

Medical History

Hepatitis B: Prevalence, Hope

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Accepted: 15th January 2019

Provenance: Internally reviewed

Key Words: Mentors, Virology,

INTRODUCTION

In the transcript of his Nobel Oration for the 1976 Award in Physiology or Medicine, Baruch S. Blumberg refers to David Surrey Dane nine times.¹ Dane joined the Queen's Belfast Microbiology Department in 1955. He was soon promoted to Senior Lecturer, then Reader. In 1966 Dane was called to a Chair of Microbiology at the University of London tenable at the Bland-Sutton Institute and the Middlesex Hospital. Baruch S. (Barry) Blumberg (Fig. 1), David Surrey Dane (Fig. 2), Michael G.P. Stoker (Fig. 3) and Wolf Szmunn



Fig 1. Baruch Samuel Blumberg (1925-2011). Oil on canvas, 1993 by Paul Brason, RP (b.1952), 118" X 86", Balliol College Portraits Collection No. 174. Master of Balliol 1989-94. Baruch Blumberg entered the U.S. Navy in 1942 and rose to command a U.S. Navy Landing Ship (Tank). Blumberg was winner of the 1976 Nobel Prize and elucidator of the hepatitis virus which still infects over 270 million persons. Reproduction rights granted solely for this Medical History.

were responsible for wide-ranging advances in alleviation of pandemic Hepatitis B. This quartet of physician scientists each had outstanding World War II records and post-war guidance: each was a personable and talented leader^{2,3,4,5,6,7}.

EDUCATION

David Maurice Surrey Dane was educated at Charterhouse School, Surrey, England (Fig.2). In October 1942 he was gazetted as a Second Lieutenant in the British Army⁸. In 1943, Dane joined the British Parachute Regiment and was seconded to the Special Air Service (SAS). Having been

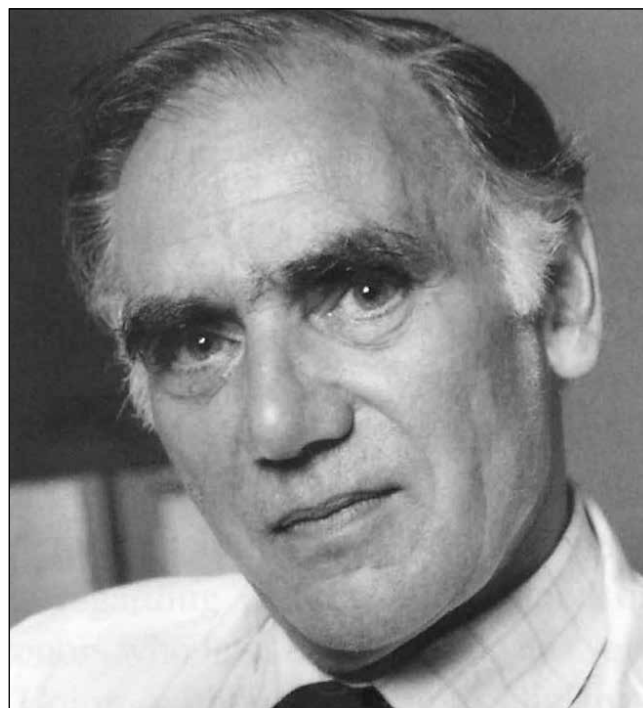


Fig 2. David Surrey Dane (1923-1998). Photograph reproduced with permission of *Vox Sanguinis*¹⁸ exclusively for this Medical History. After a distinguished academic career at Queen's Belfast and London University, Professor David Surrey Dane contributed greatly to donor screening protocols to assure the safety of the British blood supply. His approach was always, "meticulous, patient and sensible". For many years, until 1995, DSD was advisor to the U.K. Ministers of Health.

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taught in Northern Ireland to organize the construction of clandestine advanced landing strips, Dane wrote, "I saw a Coastal Command Hudson which crashed and blew up in spectacular fashion when coming in to land at Aldergrove aerodrome with a full load of depth charges on board"⁹.

Dane was dropped at 1:00 a.m. on 28th June 1944 from an RAF Stirling bomber into a field 250 miles east of Normandy^{9,10}. After exit, his parachute collapsed then reopened at low level. As part of SAS Operation Bulbasket in Nazi-occupied France, Dane organized the building of advanced landing strips; Dane's main French strip was named Bon Bon. On 7th August 1944 Wing Commander Alan Boxer and Flight Lieutenant Abbott flew two Lockheed Hudsons into Bon Bon to evacuate Allied survivors of Bulbasket: thirty-five out of fifty-five, 64 percent, had been lost⁹. Dane had to wait at Bon Bon for four more days until a USAAF C-47 (DC3) arrived, piloted by Colonel Clifford Heflin who picked up Dane, five USAAF pilots shot down by German forces, and two British signalmen⁹. Colonel Heflin later became commander of the 216th Army Air Forces Base Unit Special Airfield for the Manhattan Project and was awarded the Legion of Merit by Eisenhower, and the French Cross of War and Legion of Honor¹¹.



Fig 3. Sir Michael George Parke Stoker CBE FRS MD FRCP (4 July 1918 – 13 August 2013). Master of Clare Hall, Cambridge University; elucidator of the polymorphism of viruses, bacteria and cancers. Central panel of triptych, black-and-white drawing of three former Masters of Clare Hall by Bob Tulloch (1950-), 1988, 13.5" by 10.25". Reproduced with permission of the artist and Clare Hall.

SAS HQ staff did not appreciate Boxer's refusal to repeat flying an RAF Lockheed Hudson into Bon Bon necessitating Colonel Heflin to fly in his C-47. SAS HQ telegraphed "Bulbaskets to you Boxer"^{9,10}. Boxer was later knighted. Boxer was technically correct: C-47s were more suited to Bon

Bon. By December 1943, one C-47 was being produced in the United States every thirty minutes¹² (Fig. 4).



Fig 4. "Green Light, Jump". Oil on canvas, 1994, 18" x 36". by Craig Koder (1956-). Reproduction courtesy of the Greenwich Workshop, Inc., Turnbull, CT, solely for this Medical History. This painting depicts the arrival of C-47s into German-occupied France in June 1944.

In the spring of 1945, Dane took part in Operation Howard in which Regiment 1 of the SAS under Royal Ulster Rifleman Lieutenant Colonel Blair (Paddy) Mayne covered the 4th Canadian Armoured Division as they advanced to the Baltic through Northern Germany¹³. For exemplary heroism in bitter fighting, fellow Ulsterman Field Marshal Montgomery recommended fellow Ulsterman Mayne for the Victoria Cross. In his Memoirs, Montgomery writes "In the end we beat the Russians to Lübeck on the 2nd May 1945 and thus sealed off the Danish peninsula with about six hours to spare before the Russians arrived"¹³ (Fig.5). Dane wrote for Field Marshal Montgomery one of three testimonials for Mayne's VC: finally it became, although almost unprecedented, a third bar to Mayne's DSO^{14,15,16,17}.

Dane arrived at Clare College, Cambridge in October 1945 to read Honours Natural Science Tripos^{18,19}. Unusual for an undergraduate, although he had been an active member of the Charterhouse Bird Club²⁰. While at Clare, Dane published three different papers on epidemics in Manx shearwaters in Skomer and Skokholm islands off Pembrokeshire^{21,22,23} (Fig.6). The co-author of one paper was Michael G.P. Stoker, Dane's and later my* Clare Medical Tutor^{23,24,25} (Fig. 3). On 2 February 1948 Dane wrote from Clare College to *Ibis* about the severe outbreaks of "disease among juvenile Manx shearwaters, *Puffinus, puffinus*" in 1946 and 1947²². Juvenile Manx shearwaters develop blisters on webs of their feet and or conjunctivitis, frequently followed by early death before leaving their natal burrow^{25,26}.

It has been estimated that approximately half of the world's Manx shearwaters are born on the coasts of St. George's and North Channels. The 300-acre Old Lighthouse Island, situated two-and-a-quarter miles off the coast from Donaghadee North Down, Northern Ireland, is the second most prolific site of hatching²⁷.

About five weeks after hatching, parents leave the area, and the offspring a week or so later. By banding it has been shown

* This and any other first-person references refer to the first author.

that Manx shearwaters migrate across the Atlantic to Brazil and the United States^{27,28}. On the way they seem to rest and refresh at human watering holes like Biarritz and the beaches of Sao Paulo, Brazil. Currently, twenty-six are visiting Cape Cod, Massachusetts²⁸. Manx shearwaters can take as little as twelve days to fly from Boston's Logan Airport area beaches to Northern Ireland or the West of Scotland—roughly the same time duration as the 1846 news of the success of diethyl ether in anaesthesia and surgery²⁹.



Fig 5. Field Marshal Bernard Law Montgomery (1887-1976), the First Viscount Montgomery of Alamein, KG, GCB, DSO, Hon. LLD Queen's University Belfast: son of the Rt Rev H.H. Montgomery KCMG and Lady Montgomery, by Terence Tenison Cuneo (1907-1996), 1972, oil on canvas, 125 cm x 100 cm. From the collections of the Defense Academy of the United Kingdom, Watchfield, Shrivenham, Oxfordshire, and reproduced with their permission, solely for this Medical History.

After passing Conjoint in 1951 from St. Thomas's Hospital, Dane emigrated to Australia. In the spring of 1955, Dane returned from the Institute of Medical and Veterinary Science in Adelaide^{18,19,30} to Clare and Cambridge, from which in 1955 he received an M.B., and I received a B.A. Also in 1955 David Surrey Dane married Veronica Tester Hope, a widow, with two children Kerin and Alex. This family of four moved forthwith to Belfast, where the Danes later had three additional children: Roland, Penelope and Thomas^{18,19}. That same year, 1955, Dane joined Professor George Dick's Department at Queen's University, Belfast, where in the winter of 1956 they developed plans for a Virus Reference Laboratory which became operational within the year^{18,19,30,31}. Dane also started a research programme "which aimed at

identifying human hepatitis viruses by electron microscopy"³². In 1969, "some doubted whether Australian antigen was specifically related to hepatitis B virus"³². In a letter invited by Eugene Garfield to *Current Contents* in 1980, Dane wrote that he "thought that [by the 1960s] EM and negative staining techniques had developed to the stage where they could be used by virologists"³². Dane and his Belfast coworkers used specimens negatively stained with "4% phosphotungstic acid at pH 6.5 and applied to formvar/carbon grids before examination in an A.E.I. EM 801 electron microscope"³³. Hepatitis B virus was found by Dane to be a particle 42 nm in diameter with DNA and DNA polymerase^{3,32}, later eponymously named the "Dane particle"³². Dane wrote that "I never discovered whether the person who originally referred to it this way was a well-wisher who thought we were right or someone who hoped we were wrong"³².

OXONIAN MYSTERY

In 1978, 19 Manx shearwaters sick with puffinosis were transported live to Oxford from Skomer and Skokholm islands. A homogenate from each freshly decapitated bird was injected separately into Oxford Dunn Pathology mice randomly inbred since 1953. One to 3 day old suckling mice were injected intracerebrally and subcutaneously. Eight to 11 day old fertile hens' eggs were injected as also were various cell cultures.

Two days after inoculation, two of the mice showed clinical signs of infection, one with paralysis. Sera from the Manx shearwaters were not collected after inoculation due to "difficulties keeping the birds" in Oxford²⁶. The virus that was isolated differed from that found in 1948 by Stoker³³. Probably the coronavirus at Oxford they discovered was from an Oxford Dunn School of Pathology mouse. Electron microscopy was non-diagnostic of puffinosis. Nuttall and Harrap, whose work was funded by the National Environment Research Council (NERC), stated "We are studying puffinosis because, unlike many epizootics in wild animal populations detailed investigation is possible"²⁶.

According to Michael Stoker on a visit to me at Harvard Medical School³⁴, David Dane thought that the Oxonians had wider aims. Stoker told me that the study had led to Clare discussions. Did Oxford want to allot to Manx shearwaters the role of carrier pigeons? Or were they manufacturing an opportunity to test their electron microscopy specimen preparation and imaging techniques? We concluded, said Stoker, we should not ascertain.

ADVANCES AGAINST HEPATITIS B IN THE U.S.

Warsaw-born Wolf Szmunes, who had studied medicine in Italy, returned to his family in Poland after the 1939 German invasion. He then fled to the Soviet Union where he was confined to a Siberian labour camp at which he was eventually assigned duties of sanitation management and epidemiologic records. Post-release he received a medical degree from the University of Tomsk in 1950, an advanced scientific degree from the University of Kharkov in 1955 and



an additional degree from the University of Lublin in 1964. In 1968 he left Poland with his family and emigrated to the United States where he met with Dr. Aaron Kellner, President of the New York Blood Center to discuss career prospects^{2,4}. They consulted Barry Blumberg (Fig.1) and together decided that Szmunes should work as Kellner's technician. Wolf Szmunes published in 1980 on the efficacy of Blumberg anti-hepatitis B vaccine produced by Merck in a Controlled Clinical Trial in a high-risk New York Population⁵.

DAVID SURREY DANE'S AND MY MEDICAL TUTOR AT CLARE

Michael Stoker was born in Taunton, Somerset on 4 July 1918 just after his Corkonian physician father, Cork Medical School-educated, had returned from France with an M.C.^{24,35,36,37,38,39} and relocated the family to Market Harborough. Michael, aged 8, was sent as a boarder to Oakham and thence to Sidney Sussex, where the pre-Cromwellian silver fascinated him and Veronica English. They married in 1942, the year Michael passed conjoint. In 1943 Michael was sent as an RAMC Lieutenant to the 3rd/9th Ghurkas in Northern India³⁹. Douglas Black, later PRCP, London, arranged for Stoker to enroll in a course in laboratory medicine run by William Haye, a bacterial geneticist in Poona. Together they studied virus activity in Herpes simplex and the bacterial antigenic variation of Rickettsiae. After World War II, Henry Thirkill, M.C., Master of Clare, called Michael Stoker and Veronica and their son to Clare, with Michael as Clare Medical Tutor for Honours Natural Science Tripos.

From Clare, Michael Stoker expanded the horizons of H.R. Dean's Cambridge Department of Pathology. Stoker used electron microscopes in the Cavendish Laboratory of Rutherford and later Pippard⁴⁰.

As we were Stoker's tutees our job was to educate Stoker: subjects such as Antigenicity versus Infectivity. Polymorphism—"have you chased the Beagle?" What about the scientific verse of Grandfather Erasmus? What about Medical Management of the aftermath of the Quetta Earthquake?^{41,42} Much of these discussions took place in Veronica's house, not at Clare.

LONG TERM EDUCATION

After I went down from Cambridge, Stoker, for decades would send me, his "perpetual student", a postcard after I had published in the Scientific or Medical Literature. Nearly all messages were short. "Congratulations." "Surprising but believable". "Talk to Aage Bohr". Re: our ICU and Thomas Huckle—"Do it"^{43,44}.

In 1961-1962 while I worked on "impaired oxygenation in surgical patients" at Harvard^{45,46}. Michael Stoker, now Professor of Virology at Glasgow, advised as to the management of viremia⁴⁴. My Harvard Department Heads E.D. Churchill and H.K. Beecher⁴⁷ along with M.G. Stoker declined co-authorships:"that is not our style"^{44,46}.

STOKER FAMILY RELOCATIONS

After Clare, the Stokers had nine years in Glasgow, then California, then great success from 1968 at the Imperial Cancer Research Fund Laboratories introducing Genetics and more fundamental Molecular Biology. Michael used to say his co-workers and tutees converted him from Virology to Cell Biology. Knighted in 1980⁴⁸, from London he and Veronica went back to head up Clare Hall for seven happy years. Then Michael returned to his Cambridge Pathology Laboratory to continue work on hepatitis B and hepatocellular cancer^{49,50,51,52}.



Fig 6. Manx Shearwaters over the Sea, lithograph of 1967 painting by Keith Shackleton (1923-2015).

GLOBAL SITUATION

Each year an estimated 887,000 humans are killed by hepatitis B⁵³; how many thousands of non-humans we do not know. Hepatitis B has solely infected humans and other hominidae and simian species for at least the last 7,000 years^{54,55}. Currently hepatitis B infects 257 million people worldwide^{53,56}. The "Northern Ireland Hepatitis B and C Managed Clinical Network" has reported that Northern Ireland is a "very low prevalence country" for hepatitis B⁵⁷. Much progress has been made in vaccination of healthcare workers, as well as mothers and their offspring^{58,59}.

Investigators from the Regional Virus Laboratory at the Royal Victoria Hospital, Belfast, with colleagues from the Liver Unit, Department of Genitourinary Medicine and HIV and the Public Health Agency of Northern Ireland have recently suggested a higher than expected rate of progression from acute to chronic hepatitis B among persons aged 50 and over in Northern Ireland⁶⁰. Patients co-infected with HIV show hepatitis B chronicity rates as much as six times higher than hepatitis B patients who are HIV seronegative. While such co-infection is relatively rare in Northern Ireland, the overall aging of the population amid higher hepatitis B chronicity rates emphasizes the importance of vaccination and provision of accurate information to patients.⁶⁰

"This plague has come upon us by infection and will spread still further"⁶¹ †. Before you travel to foreign parts ascertain your vaccination status⁵⁶.

† "...dedit hanc contagio labem et dabit in plures..." (Juvenal, Satvra II, 78-9).

ACKNOWLEDGEMENTS

The authors wish to thank Ms. Anna Sander, Archivist and Curator of Manuscripts, and Professor Seamus Perry, Balliol College Oxford, for assistance with permission to reproduce the portrait of Baruch S. Blumberg. The authors wish to thank Mrs. Catherine Smith, Archivist, Charterhouse School, for archival material about alumnus David M. Surrey Dane. The authors wish to thank the editors of *Vox Sanguinis* for permission to reproduce the photograph of David Surrey Dane. The authors wish to thank Prof. Frances Spalding and the Fellows of Clare Hall, and artist Bob Tulloch for permission to reproduce the portrait of Sir Michael Stoker. The authors wish to thank the staff of the Defense Academy of the United Kingdom for permission to reproduce the portrait of Field Marshal Montgomery. The authors wish to thank the representative of the estate of the late Keith Shackleton, for permission to reproduce the lithograph based on Shackleton's 1976 painting "Manx Shearwaters over the Sea."

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