Queen Anne’s Lupus: Phospholipids and the Course of the Empire

Queen Anne, studio of John Closterman, oil on canvas (circa 1702); © National Portrait Gallery, London.

United Nations shall combine
To distant climes their sound combine
That Anne’s actions are divine
And this the most important day!
The day that gave great Anne birth
Who fix’d a lasting peace on earth.

—G. F. Handel, “Ode for the Birthday of Queen Anne”, 1713 (1)

George the Third
Ought never to have occurred.
One can only wonder
At so grotesque a blunder.

—E. C. Bentley, “George III”, 1929 (2)

HEIRLESS IN LONDON

Were it not for the antiphospholipid antibody syndrome, the United States might now have a National Health Service. That’s my conclusion from finding direct links between the most prominent victim of the syndrome—Queen Anne—and current debates over Scotland’s imminent secession from England. This September, Scots will hold a plebiscite on whether to dissolve a partnership that has lasted since Queen Anne presided over the “Acts of Union” (1707) (3). As Simon Schama quipped (4), Anne saw to it that the United Kingdom, which “began as a hostile merger would end in a full partnership...”. But, that was three centuries ago, and the going is tougher these days. Scotland’s prime minister has had to reassure anxious voters that a future spinoff would retain its popular National Health Service. He’s also told them that Queen Elizabeth II would remain head of state in Scotland (as she has in Canada, Australia, and New Zealand). He then set Scottish Independence Day to commemorate the UK’s founding mother, Queen Anne (3).

The Queen, a childless widow, died in 1714, sickened by “gout, dropsy, hemorrhage and stroke” (5). If poor Anne had produced a Stuart heir, a National Health Service in the United States today might look a lot like those in Scotland, Canada, or Australia.
ROYALTY AND AUTOIMMUNITY

Queen Anne’s life and the Stuart dynasty were undone by systemic lupus erythematosus (SLE) and its harrowing companion, the antiphospholipid antibody syndrome, which produces bleeding, clotting, stroke, and obstetrical calamity (6). Anne and her husband, George Oldenburg, sweated out at least 17 pregnancies from 1684 to 1700 (Table 1); all but one resulted in miscarriages, stillbirths, or infant death (7). Anne’s only surviving child, William, the last Stuart of Kensington Palace, died at age 11, after infantile seizures, childhood dyskinesias, and gross hydrocephalus, symptoms now recognized as those of neonatal lupus (8).

It’s clear that Anne suffered from SLE, an autoimmune disease that chiefly affects women of childbearing age and their newborns. The Queen’s contemporaries describe four clinical features that add up to current criteria for the diagnosis: a blotchy, pitted face with a malar rash; recurrent polyarthritis; facial and leg edema; and repeated seizures, nosebleeds, and lethal stroke (9). Official portraits of Queen Anne show variable joint swellings, obvious facial edema, and the classic lupine rash. Add her obstetrical history, and we arrive at the diagnosis of the antiphospholipid antibody syndrome. The syndrome is often tagged “Hughes syndrome”, after my colleague Graham R. V. Hughes, who described a patient in London with ailments similar to those of Queen Anne. His seminal 1983 article in the British Medical Journal sums up the problem: “Thrombosis, abortion, cerebral disease and the lupus anticoagulant” (10).

Table 1. Children of Anne Stuart, Queen of Great Britain, and George Oldenburg, Prince of Denmark

| Stillborn daughter 1 Oldenburg b. 12 May 1684, d. 12 May 1684 |
| Stillborn son 1 Oldenburg b. 22 Oct 1687, d. 22 Oct 1687 |
| Stillborn son 2 Oldenburg b. c. Oct 1688, d. c. Oct 1688 |
| Stillborn child 1 Oldenburg b. 21 Jan 1687, d. 21 Jan 1687 |
| Stillborn child 2 Oldenburg b. 14 Oct 1690, d. 14 Oct 1690 |
| Stillborn daughter 2 Oldenburg b. 17 Apr 1692, d. 17 Apr 1692 |
| Stillborn daughter 3 Oldenburg b. 23 Mar 1693, d. 23 Mar 1693 |
| Stillborn daughter 4 Oldenburg b. 21 Jan 1694, d. 21 Jan 1694 |
| Stillborn son 2 Oldenburg b. 25 Mar 1696, d. 25 Mar 1696 |
| Stillborn son 3 Oldenburg b. 25 Mar 1697, d. 25 Mar 1697 |
| Stillborn son 4 Oldenburg b. 10 Dec 1697, d. 10 Dec 1697 |
| Stillborn son 5 Oldenburg b. 15 Sep 1698, d. 15 Sep 1698 |
| Stillborn son 6 Oldenburg b. 25 Jan 1700, d. 25 Jan 1700 |

“See ref. (7).”

Hughes syndrome, which can also occur in the absence of lupus, results from antibodies directed against anionic phospholipids (presenting as lamellar bilayers on cell surfaces) and/or an associated plasma protein (β-2 glycoprotein) (11–13). Closely related antibodies, i.e., Hughes’s “lupus anticoagulant”, inhibit the phospholipid-dependent coagulation of normal blood. Each of these autoantibodies can induce cascades of injury against self or any product of the womb. Recent, multicenter studies show that in pregnant patients with antiphospholipid antibodies, measurements of the lupus anticoagulant are the best predictor of adverse outcomes. Antibodies to cardiolipin or to β-2 glycoprotein, do not predict adverse pregnancy outcomes, unless the lupus anticoagulant is also present (14). Graham Hughes has earned his eponym: it’s fitting that he directs a unit at St. Thomas’ Hospital, down Royal Street and a bridge away from Westminster Abbey, where Queen Anne lies forever.

“A LASTING PEACE ON EARTH...”

Before the reign of Queen Anne (1702–1714), England was torn by religious and family spats that ranged in intensity somewhere between today’s Sunni/Shiite conflicts and the family squabbles of the Cheney sisters. The House of Stuart regained power in 1660 after Cromwell’s Puritan misadventures. Anne’s uncle, Charles II, restored the monarchy, presided over Restoration comedy, and chartered the Royal Society (15). Chuck 2 (as American royalists have it) was a middling Protestant, and Anne was brought up as such. But, next in line came a very partisan Catholic, James II, who happened to be Anne’s father. After a short 3 years in power, James was overthrown in 1683 by Anne’s Protestant brother-in-law (and cousin) William III. It was called the “Glorious Revolution” of 1688 and resulted in permanent exclusion of any Catholic successor (15). William III became joint monarch with Anne’s elder sister Mary II: we know the pair from that college down south. Mary II’s official biography documents that “the marriage survived although all three of her pregnancies were stillborn” (16). Two sisters, 16 stillbirths, no heirs? Time for some genomics here (17)?

Then came the younger sister’s turn: Queen Anne with her own stillbirths, her gout, dropsy, and seizures. But, these days, her reign is remembered less for disease than for peace and prosperity. The “War of the Spanish Succession” had broken out on both sides of the Atlantic the year before her coronation. It pitted the great powers—England, Austria, and Holland versus France and Spain—in battles from the Alps to the Canaries, from Jamaica to the Arctic. Handel’s musical tribute (above) celebrated Anne’s major achievement, the Treaty of Utrecht (1713). The treaty not only established a peace that would last to midcentury but also left Britain in possession of Newfoundland, Nova Scotia, the Hudson Bay Territory, and Gibraltar (15). Schama had it right—that full partnership of the U.K.
had become “the most powerful going concern in the world”.

Anne followed a path set by grandfather Charles II as custodian of arts, science, and the commonweal. She was a patron of Christopher Wren, knighted Isaac Newton in Cambridge, and appointed Jonathan Swift the dean of St. Patrick’s in Dublin. By proclaiming the “Statute of Anne” (1707) for the “Encouragement of Learned Men to Compose and Write useful Books”, she established the basis of copyright law in Anglophone countries (18). In the American colonies, which comprised her contested subjects, she is renowned in name and deed. That town in Chesapeake Bay, Annapolis, is named for her, (19) as are Cape Ann in Massachusetts and Fort Ann in Washington County, NY. She is remembered for a unique “Act of Denization” granted to Luis Gomez, a Jewish refugee from the Spanish Inquisition in 1705. The document allowed him to conduct business, own property, and live freely within the colonies. His mill in Marlboro, NY, is a tourist site today (20). Among her other acts, deeds, and grants that remain in the news are those 215 acres the Queen bestowed on Trinity Church in Manhattan in 1705. The church elders are debating what to do with the $2 billion it’s worth today (21).

Not bad for 1 dozen years of Stuart-ship, and again, one wonders what a living heir would have meant.

“SO GROTESQUE A BLUNDER”

Trouble came when the Hessians followed the Stuarts. Worried over Anne’s afflicted womb, Parliament passed the “Act of Settlement” (1701), which assured a Protestant line of succession. The nearest skein of that line led to Hanau (Hanover) and the three Georges—no Graces, they—who ruled from 1714 to 1820 (22). George I, a Hessian, who barely spoke English, kept several mistresses; in return, his wife eloped with a Swedish count, who was killed and dumped in a river on George’s order. He then had his young son, George II, arrested for siding with his mother and excluded from public ceremonies. When his father died of a stroke on one of his frequent trips home to Hanover, George II assumed the British throne and—one generation after Anne’s “lasting peace”—took the country to war again. George II personally commanded British troops in the War of the Austrian Succession: truce sans peace was the result. Both George I and II faced repeated insurrections from Scots unhappy with Hessian authority. The issue was settled in 1745, when “Bonnie Prince Charlie” and his Highlanders were defeated by the Redcoats at Culloden (23). In 1751, after George II’s eldest son Frederick died suddenly of mysterious injuries (attributed to a tennis ball!), the crown passed to George III, grandson of the warrior (24).

George III assumed leadership of the British Empire in 1760 at age 22. The official website of the Crown states that he is best remembered for provoking American independence and for going mad (25). Alan Bennett’s popular play and film, “The Madness of King George” (1994), revived the story of a nutty monarch, crazed by “variegate porphyria” (26). Modern analyses reject that diagnosis but not its symptoms: blindness, deafness, and madness—episodic bouts of which followed loss of the American colonies (27). When his Redcoats and Hessian mercenaries were defeated by the Americans, he declared a General Day of Fast in 1778—a gesture understood as pitiful at the time.  

First General Gage commenc’d the war in vain;  
Next General Howe continued the campaign;  
Then General Burgoyne took the field and; and last  
Our forlorn hope depends on General Fast (28).

Whether his madness was caused by, or was coincident with, loss of his American colonies remains in doubt. What is certain is that George III blundered into his American quagmire through economic miscalculation. The empire was going broke, thanks to the costs of those successful wars with France and Spain and expenses of the East India company that ran India for the crown (29). By the 1770s, at a time when there were no income taxes, the United Kingdom required £4 million (£500 million today) simply to service its debt. The answer was to tax items in demand among the more prosperous of American colonies. George had figured out a solution. In a letter of the early 1770s, he wrote, “While the Sugar Colonies [the Caribbean] added above three millions a year to the wealth of Britain, the Rice Colonies [South Carolina, etc.] near a million, and the Tobacco ones [Maryland, etc.] almost as much; those more to the north [Pennsylvania on up], so far from adding anything to our wealth as Colonies . . . rivaled us in many branches of our industry, and had actually deprived us of no inconsiderable share of the wealth we reaped by means of the others” (25).

The answer was clear: impose taxes on sugar, tea, and commercial transaction. The Brits were sure that those moneymaking rivals would return some of the “not inconsiderable wealth” in the form of taxes. The result of that miscalculation was the American Declaration in Philadelphia of July 4, 1776, which lists in detail a litany of “. . .the patient sufferance of these Colonies . . . rivaled us in many branches of our industry, and had actually deprived us of no inconsiderable share of the wealth we reaped by means of the others” (25).

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Gerald Weissmann
Editor-in-Chief
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22. Idem, 377


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