

*Occasional Notes***CLINICAL INVESTIGATION  
OF SMALLPOX IN 1767**

**I**N 1767, William Watson was the physician for the Hospital for the Maintenance and Education of Exposed and Deserted Children, universally known as the Foundling Hospital, which was established in 1739 to provide a home for some of London's abandoned children. His practice was devoted entirely to the care and treatment of children accepted into this charitable establishment. At the time, the leading cause of death among children in London was smallpox. The infection was endemic and killed about one in four children born in the city. When the Foundling Hospital was opened, the board of governors recognized that because large numbers of children were housed in dormitory rooms, they were at high risk for contracting the disease. To protect their charges, the governors ordered that all children who were not already immune to smallpox be inoculated.

Introduced in 1721 — 75 years before Jenner's studies of vaccination — inoculation was the practice of infecting a patient with a tiny amount of fluid from a smallpox pustule placed in a small incision or puncture wound, usually on the upper arm. Quantitative studies reported by James Jurin in 1722<sup>1</sup> and by Zabdiel Boylston in 1726<sup>2</sup> had established that mortality among inoculated persons was about 1 in 50, whereas mortality among patients with naturally acquired smallpox was about 1 in 6. By 1765, refinements in the technique of injecting the virus and complicated formulas for the pretreatment of recipients had reduced mortality to less than 1 in 500.

Although inoculation was widely used and relatively safe, there were a number of controversies about specific aspects of the practice. Watson had already satisfied himself that when the eruption appeared, allowing the inoculated children to play freely on the hospital grounds was preferable to keeping them in bed. Now he decided to study two other questions: What was the best source of the inoculum? Was mercury, then a popular component of the pretreatment regimen, beneficial?

Most doctors preparing patients for inoculation used a combination of a meatless diet and purgatives to expel matter from the stomach and bowels. Many also prescribed antimony and mercury, a mixture first suggested by Hermann Boerhaave as an antidote to the "variolous poison" that was thought to cause smallpox. Watson doubted that the poisonous mercury was beneficial, but since most fashionable phy-

sicians used it, he needed to have convincing evidence of its lack of efficacy before he rejected the substance. There was also no consensus on the best source of the inoculum. Some physicians used a very early lesion, some a mature pock, and others a late, almost resolved lesion as the source of the inoculum.

**AN EXPERIMENTAL DESIGN**

Watson designed a group of experiments to explore both issues. He recognized that he needed to study large groups of children of similar ages and both sexes, instead of testing only one or two children at a time. In addition, he took pains to make certain that all the children had the same diet, wore similar clothes, played in the same fields, and slept in the same dormitories. In each experiment, the children were inoculated at the same time and place with the same material. The only difference was the medical treatment they received. Watson understood that "it was proper also to be informed of what nature unassisted, not to say undisturbed, would do for herself."<sup>3</sup> In other words, he introduced an untreated control group.

On October 12, 1767, Watson performed his first experiment. Thirty-one children were divided into three groups and inoculated. Ten children (5 boys and 5 girls) received a mixture of mercury and jalap (a laxative) before and after the puncture, 10 children (5 of each sex) received an infusion of senna and syrup of roses (a mild laxative) on three occasions, and 11 boys received no medicines. Thin "watery ichor" from an early lesion on a patient with natural smallpox was used as the inoculum in all three groups.

Watson's brilliant idea was his method for measuring the effect of inoculation, which allowed him to compare the results in the three groups. At that time, physicians usually resorted to qualitative statements, such as "They all did well" or "They had few symptoms." Watson made the experiment quantitative. He had the hospital attendants count the number of pustules, or pocks, that appeared on each child. For over a century, physicians had known that there was a close correlation between the number of pocks and the prognosis. An eruption characterized by a small number of discrete pocks was associated with a favorable prognosis; an eruption in which the pocks were so numerous that they were confluent was associated with a poor prognosis. The results of this experiment are shown in Table 1.

Watson was concerned that an effect of mercury might not have been demonstrated because he had combined it with a strong laxative. Could it have passed through the children too quickly? On November 1, he performed a second experiment. A group of four boys and four girls were given three doses of mercury, a second group of four boys and four girls were given the infusion of senna and syrup of roses,

**TABLE 1.** POCK COUNT ACCORDING TO THE PREPARATORY REGIMEN IN CHILDREN INOCULATED WITH SMALLPOX.

PRETREATMENT	NO. OF CHILDREN	SOURCE OF INOCULUM*	NO. OF POCKS	MEAN†	P VALUE‡
Experiment 1		Early lesion			0.59§
Mercury plus jalap	10		25, 13, 12, 6, 5, 4, 4, 3, 0, 0	7.2	
Senna plus rose syrup	10		30, 5, 5, 5, 4, 4, 2, 2, 0, 0	5.7	
None	11		200, 17, 16, 16, 16, 16, 3, 2, 2, 0, 0	26.2	
Experiment 2		Mature lesion			0.06§
Mercury	8		440, 25, 21, 21, 21, 21, 20, 7	72.0	
Senna plus rose syrup	8		64, 26, 26, 26, 26, 26, 18, 3	26.9	
None	7		60, 15, 15, 15, 15, 3, 2	17.9	
Experiment 3		Late lesion			0.09¶
None	20		250, 168, 93, 45, 45, 45, 45, 45, 45, 45, 45, 4, 4, 4, 2, 0, 0	51.0	

\*The early lesion was from a patient with naturally acquired smallpox; the mature and late lesions were from inoculated patients.

†The mean was known to Watson as the “medium” and was the only calculation he could perform.

‡The P values were obtained with the Kruskal–Wallis test.

§The P value is for the comparison between either preparatory regimen and no pretreatment.

¶The P value is for the comparison of the results in the three no-pretreatment groups according to the source of the inoculum.

and a group of six boys and one girl were given nothing. The results are shown in Table 1. On this occasion, pus from a mature pock on an inoculated patient was used to induce the disease.

In his final experiment, Watson used “fully concocted matter” (i.e., a late lesion) from an inoculated patient as the inoculum. Ten boys and 10 girls were inoculated without being given any preparative medicine. The results are shown in Table 1.

#### INTERPRETING WATSON’S DATA

None of the sophisticated statistical tools used in modern scientific medicine were available in 1767. Watson relied on the “medium,” the average number of pustules in each group. It was not known at the time how to take into account the small number of children with very high pock counts. He concluded that mercury added nothing to pretreatment with a mild laxative and that there was little difference between fluid from an early lesion and pus from a mature lesion as the inoculum, but both had better results than the “fully concocted matter.”

However, Watson could not detect the most interesting finding. When his data are analyzed with the use of the Kruskal–Wallis test, a nonparametric meth-

od of comparing independent groups, it is clear that there were no significant differences between any pretreatment and no pretreatment or between any of the sources of the inoculum.

Watson noted that the total number of pocks on the 74 children was 2353, which was a smaller number than would be found on the arm of a patient with the confluent pattern of natural smallpox. Almost half the pocks occurred on just 5 children; the mean number of pocks among the other 69 children was 17. Watson concluded, “I hold it as a truth, and I am not singular in my opinion, that inoculation, practised by any person whatever, in any manner yet devised, and at any time, carries with it, in general less danger to the patient than the natural smallpox, under the direction of the most able and experienced physician.”<sup>3</sup>

Before Watson’s experiments, there were only two reported investigations that bore any resemblance to modern clinical trials. When inoculation was first practiced, Jurin and Boylston each collected data on deaths among inoculated persons and those with naturally acquired smallpox. But in both cases, there was no study design, no deliberate matching of subjects, and no quantitation, apart from a tally of the number of deaths. In 1753, James Lind<sup>4</sup> reported the effects of

various treatments in a group of 12 sailors who had scurvy. He noted that the two sailors who were given citrus fruits recovered. However, his trial lacked the deliberate design, quantitative analysis, and use of controls that characterized Watson's studies. If the word "mice" were substituted for "children" in Watson's studies, they would resemble a typical 20th-century biology experiment. Clinical science began in 1767.

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