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Medical History

Measles: Progress and Failure

John Hedley-Whyte, M.D., F.A.C.P., F.R.C.A. Debra R. Milamed, M.S.

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INTRODUCTION

"Every boy should know about Herd Immunity", replied Professor Rutherford Morison to me[1] at the Annual (1938) Dipping of Cheviot sheep. My question to Professor Rutherford Morison had been suggested by my maternal grandfather who was a farmer and landowner of fields near Newcastle-upon-Tyne, where my father had been an Assistant Surgeon to Professor Rutherford Morison. As surgeons they both knew that I should be away from our home where my mother was being treated for post-partum thrombosis. Aged almost 5, I was staying with another famous surgeon, George A. Mason, later CBE, and his family nearby on Cheviot's north side.

MUSGRAVE ENCOUNTERS

My first meeting with Director Ted Badger was in Hut 1, Musgrave Park[1,2,3,4]. He asked me if I had had measles. I replied, "Yes, I had been treated in the dark to protect my conjunctivae". "Good," Badger replied. That was what ophthalmologist Rycroft—my brother's godfather—had told him[5,6]. I asked Badger if he had missed the Faroes in his small yacht sail from Yale[7]. "Yes," he said. "We are going to use measles in our counter-attack against your father's accusers, who are trying to have him court-martialed for attempting to obtain foods rich in vitamin A"[5,8]. I, said Badger, am only a stand-in for Charles A. Janeway (CAJ) (Fig. 1), who was told to stay in Boston at Harvard to continue research with John F. Enders[9,10] on the immunological control of mumps and measles in addition to his own work on plasma fractionation of blood[11,12,13]. This had been ordered by CAJ's neighbor, U.S. Secretary of War Henry L. Stimson (Fig 2). Badger informed me that "The Stimsons own thousands of acres next to the Janeways' estate in the Adirondacks. The Stimsons also have a Long Island estate with its own polo field and Highland games"[14,15,16].

Badger also told me that CAJ's father, Theodore Caldwell Janeway (1872-1917), a graduate of Yale and the College of Physicians and Surgeons of New York, was recruited in 1914 to be the first full-time Professor of Medicine at Johns Hopkins School of Medicine. He resigned this post in 1917 to enter the U.S. Army Medical Services as Major, and was assigned to the Office of the Surgeon General. CAJ's father died of pneumonia on December 17, 1917, when his son, CAJ, was my age.

Theodore Janeway's father, Edward Gamaliel Janeway (1841-1911), a graduate of Rutgers with a Medical Degree from the College of Physicians and Surgeons of New York, had answered a call to Buffalo, NY six days after President William McKinley had suffered an assassin's abdominal wound. Edward Gamaliel Janeway arrived too late to prevent the President's death[11,17].

Edward Gamaliel Janeway was also a contemporary and neighbor of then Secretary of War Henry L. Stimson's father, Lewis Atterbury Stimson (1844-1917). The latter graduated from Yale in 1863 and proceeded to study medicine at Bellevue Medical College in New York City. Lewis Atterbury Stimson had been the first in the U.S. to demonstrate and practice Lister's method of antiseptic surgery, and in 1883 performed surgery on former president Ulysses S. Grant[14,15].

TED BADGER AND THE EPIDEMIOLOGY OF INFECTIOUS DISEASE

As fellow Yalies and Harvard Faculty, Badger and Enders were well acquainted with each other's work. John F. Enders and his group had started their measles research in 1939 at the Enders' estate on Long Island Sound at the time when Badger's group were assessing the long-term health, including measles, of student nurses within the Harvard Medical School and its hospitals[18,19].

Badger later told me, while visiting our Windy Edge, Dunmurry home, that he had spoken to Rycroft further about the importance of vitamin A and health and nutrition for both the prevention of night-blindness and the amelioration of measles[5,8,20,21,22]. CAJ was also passing this information on promptly to his Adirondacks neighbor, Henry L. Stimson. Did my father know that Stimson's father had spread Lister's anti-surgical antisepsis heritage in New York? CAJ's father had been Head of Medicine at Hopkins after Osler and his grandfather, Edward Gamaliel Janeway had galloped to Buffalo from their Adirondack estate to try to save President McKinley.

A late post-mortem showed, "The mortally wounded

David S. Sheridan Professorship in Anaesthesia and Respiratory Therapy
Harvard University, 1400 VFW Parkway, Boston, MA 02132-4927 USA
Correspondence to: Prof. John Hedley-Whyte
Email: john_hedley-whyte@hms.harvard.edu

1 This and other first-person references are to the first author.

president's Rutherford Morison pouch had not been adequately explored"[17]. I knew that my father had worked for Professor Rutherford Morison at the Royal Victoria Infirmary in Newcastle-upon-Tyne and I told Badger that,"In 1938 Professor Rutherford Morison and I had supervised the dipping of Cheviot sheep." Professor Morison had wanted his invention BIPP, a preparation of iodoform, bismuth subnitrate and liquid paraffin developed for treatment of war wounds during World War I added to the sheep dip[23]. This addition was declined, but used for treatment of wounded sheep.

JANEWAY'S STATESIDE CONTRIBUTION

TABLE 1. INCIDENCE OF MEASLES IN ARMED FORCES IN WORLD WAR II, RATES PER 1,000 MILITARY PERSONNEL

REPORTED CASES OF MEASLES IN THE BRITISH ARMED FORCES DURING WORLD WAR II[29]				REPORTED CASES OF MEASLES BRITISH COMMONWEALTH AIR TRAINING PLAN (BCATP) IN CANADA[30]			U.S. ARMY[31,32]	
YEAR	ROYAL NAVY	ROYAL AIR FORCE	ARMY UK ADMISSIONS TO HOSPITAL	RAF IN CANADA	RAAF IN CANADA	RNZAF IN CANADA	US ARMY IN US	US ARMY HOSPITAL ADMISSIONS TOTAL OVERSEAS
1939	0.7	1.8	1.11				1.4	
1940	0.8	2.1	0.55				3.7	
1941	1.2	1.7	0.49	5.5	24.6	15.8	9.8	
1942	0.4	0.7	0.19	5.5	10.6	11.2	4.5	1.58
1943	0.8	1.1	0.57	4.3	3.9	4.4	5.7	0.80
1944	0.3	0.6	0.34	7.5	4.7	6.3	2.7	0.57
1945	0.4	0.5	0.40				0.9	0.42

Having accepted the diktat of the U.S Secretary of War Henry L. Simson, CAJ remained at Harvard[1,2,3,11,12,13,24,25,26,27]. He thereafter did much valuable work on the prevention of epidemics. During World War I the incidence of measles in U.S. troops in Europe had been high[28], but during World War II it was low (Table 1). Geoffrey Keynes and the Lionel Whitbys closely collaborated on aspects of blood transfusion including the administration of immune serum in the treatment of measles[33,34,35,36,37]. The generations-long friendship of the Stimsons and Janeways co-existed with deep experience. CAJ's father Thomas, as Head of Medicine at Hopkins, resigned shortly before his death in

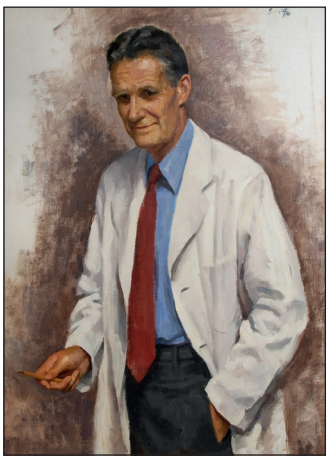

Figure 1
Charles Alderson Janeway, M.D. (1909-1981), Physician in Chief, Children's Hospital, Boston 1946-1976, and Thomas Morgan Rotch Professor of Pediatrics, Harvard Medical School. Oil on canvas, 32" x 40", 1975, by George V. Augusta, Jr. (1922-2012). From the portrait collection of Boston Children's Hospital, and reproduced with permission of the artist's estate.

1917, to advise the then U.S. Surgeon General. During World War I he attained the rank of Major and Henry Stimson that of Colonel in U.S. Artillery. John F. Enders had attained the rank of Ensign as a U.S. pilot in World War I.

Late in 1941, after Pearl Harbor, Harvard's Moseley Professor of Surgery, Elliott Carr Cutler, Harvey Cushing's successor as commandant of Harvard's 5th U.S. Army General Hospital[2,3,37] had announced that CAJ would be his Assistant Director and Head of Pathology. This appointment was vetoed by the U.S. Secretary of War, Yale graduate, Henry L. Stimson, who ordered that CAJ should stay at Harvard and continue his work on the fractionation of human blood and the gamma globulins. Stimson and CAJ were both elected to Skull and Bones, "The inner circle of Yale good-fellowship", while undergraduates at Yale[14] (Fig.1) (Fig.2).

Figure 2
Colonel Henry Lewis Stimson (1867-1950), U.S. Secretary of War under President William H. Taft (1911-1913), and later under FDR (1940-1945), by Julius G. Melchers (1860-1932), 1913. Oil on Canvas, 51.5" x 30.74", from the collections of the Center of Military History, Washington, DC. Stimson was appointed Governor-General of the Philippines by President Calvin Coolidge in 1927 and served until 1929, when he was appointed U.S. Secretary of State. In 1939, he was reappointed to his former post of Secretary of War by FDR.

During the U.S.'s engagement in World War I there were 2,370 deaths of enlisted soldiers in the United States and Europe attributed to measles[38]. In World War II, by contrast, even with a quadrupled pool of military personnel for twice the time, the corresponding mortality figure was reduced to 33 deaths[32,38]. The advice to the U.S. Secretary of War Stimson from Enders and CAJ on prevention and treatment was very effective, as was their close collaboration with Geoffrey Keynes and the Whitbys for United Kingdom troops, airmen and Allied Navies[29,35,36,37](Table 1) .

Gamma globulin (human immune serum globulin) obtained as a product of human plasma fractionation was an effective means of prevention or amelioration of measles[11,12,13]. Measles never became a serious military problem during World War II[29,30,31,32,38] (Table 1).

SEQUELAE: THE LEGACY OF JOHN ENDERS

In 1959 CAJ recruited my wife from St. George's Hospital London to be Sidney Farber's intern and later to work in the John Enders Building opened in 1972 at Harvard's Children's Hospital in Boston[1,39].

John Enders, trained by Zinsser[40,41,42,43,44,45], started in 1939 with cultivated human renal cells to allow production of more renal cells to propagate measles virus in quantity[46]. The Edmonston-Enders virus strain is still used in standard measles, mumps and rubella vaccine (MMR)[47,48,49,50]. The wide-spread use of the Enders Measles vaccine led to the

United Kingdom, the United States and a number of other countries being declared measles-free[51,52]. The World Health Organization (WHO) defines elimination of measles as "the interruption of measles transmission in a defined geographical area that has lasted at least 12 months"[53]. Because of its high infectivity, "the herd protection threshold for measles is the highest of all vaccine-preventable diseases and varies in different settings ranging from 89% to 94%"[53]. Now in 2020, Boston has registered two confirmed cases of measles in the past 4 months[54] (Fig. 3). Air travel to both the U.K. and U.S. warrants closer monitoring: Koplick spots are easily recognizable. The WHO has reported global annual incidence of measles of approximately 6,733,000 cases resulting in 109,638 deaths as recently as 2017[53,62,63]. Complications such as blindness, encephalitis, pneumonia, as well as death, are more frequent among malnourished or vitamin-A deficient children, or those with immune systems weakened by HIV/AIDS or other causes[51,52,62,63]. Measles may disrupt the function of F protein and result in neurological sequelae including "primary measles encephalitis, acute post measles encephalitis, subacute sclerosing panencephalitis (SSPE) and measles inclusion body encephalitis (MIBE)"[64].

WHO has reported that during the period 2000-2017, measles vaccination prevented an estimated 21.1 million deaths worldwide, a decline of 80 percent during that time

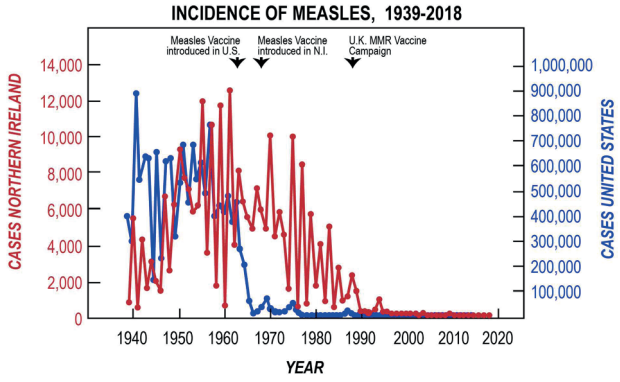

Figure 3

Incidence of Measles in Northern Ireland and the United States, 1939-2018. The incidence of measles in Northern Ireland[55](red) and the United States[56,57,58,59] (blue), reflects natural patterns of outbreaks and acquired immunity prior to the implementation of vaccination programs in 1963 in the U.S[60] and in 1968 in Northern Ireland[61]. In Northern Ireland, the steepest decline in reported cases occurred after the introduction in 1988 of the combined measles-mumps-rubella (MMR) vaccine given at age 15 months[61] . This was followed by a UK-wide campaign for vaccination of all school children in 1994[61]. More recently in Northern Ireland, as in the U.S., cases are mostly "imported" by air-travel[60,61].

period[62]. As of 2017, about 85 percent of children world-wide received one dose of measles vaccine by 12 months of age, but two doses are recommended, since approximately 15 percent of children do not develop immunity after the first dose. WHO estimates that 67 percent of children received a second dose of measles vaccine. At the same time, 8.1 million or 39 percent, of the 20.8 million infants not receiving at least one dose of vaccine, were in India, Nigeria and Pakistan[62], where clinical vitamin A deficiency remains an ongoing public health concern[5].

While WHO has reported an 88 percent global decrease in incidence of measles during the period 2000-2016, from 145 to 18 cases per million persons, by 2019 the incidence had risen again to 120 cases per million, its highest rate since 2001[65]. Sixty-two percent of countries reporting in 2019 included viral genotype information. The WHO reported that twenty out of twenty-four recognized measles genotypes could be eliminated by vaccination[65]. Global estimates of measles mortality increased nearly 50 percent between 2016, which had the lowest rates recorded since 2000, and 2019. Failure to vaccinate is recognized as the main cause of resurgence[65]. The 2020 coronavirus pandemic has led to further decreases in vaccination and surveillance[66].

BELFAST AND BOSTON

The late Distinguished Professor Emerita of Neuropathology Dame Ingrid Allen (Fig. 4) and her colleagues, including Professor Bertus K. Rima of the Center for Experimental Medicine, Queen's University Belfast, identified the primary cell types infected with measles virus as those of the immune system—lymphocytes, macrophages and dendritic cells. In addition, they identified a small number of infected epithelial cells[67]. This group also studied the role of the F-gene as a major determinant of neurovirulence[67].

Figure 4

Professor Dame Ingrid Allen (1932-2020), oil on canvas, 108 cm x 93.5 cm, No. QUB 6, by Tom Hallifax (1965-). From the collection of the Naughton Gallery, Queen's University, Belfast and reproduced with permission.

Professor Allen established the Regional Neuropathology Service for Northern Ireland in 1972 and served as its first leader. In 2006 she began a review of Pathology Services in Northern Ireland which led to the establishment of the Northern Ireland Pathology Network[68]. Post-measles immunosuppression and its long-term immunologic sequelae were elucidated. Measles vaccination (MMR), using Enders' attenuated Edmonston strain aids prevention of all infectious disease and promotes "polymicrobial herd immunity"[69,70]. Recent work by Michael J. Mina, now at Harvard University, and his U.S. and international colleagues, demonstrates that measles causes "elimination of 11 to 73% of the antibody repertoire across individuals"[69,70]. The impairment of immune cells increases the risk of secondary infection

leading to many of the deaths attributable to measles[69,70]. Adaptive immunity will also play a role in determining response to coronavirus disease vaccines[71].

TUTORING

My Clare College Physiology tutor, E.N. Willmer, FRS, has described in detail Enders' tissue culture technique[46,72]. Willmer opined that herd immunity for measles would require the immunity of at least 96 percent of the population. This prediction to me in 1954 occurred in the Fellows' Garden, that Willmer designed and supervised. The Cam flows past.

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