#### Biomedical Research: Using Animals and Humans in Science Research

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Summer Research Program

#### Subject Area:

Reading and Writing in the Science Classroom (Biology 1 class, Unit on Being a Scientist)

#### Grade Level:

9-12 High School

#### Purpose:

This lesson is intended to introduce the students to the necessity of biomedical research; using animals and humans in science research. This lesson will include case studies as well as videos to introduce biomedical research. Many, if not all, of the students have a direct connection to animal and human testing due to illnesses, immunizations, and other life issues. This lesson plan will not only inform the students about scientific discoveries that have led to better health in humans and other animals but it allows the students to read and understand scientific, academic language. Bringing scientific literature into the classroom is important for the students to understand science.

#### Length of Lesson:

Five days, 45 minute periods each

Day 1: Introduce the topic of Biomedical research (using animals and humans in science research), students take a survey on their beliefs about various uses of animals in society, students write a paragraph on what they believe to be true about animal testing and its risks and benefits, watch 2 video clips on animal research and care. Take notes on the videos for future discussions.

Day 2: Define and explain the vocabulary words. Show a PowerPoint presentation on Rabies and Smallpox, read case studies on scientific discoveries about Rabies and Smallpox, students write a paragraph on what they believe to be true about human testing and its risks and benefits, class discussion about why we need to use animals and humans in biomedical research.

Day 3: Complete a "Direct Impact" activity to highlight the various aspects of their lives affected by biomedical research, student's research a topic based on the "Direct Impact" activity. This activity will utilize computer skills and research.

Day 4: Students share out on their research topic (no more than 5 to 10 minutes), students retake the survey about their beliefs on various uses of animals in society, students write a three to five paragraph

essay about their beliefs and concerns after learning about animal and human research (this activity is a homework assignment).

Day 5: Students have a discussion about biomedical research and chose a topic to study about biomedical research outside of the classroom. This activity will utilize computer skills and research.

#### **Objectives:**

- 1. Students will be able to discuss controversial ideas from different viewpoints with their peers.
- Students will utilize the internet to find information.
- 3. Students will discuss and evaluate reasons for and against animal research.
- 4. Students will relate ways in which animal research has helped people as well as animals.
- 5. Students will be able to read and understand a scientific case study.
- 6. Students will be able to identify the cause and effect relationship between animal and human testing and cures for diseases.
- 7. Students will be able to convey their opinions and thoughts about a scientific topic through writing.
- 8. Students will be able to defend their stand on a controversial topic in science using facts and data to support their conclusions.
- 9. Students will learn the academic language of the study of immunology.
- 10. Students will understand how the immune system of the human works.

#### Standards:

#### **Colorado Science Standards**

Standard 3: Life Science: Students know and understand the characteristics and structure of living things, the processes of life, and how living things interact with each other and their environment. (Focus: Biology-- Anatomy, Physiology, Botany, Zoology, Ecology)

Benchmarks 1, 5, 12, 13, 14, 16, 17, 18

Standard S: Students understand that the nature of science involves a particular way of building knowledge and making meaning of the natural world.

Benchmarks 1, 2, 3, 4, 5, 6

#### Colorado Reading Standards for Informational Text in the Science Classroom

- 2. Determine a central idea of a text and analyze its development over the course of the text. Including how it emerges and is shaped and refined by specific details; provide an objective summary of the text.
- 4. Determine the meaning of words and phrases as they are used in text, including figurative, connotative, and technical meanings; analyze the cumulative impact of specific word choices on meaning and tone (e.g. how the language of a court opinion differs from that of a newspaper).

#### Colorado Reading Standards for Literacy in the Science Classroom:

2. Determine the central ideas or conclusions of a text; trace the text's explanation or depiction of a complex process, phenomenon, or concept; provide an accurate summary of the text.

#### Colorado Writing Standards for Literacy in the Science Classroom:

- 2. Write informative/explanatory texts, including the narration of historical events, scientific procedures/experiments, or technical processes.
- 4. Produce clear and coherent writing in which the development, organization, and style are appropriate to task, purpose, and audience.

#### **National Science Standards**

Unifying Concepts and Processes - Unifying concepts and processes help students think about and

U2 a, c; U4a; U5 a, b

Science as Inquiry – Science as inquiry requires students to combine processes and scientific knowledge with scientific reasoning and critical thinking to develop their understanding of science.

A1 a; A2 a, f

Life Sciences – Life sciences focuses on science facts, concepts, principles, theories, and models, that are important for all students to know, understand and use.

C4 e; C3 a; C6 b

Science and Technology -- An understanding of science and technology establishes connections between the natural and designed world, linking sciences and technology.

E1 a, b, c, d, e; E2 a, b, c, d, e

Science in Personal and Social Perspectives – A personal and social perspective of science helps a student to understand and act on personal and social issues. This perspective builds a foundation for future decision making.

F1 b; F5 b; F6 b, c, d

History and Nature of Science – The history and nature of science illustrate different aspects of scientific inquiry, the human aspect of science and the role that science has played in the development of various cultures.

G1 b, c; G2 a, b, c; G3 a, b, c, d

#### Vocabulary:

The following terms will be defined prior to viewing the PowerPoint presentation and reading the case studies. The students will write the definitions in their science notebooks to use as a reference when reading the case studies.

immunization	inhalation	immunity	virulence
inoculant	variolation	cow Pox	eradication
virus	infection	escarification	virologist
bacteria	symptomatic	small Pox	rabies
hydrophobia	disease	exanthems	inoculation

### Materials:

in vivo

Copies of case studies for students to read

Triumph and Controversy Pasteur's Preventive Treatment of Rabies as Reported in JAMA by Leonard J. Hoenig, MD

Edward Jenner and the history of smallpox and vaccination by Stefan Rieder, MD, PhD

Video clips (computer, overhead projector) http://www.fbresearch.org

Handouts of pre and post surveys http://www.fbresearch.org

Handout of "Direct Impact" questions http://www.fbresearch.org

Examples of how to write a good paragraph (graphic organizer)

Rubric to provide requirements for good paragraph writing and for grading purposes (can be modified for ELL and Special Education students)

#### **Preparation and Procedures:**

There should be enough copies of the following materials for all students:

- 1. Survey
- 2. Case study on rabies
- 3. Case study on smallpox
- 4. Questions for the "Direct Impact" activity
- 5. Rubrics
- 6. Writing template

The times for each activity will vary depending on the reading level of the students; the availability of computers for the research; and the number of students in the class for sharing presentations, think pair/share, and other questions that arise.

The survey should take no longer than 10 to 15 minutes. The discussion about the student's answers will take 15 to 30 minutes depending on the questions.

The "Direct Impact" activity should take no more than 15 minutes. Then the teacher must assign the appropriate topic to each student. The research can take 30 to 45 minutes depending on the availability of computers and computer skills of the students. If the research is not completed during the class period, the student needs to work on this at home as homework.

The response writing should not take more than 5 to 10 minutes at the end of the period. These quick writes are to make sure the students understand the discussions, case study readings, and video segments watched.

There are 5 days to complete this unit. If the activities are running long, or short, the teacher can adjust the times and eliminate one day altogether if needed.

#### Safety:

This lesson does not require any materials other than written case studies and video clips. No chemicals or equipment are necessary.

Questions to Ask: (HOOK, to get the students interested in the topic)

- 1. Do you think you have any connection to animal or human research and testing? If so, what are they?
- 2. Would you be willing to let scientists use you or your family to test a new drug?
- 3. How would your life change if there were no medicines or vaccines?

#### Analysis Questions (Formative Assessments):

These questions can be asked during whole class discussions. The students will need to be able to defend their answers using examples from the case studies read and the video clips viewed. They also can state personal examples to support their opinions.

- 1. What would happen if we were not immunized as children?
- 2. Do you think that animals are necessary in research to develop cures for diseases?
- 3. What would happen to humans if we could not use animals or humans in research for cures for diseases?
- 4. Explain what you would do to avoid medicines, products, and treatments that were researched on animals.

5. You are a doctor. A patient is going to receive a medicine that has not been researched on any living organism and he/she is one of the first to receive it. Explain what you would say to that patient to reassure him/her.

#### **Suggestions for Assessments:**

Students take a pre and post survey on their beliefs about various uses of animals in society.

Students participate in a "Direct Impact" activity to see which students have connections to certain events using animals and humans in biomedical research and write a paragraph on the topic that relates to them individually.

Students participate in whole class discussions, and think/pair share discussions.

Students write a three to five paragraph essay stating their conclusions, and opinions about the pros and cons of biomedical research based on the case studies read, video clips watched, and class discussions.

#### Where to Go From Here:

1. Students can research a new disease and see what is happening with it in regards to immunizations.

Additional research topics for students:

- a. Does immunity wear off as we age?
- b. Should there be animal and human testing to discover cures for new diseases?
- c. What should be done for those countries that do not have a good immunization program?
- d. What would happen if we stopped all research involving animals or humans?

#### Support for ELL and Special Ed Students:

Utilizing the ESL Para, have the students read the material in small groups, translate the case studies into Spanish, answer direct questions about the reading (See attached questions).

Give the students a modified version of the case study that is not as long or as detailed.

Have Para available to translate the video content if necessary.

Modify the writing assignment for the students using a modified rubric.

Allow students to work on "Direct Impact" research project as a group and not individually.

#### References and Resources

JAMAnetwork.com

Frontiers in IMMUNOLOGY

#### Student Activity Plan

#### Purpose of Activities:

This lesson is intended to introduce you to the necessity of biomedical research; using animals and humans in science research. This lesson will include case studies as well as videos to introduce you to animals and humans in research. Many if not all of you have a direct connection to animal and human testing due to illnesses, immunizations, and other health issues. This lesson plan will not only inform you about scientific discoveries that have led to better health in humans and other animals but it also allows you to read and understand scientific academic language. Bringing scientific literature into the classroom is important for you to understand science.

#### **Activities:**

You will be reading articles, watching video clips, taking a survey and working on a report that you will present to the class. After all of the above activities are completed, you will then write a 3 to 5 paragraph essay to support your views on biomedical research using animals and humans.

#### Materials:

You will be given the surveys and requirements for the research and report. You will also be given a template to help you plan your paragraph and a rubric to guide your writing.

#### Questions for the ELL or Special Education Learner

#### <u>Smallpox</u>

- 1. Where did smallpox originate?
- 2. What were some of the effects of smallpox?
- 3. What is the name of the virus that causes smallpox?
- 4. Who was Edward Jenner?
- 5. How is smallpox and cowpox related?
- 6. How did Jenner treat people with smallpox?
- 7. How are James Phipps and Sarah Nelms connected?
- 8. How did they help to find a cure for smallpox?
- 9. Do we still have smallpox disease today?

#### **Rabies**

- 1. Where did rabies originate?
- 2. What were some of the effects of rabies?
- 3. Who is the primary carrier of rabies?
- 4. What is the name of the virus that causes rabies?
- 5. Who was Louis Pasteur?
- 6. How did Pasteur treat people with rabies?
- 7. Is there a cure for Rabies today?

THAT REALLY BITES!!!
THE STORY OF RABIES

Scientist Louis Pasteur
was a French chemist and
microbiologist.

One of the most important
founders of medical
microbiology.

Remembered for his
remarkable
breakthroughs in the
causes and preventions of
diseases

LOUIS PASTEUR

Caused by the Rhabdovirus

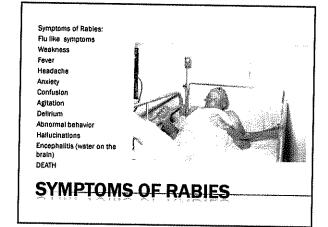
Rabies is Latin for "Madness"

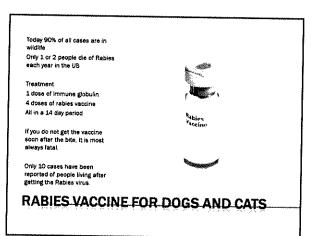
RABIES VIRUS

Domestic animals such as dogs, cats, ferrets, and cows

Wild animals such as raccoons, foxes, skunks, coyotes, and bats

Contracted through the saliva of the animal as well as brain tissue





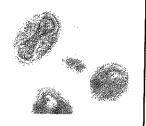
SMALLPOX
NO LONGER A THREAT

Edward Jenner
was a n English
Physician and
scientist.

He is considered
to be the "Father
of Immunology".

EDWARD JENNER

The smallpox virus is called either variola major or variola minor.



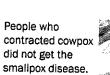
**SMALLPOX VIRUS** 

Virus that is related to the smallpox virus. It is found on cow's udders.



**COWPOX VIRUS** 

Sores on the cow's udders. People who milked the cows got this disease.





**COWS WITH COWPOX** 

Symptoms:
Flu like symptoms
Muscle aches
Headaches
Lesions
Blisters
Affect the blood vessels of the
skin, mouth, and throat
The blistars are fluid filled and
leave acers, blindness, and limb
deformities.

Get the virus by breathing it in have to be within 6 feet of the
carrier.

It is a highly contagious person
to person disease.

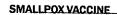
SMALLPOX

People are now given the vaccine and the last case of smallpox was found October 26, 1977.



INOCULATING A PATIENT WITH SMALLPOX VACCINE

We are now immunized against smallpox and it is no longer a threat to the health of the world.







# The Use of ANIMALS IN BIOMEDICAL RESEARCH

## ANIMAL USE OPINION SURVEY

A	uge.	L 3-1U	LJ11-20	LJ 21-30	L_J 41-50	over 51							
Se	ex:	Female	☐Male										
R	ead e	ach of the follo	wing statements	s and respond by c	ircling the number	er which BEST ron	****		·				
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1.			t, or other anima	al as a pet?			6	51 OK	.AT 4	2	~	OKAY	
2.		utering/spaying					6	5		3	2	1	
3.		eping animals ir	•				6	5	4	3	2	1	
4.			pets at school?				6	5	4	3	2	1	
5.			· s, or other anim	als?			6	5	4	3	2	1	
6.		ing meat?					6	5	4	3	2	1	
7.	Usi	ng animals for c	lissection in the	classroom?			6	5	4	3	2	1	
8.		ning or hunting					6	5	4	3	2	1	
9.	Fish	ning or hunting	for food?				6	5	4	3	2	1	
10.				y of household pro	oducts?		6	5	4	3	2	4	
		lawing a pet car					6	5	4	3	2		
12.	. Wea	aring fur coats?					6	5	4	3	2	4	
13.	. Wea	aring or using it	ems made from	leather?			6	5	4	3	2	1	
				tiveness of new dr	uas?		6	5	4	3	2	1	
		ull fighting?			<b></b>		6	5	4	3	2	1	
16.	Usin	ng animals to tra	in surgeons on	surgical technique	5?		6	5	4	3	2	1	
17.			litary researchin	-			6	5	4	3	2	1	
				- id cures for pet an	imals?		6	5	4	3	2	1	
			gs to assist the b	•			6	5	4	3	2	1	
				ople in collapsed	buildings?		6	5	4	3	2	1	
			ormances at a cir		<u>.</u>		6	5	4	3	2	1	
22.	Shov	wing cats and/or	dogs at shows?				6	5	4	3	2	1	
23.	Train	ning animals to a	act for TV and co	ommercials?			6	5	4	3	2	1	
24.	Using	g therapy dogs t	for the elderly o	r mentally retarde	d?		6	5	4	3	2	1	
			from sheep wo				6	5	4	3	2	1	
			ing dairy produc				6	5	4	3	2	1	
			r school team m				6	5	4	3	2	1	
			a cows in radeo				_			-		•	

#### DIRECT IMPACT

Take this list and mingle with others in the room. If someone can answer "yes" to one of the questions, have them write their name in the appropriate blank. Each person in the room may write their name only once on each person's sheet. The goal is to get a different name by each item.

Do you know someone who ...?

- I. Takes medicine for high blood pressure.
- 2. Is a survivor of cancer.
- 3. Has a cat that gets an annual Rabies vaccination.
- 4. Has had a broken bone repaired.
- 5. Has taken antibiotics for an ear infection.
- Uses detergent to wash dishes.
- 7. Takes cough syrup for a cough.
- 8. Puts adhesive bandages on a scraped knees or elbows.
- Has had some type of surgery.
- 10. Receives regular fluoride treatments on their teeth.
- 11. Takes pain reliever for a headache.
- 12. Currently has polio.
- 13. Is receiving regular shots for allergies.
- 14. Uses toothpaste everyday.
- 15. Feeds their pet(s) pet food everyday.
- 16. Has taken antibiotics for a cold or flu.
- 17. Uses fabric softener on their laundry.
- 18. Has had smallpox.
- 19. Has a dog that takes heartworm prevention medicine.
- 20. Received an organ transplant.
- 21. Wears contact lenses.
- 22. Receives insulin shots for diabetes.
- 23. Takes a daily vitamin.
- 24. Has had a sprained ankle or twisted knee.

Topic Sentence		
Key Idea/Detail	Explain	
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ey rucuy Detail	Explain	
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y Idea/Detail	Explain	

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# The "Kid-Friendly" 4-Point Rubric for Students

— 4 Points: My writing is clear and does what the prompt asked me. My errors in spelling and punctuation are so few they wouldn't bother you.	— 3 Points:  My writing is pretty good. I did what the prompt asked of me, but I did not give enough information or details with my answer. I need to add more. I made very few errors in spelling and punctuation.	— 2 Points:  My writing is not clear enough, and I drifted away from the prompt. I need to use more details and be sure they are accurate. I did not notice the errors I made in spelling and mechanics.	— 1 Point:  My writing needs to be focused and organized. I need to write more to the prompt and include a lot more details and information. I have too many mistakes in spelling and mechanics.
Content and Organization  — I used important details and information.  — I did not forget or lose the main idea when I added interesting details.  — I was careful to organize the ideas	Content and Organization  lexplained my main idea, but I need to add more information. I need to choose more important details and take out those that aren't. Sometimes my writing moves	Content and Organization  I need to write more clearly and be sure I keep the purpose in mind. I need to be sure I have told all that I can to make my paper complete.  I may not have included enough	Content and Organization  I have not paid enough attention to what I am supposed to write.  I need to include a lot more information.  I need to organize my ideas so that my writing is clear.
logically and effectively.  — I made sure all of my details connect to the prompt.	away from the main point or details get in the way of the main point.  — I need to put my writing in a more logical order.  — I need to connect ideas so that they all fit well together.	details, or I may have spent too much time on the details and forgot the purpose.  — My writing may seem more like a list than like a paragraph with ideas that go together.  — I need to be sure my writing stays on topic.	<ul> <li>I need to make sure my writing is complete and about the topic.</li> </ul>
Style and Fluency  — My word choice is powerful. The words fit the prompt well.  — I used interesting words or descriptions to make pictures in the reader's mind.  — My sentences are not all the	Style and Fluency  — Most of my words go well with the purpose.  — At times I could have chosen better words.  — My sentences are well written, but I did not try different kinds of	Style and Fluency  — I need to use words that are strong and effective.  — My writing is not smooth, and I repeat myself at times.  — Sometimes you can't read my writing, and I need to be more	Style and Fluency  I need to write so that others can read it.  I need to choose a variety of words and be sure that they are just right.
same. I used different types of sentences.  — My writing is neat and almost perfect.	sentences.  — Most of my paper is neat and easy to read. — I may have made a mistake in grammar, spelling, or punctuation, but you can still understand what I mean.	careful about spelling and mechanics.	I need to write complete sentences.  My mistakes in spelling and mechanics keep my reader from understanding what I meant.

The state of the s	4 (Advanced) 100-90 pts.	3 (Proficient)90-80 pts.	2 (Partially Proficient)	1 (Unsatisfactory) 70-60 pts.
Demonstrates	Fully focused on the	- Reasonably focused	Dartially formed on	att no sinct form
Understanding	topic/skills	on the topic/skills	the topic/skills	topic/skills
	<ul> <li>Information is relevant</li> </ul>	Information is	<ul> <li>Information is</li> </ul>	Information is
	& insightful	relevant	incomplete or	irrelevant or missing
	<ul> <li>Main ideas &amp; supporting</li> </ul>	<ul> <li>Main ideas &amp; details</li> </ul>	irrelevant	Does not provide main
	details are thoroughly	are clear	<ul> <li>Main ideas &amp; details</li> </ul>	ideas or details
	developed	<ul> <li>Includes accurate</li> </ul>	are missing or vague	Includes limited or
	<ul> <li>Answers are accurate &amp;</li> </ul>	information straight	<ul> <li>Includes partially</li> </ul>	inaccurate information
	in student's own words	from the text	accurate information	
	(paraphrased)			
Completion &	Exceeds assignment's	Meets assignment's	Meets most of	Meets few of the
Organization	requirements	requirements,	assignment's	assignment's
	<ul> <li>Effectively organized in</li> </ul>	<ul> <li>Is organized in an</li> </ul>	requirements; some	requirements
***************************************	an easy to follow	easy to follow	elements may be	Disorganized; difficult
	manner	manner	missing	to follow
			<ul> <li>Limited organization;</li> </ul>	
			may be difficult to	
			follow.	
Language Usage	<ul> <li>Sophisticated use of</li> </ul>	Correct but simplistic	Mostly correct	Incorrect use of
	language skills (includes	use of language skills;	language skills; may	language skills; errors
	advanced vocabulary &	may lack precision	include errors that do	impede understanding
	varied sentence	(subject/verb	not impede	(includes many
	structure, etc.)	agreement, modifiers,	understanding (may	sentence fragments or
		punctuation,	include sentence	run-ons, incorrect
		paragraphing,	fragments or run-ons,	punctuation & spelling,
		complete sentences,	incorrect punctuation	etc.)
		spelling, etc.)	& spelling, etc.)	***************************************

#### History of Neurology

# Triumph and Controversy

# Pasteur's Preventive Treatment of Rabies as Reported in JAMA

Leonard J. Hoenig, MD

• Louis Pasteur's vaccine against rabies, introduced 100 years ago, was greeted by the American medical community with a mixture of praise and skepticism. These sentiments as well as details of Pasteur's landmark discoveries appeared in late-19th-century articles in The Journal of the American Medical Association.

(Arch Neurol 1986;43:397-399)

For the next few moments let us gaze into medicine's past. The time is 100 years ago and the events center around one of the great achievements in scientific history. Our vision will be guided by words written a century ago, exactly as they appeared in The Journal of the American Medical Association.

#### TRIUMPH

The following communication entitled "Letter from Paris" appeared in JAMA in 1885 and was filed by JAMA's foreign correspondent. It concerns the first human trial of a new preventive technique against rabies, developed by a noted Frenchman named Louis Pasteur:

Before his departure for Arbois, M. Pasteur had under treatment a little boy of nine years of age, brought by his parents from Alsace, where he had been bitten in the haunches, on both legs, and in the hand. This child was taken direct to M. Pasteur, who, for the first time, applied his method, but whether it be successful or not remains to be seen. The accident occurred about three weeks ago.

Some weeks later there appeared in JAMA an update entitled "Letter from London" on the condition of Joseph Meister, the young lad bitten by the rabid dog:

In the space of ten days the child was inoculated no fewer than thirteen times on the same system as M. Pasteur has successfully tried with dogs. This was three months ago, and until now nothing has occurred in the condition of the patient to shake the operator's faith in his method.

Accepted for publication March 28, 1985. From the Department of Internal Medicine, Division of General Internal Medicine, University of South Florida, Tampa.

Reprint requests to 12901 N 30th St, Box 19, Tumpa, FL 33612 (Dr Hoenig).

Pasteur's method for preventing rabies after a bite was the culmination of five years of careful research. Prior to his efforts, little was known about the cause of this ancient and feared disease other than it was somehow transmitted through the bite of a rabid animal and by contact with its saliva. There was no successful treatment for this invariably fatal infection, although 19th-century medical literature was filled with anecdotal "cures" that employed dubious methods such as galvanism and asparagus feedings.<sup>3</sup>

There were two preventive measures in use, however, that were beneficial. Local wound care had been practiced since the days of Celsus and, in retrospect, probably helped to reduce viral titers transmitted by the bite. In addition, following the demonstration by Zinke in 1804 that rabid dog saliva was infectious, muzzle laws were passed in several Scandinavian countries. These measures helped to curtail human exposure to the virus.

Pasteur's own interest in rabies came at the end of his long and brilliant scientific career. His earlier work on fermentation had revealed how microorganisms participated in the biological processes of life.' This research, along with his subsequent publications on anthrax and chicken cholera, helped to establish the germ theory of disease. This novel concept proposed that unseen pathogens caused illness.

Pasteur was especially interested in the phenomenon of immunity. Jenner's cowpox inoculation was the only human vaccine in use at that time. How this technique successfully prevented smallpox, however, was not understood. While investigating anthrax and avian cholera, Pasteur had discovered that the key to producing a successful vaccine was to find methods to decrease the virulence of the pathogen and then to inoculate the weakened forms to induce immunity against the disease.'

Pasteur's research on rabies highlights the entire thrust of his life's work. Although he would never actually observe the microorganism responsible for rabies, he had no doubt that he was dealing with an infectious agent whose size was simply beyond the resolution of his microscope.\* He called rabies a "virus" although he did not realize that he was dealing with a new class of infectious agents that was different from bacteria.

Pasteur's initial work on rabies had established for the first time in medical history that an infection involved the central nervous system. He had demonstrated that rabid nervous tissue was infectious especially when inoculated beneath the dura mater.

Pasteur could not establish an in vitro means of propagating rabies in his laboratory. Instead he was forced to develop an ingenious in vivo culture technique that involved passing the disease from animal to animal by subdural inoculation of rabid nervous tissue.<sup>8,10</sup>

In 1884, JAMA published an overview of Pasteur's animal experiments on rabies. His data had revealed that serial subdural passage of the virus among different animal species could alter the incubation period: "The virulence of the poison of rabies is increased when it is transmitted from rabbit to rabbit...." Pasteur postulated that the virulence of the virus was inversely proportional to its incubation period. He termed the new virulent strain of rabies virus "fixed" because the viral incubation period had declined from two weeks to become fixed at seven days during passage among rabbits. Pasteur also found that "If the poison of rabies be transmitted from the dog to the monkey, and then from monkey to monkey, its virulence diminishes with each inoculation."

Taking advantage of this means of viral attenuation, Pasteur had successfully immunized laboratory animals:

If we apply rationally the results I have just communicated, we can easily render dogs proof against rabies. The investigator may have at his disposal the virus of rabies in different degrees of attenuation; the non-fatal kinds preserving the economy from the effects of the more active and fatal kinds."

Le ceinturon actuel fera place su ceinturon à boucle des tiseilleurs algériens; il sers mani de daux cartouchières sur le devant. Ce ceinturon serait placé sons la vareuse, dont les pans de devant serent disposés à la façon de la giuppa de l'armée italiense.

Le celature hygiénique de finnelle terz remplacée par la celature bisue des zousves.

Enfin, la chaussure ells-même sera entièrement transformée. On s'est arrâté à un modèle se rapprochant de celle des mostagnards : chaussures fortes à semelles doubles débordant l'empeigne et ganies de clous à forte tâte.

Le \$2° batellion de chasecurs, à Embrun, va être pouvu des nouveaux effets d'habillement et d'équipement; il en fera l'essai pendant les marches-mancauves qu'il est appelé à faire dans les Alpes du 4° mai au 4° août.

L'Académie des besuz-arts vient de recevoir un lege considérable. M Chenavard, belle-sœur du pieture de cenom, est morte, ces jours derniers, boulevard Beaumarcheis. Dans le but d'honorer la nom de Chenavard, elle s lestitué l'École das besuz-arts sa légatairs universelle.

L'héritage comprend une somme de trois millions et des collections artistiques importantes.

M= Chenavard a, dens son testament, spécifié irès nette-



ment les conditions qu'elle mot à ce legs. La rente ( . trois millions sers affectés à des encouragements appuris sus l'École, dans la forme que l'administration jugers la plus convenable et la plus utile. Rien de ses callections artistiques ne pourre étre vende, dispersé, L'École des bosux-erts doit egalement conserver tout son mobilier, sans en distraire ni céder quei que ce soit. Lorsqu'elle mourre, l'Etat bei fera un enterrement de première ciasso el sura le deveir de faire reveair son corps à Paris, en qualque endroit que le déces sit eu lieu.

Vendredi, on e enterre me construire la ceremonia e cité faite conformément aux indications de son tretament, dont l'administration des besurants a reçu communication odicitelle.

Le legs Chenavard est le plus important de ceux que l'Académie des beaux-aris a reçus jusqu'à ce jour.

L'administration des postes va faire modifier ses indicateurs des holtes aux lettres de Paris, placées dans les débits de labac, de manière à fournir au public, sur le départ et le distribution des lettres, des renseignements apparents et parfaitement lisibles.

Dans le souvel indicateur déjà en service, notamment à côté du théêtre Déjazet, boulevard du Temple, rue des Ma-

Louis Pasteur examining young English girl bitten by rabid dog.

Pasteur would later develop a more reliable technique for weakening the rabies virus through a process of desiccation in which "fixed" rabid spinal cord was air dried. This technique was fully described in an 1891 article that appeared in JAMA:

Immediately after the death of the animal the spinal cord is removed with antiseptic precautions, and suspended in an aseptic flask containing some solid caustic potash, whose hygroscopic properties enable it to dry the air of the flask. When first removed the cord contains a virus of high but constant virulence, but gradually loses this virulence during the drying process, and in 15 days the poison has completely disappeared.<sup>12</sup>

To produce immunity, Pasteur progressively inoculated animals first with the fully dried spinal cord and on succeeding days with increasingly fresh virulent material. This technique proved successful even when administered after an exposure to rabies virus.<sup>13</sup> Pasteur's innovative use of postexposure prophylaxis took

advantage of the disease's prolonged incubation period in order to induce immunity before the illness became clinically manifest.

With his dramatic treatment of Joseph Meister, Pasteur had introduced the second human vaccine into medical history. Soon, exposed patients from all over the world would travel to Paris for Pasteur's antirables inoculations. Within a year his protocol had spread across the Atlantic, as noted by JAMA in 1886:

The first inoculation against hydrophobia ever done in America was performed July 5 by Dr. Valentine Mott, in the Carnegie Laboratory. Dr. Mott's patient was Harold Newell, seven years old, who was bitten by a dog presumably mad June 24. The inoculation was made from a solution of hydrophobic virus obtained by Pasteur himself from the brain of a dog dead from rabies, and transmitted by him through 110 rabbits.<sup>14</sup>

#### CONTROVERSY

For Louis Pasteur and his associates, Emile Roux, Charles Chamber-

land, and Louis Thuillier, the initial clinical successes were indeed a notable medical accomplishment. Unfortunately there were cases in which the vaccine failed, and patients died from rabies. Doubts and criticism began to emerge, as at an 1886 Philadelphia County Medical Society meeting in Pennsylvania. Highlights from this meeting were published in JAMA:

The paper of the evening was read by Dr. Dulles, who gave a summary of all of Pasteur's communications on the subject of hydrophobia, and endeavored to show that the evidence adduced from time to time by Pasteur in support of his various theories does not recommend them very strongly.<sup>15</sup>

Dr Charles Dulles was a Fellow of the College of Physicians and of the Academy of Surgery of Philadelphia. He was of the firm opinion that rabies was not an infectious disease and he even doubted the existence of rabies as a unique illness. Dulles strongly opposed Pasteur's preventive treatment of rabies, and in 1894 he leveled the following charges in a report to the Pennsylvania Medical Society, excerpts of which appeared in JAMA:

... that not only has Pasteur's method "increased the number of deaths from hydrophobia," but that "there has been added to these a large number of deaths due to inoculation of what ought to be called 'Pasteur's disease.'"

By "Pasteur's disease" Dulles was probably alluding to neuroparalytic complications that were occasionally noted following vaccination against rabies. It was unclear at that time whether these paralytic events represented a variant form of clinical rabies ("dumb" rabies) or were instead a direct complication of Pasteur's method of treatment.

Years later it would be demonstrated that injection of uninfected nervous tissue into laboratory animals could produce paralytic disturbances with central nervous system inflammation and demyelination, presumably on an allergic basis. 14, 19 These findings suggested that to develop a safe rabies vaccine, the nerve tissue content of the inoculum had to be minimized or eliminated. The duck embryo vaccine and the currently recommended human diploid cell vaccine were produced to meet this goal.

A somewhat less emotional evaluation of the Pasteur treatment came in the form of an 1887 report from the British hydrophobia commission that had been appointed to inquire into the validity of Pasteur's claims. An abstract of this report appeared in JAMA in 1887 and it listed the problems faced by the committee in assessing the true benefits of the vaccines:

1) the difficulty of determining whether the bites were really those of rabid animals; 2) the probability of hydrophobia in persons bitten by dogs that were certainly rabid depending very much on the number and character of the bites, whether they were on exposed parts or parts protected by clothing; and in all cases in the amount of bleeding; 3) in all cases the probability of infection may be affected by speedy cauterising or excision of the wounded parts, or by various washings, or other methods of treatment; 4) the unequal danger of bites of different species of animals. and even of different dogs. In some groups of cases the percentage of deaths among persons bitten by dogs believed to have been rabid has been estimated at only 5 per cent., in others at 60 per cent.; and the mortality from the bites of rabid wolves has been variously estimated at from 35 to 90 per cent.20

Comparing Pasteur's data with his-

torical controls, the commission, however, concluded that

The committee think it, therefore, certain that the inoculations practiced by M. Pasteur have prevented the occurrence of hydrophobia in a large proportion of those who, if they had not been so inoculated, would have died of that disease.<sup>20</sup>

In 1889 the eminent pathologist William H. Welch reviewed the rabies debate. Welch was a remarkable physician who had studied under the great Robert Koch and other distinguished European scientists.21 In 1884, at the age of 34, he was appointed professor of pathology at the newly formed Johns Hopkins University. Welch brought to Johns Hopkins the best traditions of European medicine and established an innovative training program that emphasized the importance of microbiology and pathology. Welch spoke favorably of Pasteur's prophylactic treatment of rabies and his views appeared in JAMA:

Dr. Welch collected from Pasteur's reports for the first half of 1888 those bitten on the head and face by animals proven experimentally to be rabid. There were 59 cases, with 4 deaths from rabies during treatment and 2 following treatment. Of the latter 1 was seized three days after the cessation of treatment, and it is reasonable to suppose that in this case the treatment was begun too late. If this case and those dying during treatment be excluded, there remain 54 cases with 1 death, a mortality of 1.85 per cent.

In view of the universally conceded high death rate following bites on the head and face by rabid animals, this result leaves no room for doubt as to the efficiency of Pasteur's treatment, although it is not unfailing.<sup>22</sup>

Despite the supportive comments of Welch, Pasteur's antirables treatment has remained controversial largely because it never was subjected to an experimentally controlled study in man. Use of a control group in research was not unheard of during the late 19th century. Pasteur himself had dramatically used animal controls to prove the value of his anthrax vaccine during a large public demonstration in 1881 at Pouilly-le-Fort.

However, when it came to treating people, Pasteur felt reluctant to withhold his vaccine from those whom he felt were in danger simply to prove an academic point. Perhaps it was a mark of Pasteur's greatness that he allowed his humanistic concerns to override his usual scientific rigor.

#### CONCLUSION

Perched atop the 20th century we have briefly looked back on the monu-

mental work of one remarkable man. On the centennial anniversary of Louis Pasteur's brilliant investigation of rabies virus infection let us conclude with a quote from an 1891 issue of *JAMA*, which properly assessed his place in medical history:

Great as has been the good accomplished by PASTEUR in treatment of hydrophobia, his greatest honor lies in the possibility which he has opened up of preventing other infectious diseases by conferring an artificial immunity. His glory is as great as that of JENNER.<sup>13</sup>

The Figure is reproduced from L'Univers Illustré (April 16, 1886) with the permission of the Pasteur Institute, Paris.

I appreciate the efforts of Trude Feldman in typing the manuscript.

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# Edward Jenner and the history of smallpox and vaccination

STEFAN RIEDEL, MD, PHD

In science credit goes to the man who convinces the world, not the man to whom the idea first occurs. —FRANCIS GALTON

Por many centuries, smallpox devastated mankind. In modern times we do not have to worry about it thanks to the remarkable work of Edward Jenner and later developments from his endeavors. With the rapid pace of vaccine

development in recent decades, the historic origins of immunization are often forgotten. Unfortunately, since the attack on the World Trade Center on September 11, 2001, the threat of biological warfare and bioterrorism has reemerged. Smallpox has been identified as a possible agent of bioterrorism (1). It seems prudent to review the history of a disease known to few people in the 21st century.

Edward Jenner (Figure 1) is well known around the world for his innovative contribution to immunization and the ultimate eradication of smallpox (2). Jenner's work is widely regarded as the foundation of immunology—despite the fact that he was neither the first to suggest that infection with cowpox conferred specific immunity to smallpox nor the first to attempt cowpox inoculation for this purpose.

#### SMALLPOX: THE ORIGIN OF A DISEASE

The origin of smallpox as a natural disease is lost in prehistory. It is believed to have appeared around 10,000 BC, at the time of the first agricultural settlements in northeastern Africa (3, 4). It seems plausible that it spread from there to India by means of ancient Egyptian merchants. The earliest evidence of skin lesions resembling those of smallpox is found on faces of mummies from the time of the 18th and 20th Egyptian Dynasties (1570–1085 BC). The mummified head of the Egyptian pharaoh Ramses V (died 1156 BC) bears evidence of the disease (5). At the same time, smallpox has been reported in ancient Asian cultures: smallpox was described as early as 1122 BC in China and is mentioned in ancient Sanskrit texts of India.

Smallpox was introduced to Europe sometime between the fifth and seventh centuries and was frequently epidemic during

the Middle Ages. The disease greatly affected the development of Western civilization. The first stages of the decline of the Roman Empire (AD 108) coincided with a large-scale epidemic: the plague of Antonine, which accounted for the deaths of almost 7 million people (6). The Arab expansion, the Crusades, and the discovery of the West Indies all contributed to the spread of the disease.

Unknown in the New World, smallpox was introduced by the Spanish and Portuguese conquistadors. The disease decimated the

local population and was instrumental in the fall of the empires of the Aztecs and the Incas. Similarly, on the eastern coast of North America, the disease was introduced by the early settlers and led to a decline in the native population. The devastating effects of smallpox also gave rise to one of the first examples of biological warfare (1, 7). During the French-Indian War (1754-1767), Sir Jeffrey Amherst, the commander of the British forces in North America, suggested the deliberate use of smallpox to diminish the American Indian population hostile to the British. Another factor contributing to smallpox in the Americas was the slave trade because many slaves came from regions in Africa where smallpox was endemic.

Smallpox affected all levels of society. In the 18th century in Europe, 400,000 people died annually of smallpox, and one third of the survivors went blind (4). The symptoms of smallpox, or the "speckled monster" as

it was known in 18th-century England, appeared suddenly and the sequelae were devastating. The case-fatality rate varied from 20% to 60% and left most survivors with disfiguring scars. The case-fatality rate in infants was even higher, approaching 80% in London and 98% in Berlin during the late 1800s.

The word variola was commonly used for smallpox and had been introduced by Bishop Marius of Avenches (near Lausanne,



Figure 1. Edward Jenner (1749–1823). Photo courtesy of the National Library of Medicine.

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Switzerland) in AD 570. It is derived from the Latin word varius, meaning "stained," or from varus, meaning "mark on the skin." The term small pockes (pocke meaning sac) was first used in England at the end of the 15th century to distinguish the disease from syphilis, which was then known as the great pockes (8).

#### **VARIOLATION AND EARLY ATTEMPTS OF TREATMENT**

It was common knowledge that survivors of smallpox became immune to the disease. As early as 430 BC, survivors of smallpox were called upon to nurse the afflicted (9). Man had long been trying to find a cure for the "speckled monster." During medieval times, many herbal remedies, as well as cold treatment and special cloths, were used to either prevent or treat smallpox. Dr. Sydenham (1624–1689) treated his patients by allowing no fire in the room, leaving the windows permanently open, drawing the bedclothes no higher than the patient's waist, and administering "twelve bottles of small beer every twenty-four hours" (10).

However, the most successful way of combating smallpox before the discovery of vaccination was inoculation. The word is derived from the Latin inoculare, meaning "to graft." Inoculation referred to the subcutaneous instillation of smallpox virus into nonimmune individuals. The inoculator usually used a lancet wet with fresh matter taken from a ripe pustule of some person who suffered from smallpox. The material was then subcutaneously introduced on the arms or legs of the nonimmune person. The terms inoculation and variolation were often used interchangeably. The practice of inoculation seems to have arisen independently when people in several countries were faced with the threat of an epidemic. However, inoculation was not without its attendant risks. There were concerns that recipients might develop disseminated smallpox and spread it to others. Transmission of other diseases, such as syphilis, via the bloodborne route was also of concern.

Inoculation, hereafter referred to as variolation, was likely practiced in Africa, India, and China long before the 18th century, when it was introduced to Europe (9). In 1670, Circassian traders introduced variolation to the Turkish "Ottoman" Empire. Women from the Caucasus, who were in great demand in the Turkish sultan's harem in Istanbul because of their legendary beauty, were inoculated as children in parts of their bodies where scars would not be seen. These women must also have brought the practice of variolation to the court of the Sublime Porte (4, 10).

Variolation came to Europe at the beginning of the 18th century with the arrival of travelers from Istanbul. In 1714, the Royal Society of London received a letter from Emanuel Timoni describing the technique of variolation, which he had witnessed in Istanbul. A similar letter was sent by Giacomo Pilarino in 1716. These reports described the practice of subcutaneous inoculation; however, they did not change the ways of the conservative English physicians.

It was the continued advocacy of the English aristocrat Lady Mary Wortley Montague (Figure 2) that was responsible for the introduction of variolation in England (10). In 1715, Lady Montague suffered from an episode of smallpox, which severely disfigured her beautiful face. Her 20-year-old brother died of the illness 18 months later. In 1717, Lady Montague's husband, Edward Wortley Montague, was appointed ambassador to the



Figure 2. Lady Mary Wortley Montague (1689–1762). Photo courtesy of the National Library of Medicine.

Sublime Porte. A few weeks after their arrival in Istanbul, Lady Montague wrote to her friend about the method of variolation used at the Ottoman court. Lady Montague was so determined to prevent the ravages of smallpox that she ordered the embassy surgeon, Charles Maitland, to inoculate her 5-year-old son. The inoculation procedure was performed in March 1718. Upon their return to London in April 1721, Lady Montague had Charles Maitland inoculate her 4-year-old daughter in the presence of physicians of the royal court.

After these first professional variolation procedures, word of the practice spread to several members of the royal family (11). Charles Maitland was then granted the royal license to perform a trial of variolation on six prisoners in Newgate on August 9, 1721. The prisoners were granted the king's favor if they submitted to this experiment. Several court physicians, members of the Royal Society, and members of the College of Physicians observed the trial. All prisoners survived the experiment, and those exposed to smallpox later proved to be immune. In the months following this very first trial, Maitland repeated the experiment on orphaned children, again with success. Finally, on April 17, 1722, Maitland successfully treated the two daughters of the Princess of Wales. Not surprisingly, the procedure gained general acceptance after this last success.

#### THE SPREAD OF VARIOLATION

In Europe, where the medical profession was relatively organized, the new methods of variolation became known quickly among physicians. Since there was also a demand for protection against smallpox, physicians soon began the variolation procedure on a massive scale. Although 2% to 3% of variolated persons died from the disease, became the source of another epidemic, or suffered from diseases (e.g., tuberculosis and syphilis) transmitted by the procedure itself, variolation rapidly gained popularity among both aristocratic and common people in Europe. The case-fatality rate associated with variolation was 10 times lower than

that associated with naturally occurring smallpox. In the 1750s more European princes died of smallpox, giving further impetus for the use of variolation (3). Among those variolated were Empress Marie-Therese of Austria and her children and grandchildren, Frederick II of Prussia, King Louis XVI of France and his children, and Catherine II of Russia and her son. King Frederick II of Prussia also inoculated all his soldiers. In fact, variolation was widely practiced in Europe until Jenner's discovery.

The regular practice of variolation reached the New World in 1721 (9). Under the guidance of the Rev. Cotton Mather (1663–1728) and Dr. Zabdiel Boylston (1679–1766), variolation became quite popular in the colonies. Mather, a graduate of Harvard College, was always very interested in science and medicine. When a ship from the West Indies carried persons sick with smallpox into Boston in 1721, an epidemic broke out in Boston and other parts of Massachusetts. Mather wrote a cautious letter recommending immediate variolation. However, he persuaded only Dr. Boylston. With Mather's support, Boylston immediately started a variolation program and continued to inoculate many volunteers, despite many adversaries in both the public and the medical community in Boston. As the disease spread, so did the controversy around Mather and Boylston (12). At the height of the epidemic, a bomb was thrown into Mather's house.

To make their point, Mather and Boylston used a statistical approach to compare the mortality rate of natural smallpox infection with that contracted by variolation. During the great epidemic of 1721, approximately half of Boston's 12,000 citizens contracted smallpox. The fatality rate for the naturally contracted disease was 14%, whereas Boylston and Mather reported a mortality rate of only 2% among variolated individuals (12). This may have been the first time that comparative analysis was used to evaluate a medical procedure.

During the decades following the 1721 epidemic in Boston, variolation became more widespread in the colonies of New England. In 1766, American soldiers under George Washington were unable to take Quebec from the British troops, apparently because of a smallpox epidemic that significantly reduced the number of healthy troops (13). The British soldiers were all variolated. By 1777, Washington had learned his lesson: all his soldiers were variolated before beginning new military operations (14, 15). The success of variolation in the New World was not without effect on Europe. In fact, the rapid adoption of variolation in Europe can be directly traced to the efforts of Cotton Mather during the Boston smallpox epidemic in 1721. Although many British physicians remained skeptical even after Mather's success, the data he had published were eventually influential. Variolation was subsequently adopted in England and spread from there throughout Western Europe.

In 1757, an 8-year-old boy was inoculated with smallpox in Gloucester (4); he was one of thousands of children inoculated that year in England. The procedure was effective, as the boy developed a mild case of smallpox and was subsequently immune to the disease. His name was Edward Jenner.

#### **EDWARD JENNER**

Edward Jenner was born on May 17, 1749, in Berkeley, Gloucestershire, the son of the Rev. Stephen Jenner, vicar of Berkeley. Edward was orphaned at age 5 and went to live with his

older brother. During his early school years, Edward developed a strong interest in science and nature that continued throughout his life. At age 13 he was apprenticed to a country surgeon and apothecary in Sodbury, near Bristol (16). The record shows that it was there that Jenner heard a dairymaid say, "I shall never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face." It fact, it was a common belief that dairymaids were in some way protected from smallpox.

In 1764, Jenner began his apprenticeship with George Harwicke. During these years, he acquired a sound knowledge of surgical and medical practice (10). Upon completion of this apprenticeship at the age of 21, Jenner went to London and became a student of John Hunter, who was on the staff of St. George's Hospital in London. Hunter was not only one of the most famous surgeons in England, but he was also a well-respected biologist, anatomist, and experimental scientist. The firm friendship that grew between Hunter and Jenner lasted until Hunter's death in 1793. Although Jenner already had a great interest in natural science, the experience during the 2 years with Hunter only increased his activities and curiosity. Jenner was so interested in natural science that he helped classify many species that Captain Cook brought back from his first voyage. In 1772, however, Jenner declined Cook's invitation to take part in the second voyage (4).

Jenner occupied himself with many matters. He studied geology and carried out experiments on human blood (17). In 1784, after public demonstrations of hot air and hydrogen balloons by Joseph M. Montgolfier in France during the preceding year, Jenner built and twice launched his own hydrogen balloon. It flew 12 miles. Following Hunter's suggestions, Jenner conducted a particular study of the cuckoo. The final version of Jenner's paper was published in 1788 and included the original observation that it is the cuckoo hatchling that evicts the eggs and chicks of the foster parents from the nest (17, 18). For this remarkable work, Jenner was elected a fellow of the Royal Society. However, many naturalists in England dismissed his work as pure nonsense. For more than a century, antivaccinationists used the supposed defects of the cuckoo study to cast doubt on Jenner's other work. Jenner was finally vindicated in 1921 when photography confirmed his observation (19). At any rate, it is apparent that Jenner had a lifelong interest in natural sciences. His last work, published posthumously, was on the migration of birds.

In addition to his training and experience in biology, Jenner made great progress in clinical surgery while studying with John Hunter in London. Jenner devised an improved method for preparing a medicine known as tartar emetic (potassium antimony tartrate). In 1773, at the end of 2 years with John Hunter, Jenner returned to Berkeley to practice medicine. There he enjoyed substantial success, for he was capable, skillful, and popular. In addition to the practice of medicine, he joined two local medical groups for the promotion of medical knowledge and continued to write occasional medical papers (4, 18). He also played the violin in a musical club and wrote light verse and poetry. As a natural scientist, he continued to make many observations on birds and the hibernation of hedgehogs and collected many specimens for John Hunter in London.

While Jenner's interest in the protective effects of cowpox began during his apprenticeship with George Harwicke, it was



Figure 3. The hand of Sarah Nelms. Photo courtesy of the National Library of Medicine.

1796 before he made the first step in the long process whereby smallpox, the scourge of mankind, would be totally eradicated. For many years, he had heard the tales that dairymaids were protected from smallpox naturally after having suffered from cowpox. Pondering this, Jenner concluded that cowpox not only protected against smallpox but also could be transmitted from one person to another as a deliberate mechanism of protection. In May 1796, Edward Jenner found a young dairymaid, Sarah Nelms, who had fresh cowpox lesions on her hands and arms (Figure 3). On May 14, 1796, using matter from Nelms' lesions, he inoculated an 8-year-old boy, James Phipps. Subsequently, the boy developed mild fever and discomfort in the axillae. Nine days after the procedure he felt cold and had lost his appetite, but on the

next day he was much better. In July 1796, Jenner inoculated the boy again, this time with matter from a fresh smallpox lesion. No disease developed, and Jenner concluded that protection was complete (10).

In 1797, Jenner sent a short communication to the Royal Society describing his experiment and observations. However, the paper was rejected. Then in 1798, having added a few more cases to his initial experiment, Jenner privately published a small booklet entitled An Inquiry into the Causes and Effects of the Variolae Vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire and Known by the Name of Cow Pox (18, 10). The Latin word for cow is vacca, and cowpox is vaccinia; Jenner decided to call this new procedure vaccination. The 1798 publication had three parts. In the first part Jenner presented his view regarding the origin of cowpox as a disease of horses transmitted to cows. The theory was discredited during Jenner's lifetime. He then presented the hypothesis that infection with cowpox protects against subsequent infection with smallpox. The second part contained the critical observations relevant to testing the hypothesis. The third part was a lengthy discussion, in part polemical, of the findings and a variety of issues related to smallpox. The publication of the Inquiry was met with a mixed reaction in the medical community.

Jenner went to London in search of volunteers for vaccination. However, after 3 months he had found none. In London, vaccination became popular through the activities of others, particularly the surgeon Henry Cline, to whom Jenner had given some of the inoculant (4). Later in 1799, Drs. George Pearson and William Woodville began to support vaccination among their patients. Jenner conducted a nationwide survey in search of proof of resistance to smallpox or to variolation among persons who had cowpox. The results of this survey confirmed his theory. Despite errors, many controversies, and chicanery, the use of vaccination spread rapidly in England, and by the year 1800, it had also reached most European countries (10).

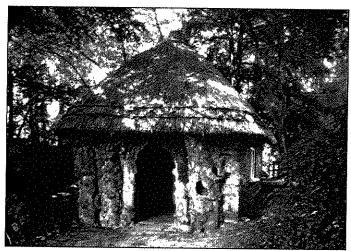


Figure 4. The Temple of Vaccinia. Photo courtesy of the Jenner Museum, Berkeley, Gloucestershire, England.

Although sometimes embarrassed by a lack of supply, Jenner sent vaccine to his medical acquaintances and to anyone else who requested it. After introducing cowpox inoculation in their own districts, many recipients passed the vaccine on to others. Dr. John Haygarth (of Bath, Somerset) received the vaccine from Edward Jenner in 1800 and sent some of the material to Benjamin Waterhouse, professor of physics at Harvard University. Waterhouse introduced vaccination in New England and then persuaded Thomas Jefferson to try it in Virginia. Waterhouse received great support from Jefferson, who appointed him vaccine agent in the National Vaccine Institute, an organization set up to implement a national vaccination program in the United States (20).

Although he received worldwide recognition and many honors, Jenner made no attempt to enrich himself through his discovery. He actually devoted so much time to the cause of vaccination that his private practice and his personal affairs suffered severely. The extraordinary value of vaccination was publicly acknowledged in England, when in 1802 the British Parliament granted Edward Jenner the sum of £10,000. Five years later the Parliament awarded him £20,000 more. However, he not only received honors but also found himself subjected to attacks and ridicule. Despite all this, he continued his activities on behalf of the vaccination program. Gradually, vaccination replaced variolation, which became prohibited in England in 1840.

Jenner married in 1788 and fathered four children. The family lived in the Chantry House, which became the Jenner Museum in 1985. Jenner built a one-room hut in the garden, which he called the "Temple of Vaccinia" (Figure 4), where he vaccinated the poor for free (10, 17). After a decade of being honored and reviled in more or less equal measure, he gradually withdrew from public life and returned to the practice of country medicine in Berkeley. In 1810, his oldest son, Edward, died of tuberculosis. His sister Mary died the same year and his sister Anne 2 years later. In 1815, his wife, Catherine, died of tuberculosis (17). Sorrows crowded in on him, and he withdrew even further from public life. In 1820, Jenner had a stroke from which he recovered. On January 23, 1823, he visited his last patient, a dying friend. The next morning Jenner failed to appear for breakfast; later that day he was found in his study. He had had a massive stroke. Edward

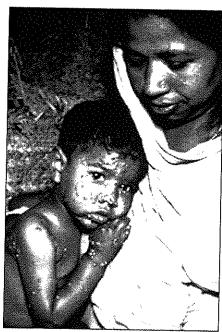


Figure 5. Smallpox in India, 1970s. Photo courtesy of the World Health Organization.

Jenner died during the early morning hours of Sunday, January 26, 1823. He was laid to rest with his parents, his wife, and his son near the altar of the Berkeley church.

#### CONCLUSION

Jenner's work represented the first scientific attempt to control an infectious disease by the deliberate use of vaccination. Strictly speaking, he did not discover vaccination but was the first person to confer scientific status on the procedure and to pursue its scientific investigation. During the past years, there has been a growing recognition of Benjamin Jesty (1737–1816) as the first to vaccinate against smallpox (21). When smallpox was present in Jesty's locality in 1774, he was determined to protect the life of his family. Jesty used material from udders of cattle that he knew had cowpox and transferred the material with a small lancet to the arms of his wife and two boys. The trio of vaccinees remained free of smallpox, although they were exposed on numerous occasions in later life. Benjamin Jesty was neither the first nor the last to experiment with vaccination. In fact, the use of smallpox and cowpox was widely known among the country physicians in the dairy counties of 18th-century England. However, the recognition of these facts should not diminish our view of Jenner's accomplishments. It was his relentless promotion and devoted research of vaccination that changed the way medicine was practiced.

Late in the 19th century, it was realized that vaccination did not confer lifelong immunity and that subsequent revaccination was necessary. The mortality from smallpox had declined, but the epidemics showed that the disease was still not under control. In the 1950s a number of control measures were implemented, and smallpox was eradicated in many areas in Europe and North America. The process of worldwide eradication of smallpox was set in motion when the World Health Assembly received a report in 1958 of the catastrophic consequences of smallpox in 63 countries (Figure 5). In 1967, a global campaign was begun under the

guardianship of the World Health Organization and finally succeeded in the eradication of smallpox in 1977. On May 8, 1980, the World Health Assembly announced that the world was free of smallpox and recommended that all countries cease vaccination: "The world and all its people have won freedom from smallpox, which was the most devastating disease sweeping in epidemic form through many countries since earliest times, leaving death, blindness and disfigurement in its wake" (22).

Scientific advances during the two centuries since Edward Jenner performed his first vaccination on James Phipps have proved him to be more right than wrong. The germ theory of disease, the discovery and study of viruses, and the understanding of modern immunology tended to support his main conclusions. The discovery and promotion of vaccination enabled the eradication of smallpox: this is Edward Jenner's ultimate vindication and memorial.

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