopping, despite the validity of the results, which are now recognized.

Basic research necessarily incorporates serendipity. In the Scripps "Case For Giving" article on the Scripps website, 2001 Nobel Laureate K. Barry Sharpless references the following phrase, which is often attributed to Pasteur: "It is axiomatic of basic science research: chance favors the prepared mind." In another characterization of the concept, Fine and Deegan (1996) refer to "serendipity as controlled chaos." In addition, one might consider the concept in an even more broad way, as John Lennon has written: "Life is just what happens to you while you're busy making other plans" (Lennon 1981).

Serendipity Among Primates

Within the sphere of research involving laboratory animals, the nonhuman primate affords researchers a unique and valuable opportunity because humans, monkeys, and apes share many physiological, biochemical, and behavioral traits. These similarities reflect close genetic relationships and make the nonhuman primate an ideal animal model for many human diseases (Rand 2003). This special relationship also presents fertile ground for the serendipitous discovery. Most of the serendipitous occasions described below present such events in the course of nonhuman primate animal studies. Some are apocryphal. In particular cases, the nonhuman primate is involved in a chance find only in the testing phase after a serendipitous occurrence with human subjects (e.g., the case of minoxidil, a drug developed to control high blood pressure).

The examples of serendipity that appear below demonstrate the classic serendipitous condition—the coupling of insight with unplanned events (Fine and Deegan 1996). The following examples are briefly described and range from gross observations to fine endocrine detail: infant behavior, birth periodicity, leprosy, cystic fibrosis, environmental enrichment, founding of a primate center, endocrinology, and drug development.

Infant Behavior

Janice Beyer (2000), when an undergraduate student at the University of Wisconsin (Madison, WI), recounted in an article in *Organizational Behavior News* an example of serendipity in a well-known experimental study. Beyer was

performing computations in the Harlow laboratory when tests revealed that a recent shipment of pregnant rhesus monkeys was infected with tuberculosis. To avoid infecting the rest of the nonhuman primate colony, the mothers were euthanized postpartum, and the infants were put into individual cages to be fed and cared for by graduate students in an area of the laboratory easily observed by occupants of the laboratory going about their daily routine. Harry Harlow, knowledgeable and well accustomed to the behaviors of infant rhesus, saw something in the behavior of this particular group that differed from his prior observational experience of nonhuman primate infants. When another shipment of pregnant rhesus was received, he again separated the newborns, even though the mothers were healthy, and so began his famous experiments on mothering. Beyer comments that research students are taught to make predictions from extant theories, and that by testing their predictions, they test the theories. Testing theory-based hypotheses is not the best way to generate new insights or help us understand phenomena but can instead block understanding (Beyer 2000). The method of understanding that Beyer supports includes observing the setting and phenomenon to be studied so that something not anticipated by extant theory, if it occurs, can be understood in context and utilized.

Harlow's studies of attachment and mother love arose serendipitously from his efforts to breed rhesus monkeys for his work on brains and intelligence. Infants, particularly in the early weeks or months, are generally sheltered by permissive adults. This period is crucial for the development of social skills. Laboratory experiments by Harlow and his associates during the 1950s and -60s demonstrated that when certain such experiences are not part of the animal's early life, the damage to the animal may be irreparable or very difficult to correct later in its life. The Harlow deprivation studies and work on social development in rhesus monkeys have been of major importance to theories of early child development and socialization and to psychiatry.

Birth Periodicity

Serendipity was active at the University of Stirling, Wales, in discovering an additional periodicity in the births of nonhuman primates as perceived by the husbandry staff. Although circadian periodicity is the rule, species active by day giving birth at night, and vice versa (Jolly 1973), may also be characterized by the following other recurrent periods: annual periodicity, especially in habitats that undergo marked seasonal changes over the yearly cycle (Lancaster and Lee 1965); and lunar cyclicity, at least for prosimians. Additionally, Lancaster and Lee discovered "circum-weekly periodicity, i.e., differences over days of the seven-day week." The authors postulate that the additional periodicity is induced by laboratory conditions that combine to create a statistically significant clustering of prosimian births in the laboratory on weekends rather than weekdays.

This clustering is influenced, they believe, by the following factors:

- The greater the difference in routine of a captive colony between weekdays and weekends;
- The more "nervous, sensitive or difficult" the species (e.g., *Cacajao rubicundus* vs. *Macaca mulatta*);
- The more normal the rearing and housing conditions (McGrew and McLuckie 1984).

With the current emphasis on establishing successful breeding colonies, these findings add a practical focus to the field of nonhuman primate research.

Leprosy

Research into the incidence and treatment of leprosy gained momentum with the serendipitous discovery of a spontaneous case of leprosy in a single sooty mangabey (Rand 2003). Experimental leprosy was subsequently established by intravenous and intradermal inoculation of the *Mycobacterium leprae* in mangabeys, rhesus monkeys, and African green monkeys, producing disease that strongly resembles leprosy in humans. Since then, it has been reported that a second monkey contracted leprosy from the first monkey (Gormus et al. 1988). The animals had been housed in direct contact with each other. Clinical symptoms appeared in the second animal nearly 7 yr after lesions first appeared in the original monkey. This development suggested that the disease either passed from animal to animal or was acquired from an unknown common third source, and that where human leprosy is endemic, a potential zoonosis exists in wild monkeys. Although it has been proven that leprosy has zoonotic potential, this serendipitous finding is important for its demonstration of transmission and the identification of an animal model for the disease.

Cystic Fibrosis

Emory University (1978) reported that "a classic textbook case" of cystic fibrosis as found in humans had been identified in a nonhuman primate, an animal in which the disease had not been described previously. An assistant veterinary pathologist (whose name was withheld by Emory) unexpectedly discovered the disease during the routine autopsy of a 6-mo-old male rhesus monkey that died of unknown causes. The diagnosis was confirmed by Victor Nassar, an Emory pediatric pathologist at Atlanta's Grady Memorial Hospital, and by John Easterly, a pathologist at the Chicago Lying-In Hospital and national authority on cystic fibrosis. The monkey, one of a group being studied for the space program, instead provided the first nonhuman primate model of cystic fibrosis. Yerkes Center Veterinary Pathologist Harold McClure said, "We are very fortunate that the rhesus monkey is the animal model that was found

by [the doctors] because more is known about this animal than about any other nonhuman primate. They are also available for research in fairly large quantities."

Environmental Enrichment

One instance of serendipity in the 1940s ultimately led to programs that promote psychological well-being programs for nonhuman primates in the research laboratory (Cohen 2003). Psychologist Donald Hebb found that rats he raised in his home, a more challenging environment than the laboratory, displayed greater intelligence and problem-solving skills. His observations developed through a number of steps into the field of Environmental Enrichment. One of the significant steps involved a group led by Mark Rosenzweig, Professor Emeritus of Graduate Studies at the University of California-Berkeley. Rosenzweig's group, in the early 1960s, reported that rats studied in environmentally enriched housing showed unexpected thickening of the cerebral cortex and increased numbers of neurons and synapses. Investigators increasingly have come to realize that animals raised without sufficient stimulation do not develop full growth of brain or full behavioral capabilities (Cohen 2004). Primate centers such as the Washington National Primate Research Center have developed sophisticated programs of environmental enrichment and psychological well-being as an outgrowth of these earlier studies.

Founding of a Primate Center

Carolyn Poirot (2002) described the following incident of serendipity in the Fort Worth Star Telegram, July 7, 2002:

"Founded 60 years ago by Texas oilman Tom Slick as an independent, nonprofit biomedical research institution, Southwest Foundation was established on a 5,000-acre ranch covered with mesquite. A serendipitous discovery in the spring of 1956 launched what would become the foundation's best-known work. . . .

A scientist from the foundation was at Louisiana State University's School of Medicine studying atherosclerosis with an LSU pathologist when a colleague sent them the aorta of a 16-year-old female baboon that had died of natural causes at New Orleans' Audubon Park zoo.

They found that the baboon's aorta closely resembled the human aorta—and, more important, the baboon had developed atherosclerotic lesions remarkably similar to those they had seen in autopsies on people who died of coronary artery disease. They knew immediately that baboons could teach them a lot about the development of human heart disease.

Two years later, the National Institutes of Health awarded the Southwest Foundation a grant to es-

establish a colony of baboons for medical research, and the Texas Heart Association awarded the institution \$10,000 a year, for five years, to construct large outdoor pens where the baboons could live in colonies. The primate center was born."

Currently, the Southwest Foundation for Biomedical Research (SFBMR¹, San Antonio, TX) is one of the largest primate centers in the world. SFBMR maintains 3,700 baboons that are used in research on a wide array of human diseases, including atherosclerosis.

Endocrinology

In a study conducted with the rhesus monkey at Duquesne University (Pittsburgh, PA), investigators attempted to determine the role of the ovary in the prepubertal hiatus of gonadotropin secretion. They concluded that the open loop activity of the gonadotropin-releasing hormone pulse generator during juvenile development of the female monkey is only partially suppressed due to prepubertal suppression of gonadotropin by the ovary (Pohl et al. 1995). The authors also report the serendipitous finding that juveniles separated from their mothers and subsequently placed in individual cages demonstrated a temporary but significant reduction in circulating gonadotropin concentrations.

Drug Development

Nonhuman primate models utilized in drug testing, compared with rodent or other laboratory models, may indicate a more predictable outcome and benefit for the human subject and decrease the time needed to advance to clinical trials. Many drugs in current use are the result of purely serendipitous events (Williams 1993). Particularly in the case of antimalarial drugs now in use, most were not developed from preidentified targets but instead, from the serendipitous identification of the antimalarial activity of natural products such as quinine and artemisinin, compounds chemically related to natural products or compounds active against other infectious pathogens (e.g., antifolates and tetracyclines) (Fidock et al. 2004.) These examples include the class of antidepressant drugs for which the animal model is not a good predictor (Palfreyman et al. 2002). Recently, neuroimaging has been utilized in drug development to identify both the biochemical and functional characteristics of particular drugs. Positron emission tomography (e.g., magnetic resonance imaging) allows a researcher to address "whether a compound has a central effect, where that effect occurs, in what relationship to dose, with what

behavioral implications, and in what relationship to other compounds" (Brown 2004). The use of this technology increases the efficacy of preclinical development using non-human primates.

The drug minoxidil is an example of serendipity in drug development. The arterial vasodilator minoxidil was originally intended to treat hypertension but was unexpectedly found to cause the growth of thick hair from follicles that normally produced only fine hair (Chader and Wyngaarden 2003). The drug operates by opening potassium channels in vascular smooth muscle. Wisconsin National Primate Research Center Hideo Uno and colleagues demonstrated that by applying it externally to the bald front scalp of the stump-tailed monkey, minoxidil both grossly and microscopically enlarges vellus follicles to the size of mid-sized and terminal follicles (Uno et al. 1987). The macaque became the animal model for androgenetic alopecia for the testing of minoxidil and later proscar and RU58841 (Kamel 2004).

Capitalizing on Serendipity

Serendipity appears to be most prevalent and productive when an investigator who is well informed and experienced in a subject carefully observes the course of a project and looks for and considers all that the project suggests, rather than simply determining whether or not it proves the hoped-for result. The serendipitous finding then fits into the following pattern: it is unanticipated, anomalous, and strategic (Fine and Deegan 1996). Every observation, to have meaning, must fit into some context in the observer's mind (Słowiczek and Peters 2000) or suggest a revolutionary new context. What the well-informed, insightful, and attentive mind discovers to be an exciting next logical step that is waiting to be discovered someone else may see as a chance, fortuitous discovery—or may miss altogether. In the former case, the result can be groundbreaking. In the latter case, the stage is set for synchronicity in the form of logical progression to the next step by multiple investigators. Serendipity, if one uses the term, favors the prepared mind, and an active field of inquiry opens the door for synchronicity.

Optimally, financing for research should provide a substantial proportion of funds to create a scenario that allows researchers to proceed in some agreed-upon general direction, yet to follow their noses wherever the trail may lead. Without a doubt, collaborative work with other departments and even other fields of interest increases the occasion for serendipity. The involvement of traditional laboratory researchers with nonacademic ventures may also increase this happenstance, as long as the focus of the combined research is not too narrow.

An example of extreme narrowing of scope occurs in the current field of pharmacological research, which traditionally involves nonhuman primates in the testing phase. According to Joseph Schlessinger, the William H. Prusoff Professor of Pharmacology at Yale University (New Haven,

¹Abbreviations used in this article: SWFBR, Southwest Foundation for Biomedical Research; WNPRC, Washington National Primate Research Center.

CT). "It is becoming more and more difficult to develop drugs in an academic setting. . . . The technology requires such a huge investment that academic labs can't compete with the Pfizers and Mercks" (Wortman 2003). Indeed, endlessly sifting data in an effort to find scientific truth is counterproductive and expensive.

The current trend is to move away from serendipity and happenstance. Science and industry, in drug investigation and development, are looking toward evidence and statistics. Rather than hunches, an automated, industrial-scale analysis of compounds, or high-throughput screening, is the norm (Wortman 2003). In such a research environment, it is critically important to maintain and develop access to the resources provided by established primate centers and similar laboratories to capitalize in a timely way on serendipitous findings such as those described in this article and to profit from valuable discoveries made in more directly targeted development investments. Serendipity without access to the necessary fundamental research tools and environments that constitute a solid foundation may produce nothing.

Comparative Genomic Analysis/High Throughput

Genomics is among the most recent branches of biology to use comparison-based strategies. This technology capitalizes on the DNA sequences of genetic information, presenting what might seem the basis for endless serendipity because nonhuman primates are likely to share most genes present in the human genome (Nobrega and Pennacchio 2003). Comparative genomic tools include phylogenetic shadowing, combinatorial paradigms, and high-throughput screening, which allow analysis of a large number of experiments at the same time (Ng 2004). In the area of antibacterial research, early work relied on serendipitous discoveries of drug-like molecules that had certain properties without regard for their action mechanisms.

Recently, significant advances in the fields of genomics, high-throughput screening, and structural biochemistry have been made in the hunt for novel drug-target pairs that will be effective against drug-resistant bacterial infections (Lerner and Beutel 2002). A rational high-throughput screen versus a serendipitous one must be used. The approach is based on automation, validation, and integration of in vitro absorption-metabolism models and database management (Rodriguez 1997). According to one researcher, such screening is where "serendipity meets prediction" (Jessen 2000). Whereas early pharmaceutical discoveries were made by serendipity through clinical testing, these technological advances in molecular and cellular biology, together with genetics and genomics, may reveal more about the disease itself and drive such research toward a disease-based approach. High-throughput screening allows a wide chemical diversity to be applied to obtain tractable leads, which can then be optimized by the medicinal chemist (Ratti and Trist 2001).

Serendipity Close to Home

The selection of the Washington National Primate Research Center (WNPRC¹) for current studies into the origins and nature of the 1918 flu epidemic came about serendipitously. Beginning in the 1970s, in response to restrictions on importation of nonhuman primates (Rand 2003), breeding programs were established for many species that included the rhesus monkey and the chimpanzee. The pigtail macaque (*Macaca nemestrina*) was chosen as the research animal-of-choice at the WNPRC because of its perineal tumescence and detumescence, making it a good model for studies into reproductive timing. This early use of the pigtail macaque and establishment of a reproductive colony supported many studies indicating that the pigtail is susceptible to a number of infectious diseases, including AIDS, and provided a useful model for the important study of this and other infectious diseases. The serendipitous result is that in addition to building on decades-long contributions to varied and valuable studies, the WNPRC was the recipient of established resources for stepping into the important arena of studying infectious diseases and pathogen-based bioterrorism.

It would not be surprising to find that these studies will themselves lead to unexpected contributions in other areas. Serendipity is opportunistic and as invasive as water. If one is to examine the world in a way that is intended to uncover new and sometimes unexpected information, then science itself is intrinsically surprising (Slowiczek and Peters 2000). To quote Dr. Sharpless, "I do chemistry the way I used to fish. . . . My training consisted of busily poking and perturbing the Manasquam River, a curriculum both urgent and leisurely, on that permitted exploration without assumptions. . . . When I became a bench- and desk-bound explorer, my method stayed the same" (Lerner 2004).

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