Coagulation abnormalities and cerebral infarction

Thrombosis is central to the major pathophysiological mechanisms of ischaemic stroke—large vessel occlusive disease, embolism and small vessel occlusion. Whilst in the majority of cases the thrombotic process becomes activated secondarily to an underlying (cardio)vascular pathology, some cases of ischaemic strokes may result primarily from an abnormality of the haemostatic mechanisms which results in unchecked thrombus formation within the cerebral circulation.

There is a requirement, in health, for the rapid and efficient sealing of breaches in the vascular endothelium, whilst at the same time uncontrolled vessel occlusion cannot be permitted. This has led to the evolution of an interactive system of cellular and fluid-phase components, activators and inhibitors designed to fulfil these requirements. The participants are blood platelets, components of the fluid phase of coagulation and their inhibitors, the fibrinolytic system and the vascular endothelium.

Platelets are highly reactive, contractile and secretory anucleate cells which have the capacity to interact with components of the vascular subendothelium within seconds of their exposure. The response requires the availability of adhesive proteins and specific platelet membrane glycoprotein receptors. von Willebrand factor (vWF), a macromolecule synthesised by vascular endothelial cells and megakaryocytes, is the principal protein involved. Subsequently platelets may interact in a process of aggregation, to form an occlusive plug. In this process fibrinogen and other adhesive proteins act as intercellular bridges by interaction with platelet membrane glycoproteins. Inappropriate platelet activation is limited by the local secretion by vascular tissues of short-lived potent inhibitors of platelet adhesion and aggregation. The most important are prostaglandin I$_2$ and nitric oxide, which exert their inhibitory action through the stimulation of cyclic nucleotide synthesis within platelets.

**Blood coagulation** (figure)

A series ofzymogens and cofactors interact in the generation of insoluble fibrin from its soluble precursor protein fibrinogen, through the action of thrombin. Thrombin plays a central role in haemostasis as it is also one of the more potent platelet agonists and in addition acts as a trigger for the activation of a major natural anticoagulant system (the protein C/S/thrombomodulin system).

The final pathway of thrombin generation from prothrombin involves the formation of an activator complex of factors X and V, with calcium, on a phospholipid surface, provided in vivo by activated platelets. This “final common pathway” brings together the intrinsic system of coagulation activation by surface contact and the extrinsic system which becomes activated by release of tissue factor (thromboplastin). The result of coagulation and platelet activation is the haemostatic plug formed of a platelet aggregate stabilised by fibrin.

**Coagulation inhibitors**

Knowledge is increasing of physiological inhibitory mechanisms which oppose uncontrolled fibrin formation.

Three important inhibitors of coagulation have been well defined—antithrombin (formerly antithrombin III), protein C and its cofactor protein S. Antithrombin is the major serine protease inhibitor, with particular activity against activated factor X (Xa) and thrombin, but also against factors XIIa, XIa and IXa in the extrinsic pathway. This inhibitory capacity is increased considerably by heparin-like molecules (glycosaminoglycans) present in vascular tissues in vivo, as well as by heparin given therapeutically.

Activated protein C inhibits the activated form of coagulation factors VIII and V (VIIIa and Va). For the full expression of protein C activation a cofactor, protein S, is necessary. Thrombin, and an endothelium-derived cofactor, thrombomodulin, are necessary for protein C activation.

**Fibrinolysis**

The fibrinolytic mechanism provides a further check on unopposed thrombus formation. Plasmin, cleaved from the zymogen plasminogen by tissue plasminogen activator (t-PA) or urokinase, is able to digest fibrin to soluble fibrin-degradation products. In common with the coagulation system, interplay between activators and inhibitors modulates the fibrinolytic process.

**The vascular endothelium**

The vascular lining is a complex secretory organ which exerts major controlling effects on haemostasis and blood flow. All aspects of haemostasis are influenced by endothelium, for example by secretion of prostacyclin, nitric oxide, vWF and t-PA. Protein C activation occurs on the endothelial surface and heparin-like molecules, responsible for massive augmentation of the inhibitory effects of antithrombin, are components of the vessel wall.
Disturbances of haemostatic mechanisms and thrombosis

In a broad sense there is an undoubted relationship between arterial occlusive disease, including stroke, and coagulation mechanisms. Fibrinogen and factor VII concentrations are at least as potent as cholesterol as risk factors for arterial occlusion. Platelet count and volume have also been implicated as risk factors. Haemostatic mechanisms are probably involved in the development and progression of atheroma as well as being central to the formation of the platelet/fibrin thrombus which occurs during the acute occlusive event. The role of ulcerated atheroma, with presumed platelet activation on exposed subendothelial material, in the genesis of transient cerebral ischaemic attack (TIA) and stroke is clear. The efficacy of aspirin, an inhibitor of platelet aggregation, in the reduction of ischaemic episodes and lowering of the incidence of completed stroke further supports the role of platelets in cerebrovascular occlusion.

The concept of a prethrombotic state has been developed, and such a condition clearly occurs in certain situations. The mechanisms, however, are as yet unclear and may be multifactorial. Thrombosis in pregnancy and that associated with oral contraceptive use and the prethrombotic state which undoubtedly accompanies malignant disease are examples.

More specifically, certain well-defined haemostatic disorders are undoubtedly associated with an increased thrombotic risk. These disorders are the “congenital thrombophilias”, due to deficiency of a natural anticoagulant (protein C, protein S or antithrombin), the acquired disorder known as the primary antiphospholipid syndrome, where the presence of an auto-antibody to phospholipids is associated with increased thrombotic risk, and the myeloproliferative diseases essential thrombocythaemia and polycythaemia rubra vera, where thrombocytopoiesis with or without increased platelet reactivity contributes to a thrombotic tendency. This review will concentrate on these conditions, although microvascular occlusion, often with neurological involvement, is a major feature also of some other disorders in which haemostatic mechanisms are disturbed, including disseminated intravascular coagulation, thrombotic thrombocytopenic purpura and the haemolytic uraemic syndrome.

Specific coagulation disorders and stroke

Antibodies to phospholipid

Considerable interest has been generated in recent years in the relationship between antiphospholipid, detected in plasma as lupus anticoagulant or in serum as antiphospholipid, and a tendency to thrombosis, both venous and arterial. A coagulation inhibitor was first described in SLE in 1952 and the term “lupus anticoagulant” has persisted, despite the paradoxical association with thrombosis rather than haemorrhage and the knowledge that these antibodies to phospholipid are common in subjects without the features of SLE.

Lupus anticoagulant is thus a member of a heterogeneous group of antibodies with varying specificities apparently for negatively charged phospholipid. Others are antiphospholipid and the antibodies responsible for the biological false positive VDRL. Lupus anticoagulant, by its activity against the phospholipid necessary for coagulation activation, especially in the common pathway, is detected by prolongation of the clotting time in phospholipid-dependent tests of coagulation (figure). Anticardiolipin is measured by solid-phase immunoassay with cardiolipin as the phospholipid antigen. It is now considered that lupus anticoagulant and anticardiolipin represent separate antibodies within a family of autoantibodies directed against protein phospholipid complexes rather than phospholipid itself. Recent data suggest these probably include a complex between an anticoagulant glycoprotein—β glycoprotein 1 (βGP1) or Apo H—and negatively charged phospholipids, and that between thrombin and phospholipid.

The occurrence of antiphospholipid

Antiphospholipid may be detected in up to around 50% of subjects with SLE and less commonly in other autoimmune diseases, including rheumatoid arthritis, temporal arteritis and immune thrombocytopenia. Transient positively tests, especially for anticardiolipin, may occur after acute infective episodes and also in chronic infections, including syphilis, malaria and some viral infections. Tissue injury may be the trigger for the development of anticardiolipin after acute myocardial infarction and in subjects with coronary artery bypass grafts. Exposure of “neoantigens”, during tissue repair may underlie the development of antiphospholipid. Other associations are Behçet’s syndrome and skin disorders, especially livedo reticularis. An apparently neurological involvement antiphospholipid occurs during medication with phenothiazines, especially chlorpromazine, hydralazine, phenytoin and some other compounds. Crucially, antiphospholipid may be found in subjects who have no predisposing or associated condition and these subjects may be at risk of thrombosis.

Thrombosis and antiphospholipid

Although causality has not been demonstrated, positive tests for antiphospholipid have been associated with
thrombotic disease. Thus in SLE, the risk of thrombotic complications is increased some 2–5 fold in subjects with lupus anticoagulant.13 Thrombosis may occur in the venous, arterial or microvascular systems. Deep venous thrombosis is most commonly seen, but stroke, sometimes in young subjects without other recognised risk factors, undoubtedly occurs.14,15 Brey et al45 reported detectable antiphospholipid in 21 of 46 (46%) subjects under 50 years of age presenting with stroke or TIA, compared with only 2 of 26 (8%) in matched controls with non-thrombotic neurological disease. Retrospective studies tend to confirm a tendency to presentation at a young age, the frequent absence of the clinical and laboratory evidence of collagen vascular disease, and a predisposition to recurrent and multiple events.17–19 In a large retrospective study, stroke recurrence occurred at a rate of 9.4% over 16 months following the presenting cerebrovascular event.20 The same group found an adjusted odds ratio of 2:4 for the presence of anticardiolipin in 248 unselected subjects presenting with stroke compared with hospitalised controls, suggesting that the presence of antiphospholipin is an independent risk factor for stroke.

Strokes are usually ischaemic and most commonly arterial events, although cerebral venous thrombosis has been described. In one study cerebral angiography was normal in over one third (37% of 49 cases) of subjects.21 This, together with the finding of branch occlusions without corresponding carotid artery lesions in many other subjects, led the authors to postulate in situ intravascular thrombosis or cardiac embolism as the cause.22 Angiographic evidence of vasculitis is uncommon.

Visual disturbance and chorea23 may be particular associations in subjects with antiphospholipid. Central retinal artery and retinal branch occlusion,24–26 retinal vein thrombosis, ischaemic optic neuropathy27 and amaurosis fugax28–30 are reported. In Sneddon’s syndrome28 cerebrovascular disease occurs in association with livedo reticularis. This purple mottling of the skin is probably a manifestation of dermal venous thrombosis and antiphospholipid have been detected in a high proportion of subjects with the syndrome, suggesting an involvement in the prethrombotic state.

Cardiac valvular lesions, especially of the mitral valve, are more common in SLE patients who also have antiphospholipid.29 The abnormalities range from valve prolapse to thickened cusps and vegetations. In subjects with antiphospholipid but no evidence of collagen vascular disease valve abnormalities have also been reported29,30 and this could clearly be relevant to the pathogenesis of stroke in such individuals.

An increased incidence of neurological conditions other than stroke, in subjects with positive tests for antiphospholipid, has also been postulated. These include migraine, Guillain-Barré syndrome, myelopathies and the neurological complications of Behçet’s syndrome.31 The precise relationship between antiphospholipid and these conditions remains speculative.

A further association is of clinical and diagnostic importance. It is apparent that in young women with antiphospholipid, either within or without the spectrum of SLE, a pronounced tendency to pregnancy complications is manifest.32 Recurrent (three or more) miscarriage,33 intrauterine growth retardation, early severe pre-eclampsia and chorea gravidarium are described. Placental infection has been noted and these associations may therefore sometimes have a thrombotic basis.

The primary antiphospholipid syndrome
This term has been used to describe the syndrome of positive tests for antiphospholipid in a subject without SLE but with one or more of the strongly associated clinical states: recurrent miscarriage, thrombosis, or thrombocytopenia.

Pathogenic mechanisms for thrombosis
Negatively-charged phospholipid is an essential cofactor in fibrin generation, hence the effect of antiphospholipid on in vitro tests of coagulation. Similar phospholipids, however, are exposed on platelet activation and, importantly, are also necessary for activation of the major anticoagulant mechanism involving proteins C and S and thrombomodulin; there is evidence for interference in the function of activated protein C, by antiphospholipid, and these antibodies could also augment platelet aggregability.30–40 Other studies suggest a disturbance of vascular endothelial function in the presence of antiphospholipid, with reduced prostacyclin synthesis and enhanced release of the platelet adhesive cofactor von Willebrand factor.41 Interaction with fibrinolytic mechanisms has also been noted,42 although not reproducibly. Vascular endothelial cell antibodies appear to be present in many antiphospholipid-containing sera.43 These could well be of pathogenic importance in thrombotic manifestations, suggesting that antiphospholipid may serve only as surrogates for markers relevant to cytotoxic auto-antibodies.

Testing for antiphospholipid
The heterogeneous nature of antiphospholipid raises important considerations relating to the laboratory route to diagnosis.44 A comprehensive approach is necessary which must include a coagulation screening test, a confirmatory coagulation-based assay and a solid-phase assay such as the well characterised and standardised enzyme-linked immunosorbent assay for IgG and IgM antibody to cardiolipin. The kaolin cephalin clotting time (KCCT) is available in almost all coagulation laboratories and is a useful screening test for lupus anticoagulant, although sensitivity is highly reagent dependent. The dilute Russell’s viper venom time (DRVVT) with a confirmatory phospholipid neutralisation step to demonstrate specificity, or the kaolin clotting time (KCT), performed with dilutions of normal plasma, are useful additional tests. These coagulation assays are sensitive to lupus anticoagulant but do not provide firm quantitative information. Recommendations for their performance and interpretation have been published.45

It is important that some lupus anticoagulant will be detected in one appropriate assay and the alternative test may be negative and also that positivity in the anticardiolipin assay is not necessarily accompanied by abnormal coagulation test results. Clinical experience suggests that those samples testing positive for lupus anticoagulant ± anticardiolipin are more commonly associated with thrombosis than those positive for anticardiolipin only and that IgG anticardiolipin are of greater pathogenic significance than IgM anticardiolipin, but these distinctions are far from absolute. Also, low titre anticardiolipin are a common finding of doubtful significance and transiently positive tests for anticardiolipin, such as those occurring in infections, may also be of less clinical importance. Such antibodies are most frequently of IgM isotype. Demonstration of persistence and, in anticardiolipin assays, isotype and titre are therefore essential in the interpretation of test results.

Hereditary thrombophilia
Of the many theoretical abnormalities of the haemostatic control mechanisms which could predispose to thrombo-
sions, only three have proved clinically important to date; these are deficiencies of antithrombin, protein C and protein S. The clinical significance of other inherited conditions, such as heparin cofactor II deficiency, hypoplasminogenemia and other defects of the fibrinolytic system, is either minor or unproven.

The association between familial deficiency of antithrombin and thromboembolism was recognised in 1965. Deficiency is inherited in autosomal dominant fashion with a prevalence estimated between 1 in 2000 and 1 in 40,000 in different series. Such deficiency accounts for 2–5% of episodes of venous thromboembolism in adults presenting below the age of 45 years. Thrombotic events are rare in childhood, but the risk of thrombosis in an affected individual is estimated to be 65% between the ages of 15 and 30 years. In 80–90% of cases there is a parallel reduction in antithrombin antigen and its functional activity, typically to a level of 50–70% of mean normal—Type I deficiency. In Type II or variant deficiency there is a point mutation in the portion of the molecule responsible for heparin or thrombin binding, with reduced functional activity but normal antigen.

Proteins C and S are vitamin K dependent proteins. Familial deficiencies were first described in 1981 and 1984 respectively. The prevalence of protein C deficiency is unclear, as although up to 1 in 200 healthy asymptomatic blood donors have low levels, symptomatic deficiency is much less common—perhaps being as low as 1 in 36,000. It thus appears that the heterozygous state can be clinically silent. It does, however, account for around 5% of episodes of venous thromboembolism in young adults and individuals in clinically affected kindreds appear to have an 80% chance of a thrombotic event by the age of 40 years. Type I and Type II defects are again recognised, in protein C deficiency. The homozygous state is most commonly associated with life-threatening thrombosis in the neonatal period, although exceptions have been noted, with survival to adult life.

Protein S exists in plasma in free form, in which it can act as a cofactor for activated protein C, but also complexed in an inactive state with the acute phase protein C4b-binding protein (C4bBP). In the more common Type I heterozygous deficiency, levels of free protein S are very low, almost all being bound to C4bBP. Type II deficiency, characterised by low levels of both free and bound protein, is rare. The thrombosis risk is similar to that in protein C deficiency.

**Stroke and inherited thrombophilia**

Unsurprisingly, sagittal sinus and cortical venous thrombosis have been reported in all three deficiency states and this is consistent with the high incidence of venous thromboembolism, which often occurs in unusual sites.

There are numerous reports of cerebral infarction due to arterial thrombosis in subjects with apparent deficiency of antithrombin, protein C and protein S. However, the relationship between stroke and inherited thrombophilia is apparently far weaker than that with antiphospholipid, and is undoubtedly extremely small compared with the risk of a venous thromboembolic event.

Protein S deficiency in subjects with angiographic evidence of intracerebral arterial occlusion has been reported. However, only rarely has familial thrombophilia been conclusively diagnosed, by demonstration of persistence of the deficiency remote from the acute event, and by detection of clinically affected family members. This is of particular relevance in protein S deficiency, as increases in C4bBP as part of the acute phase response may result in an acquired reduction in free (functional) protein S which is not necessarily causal in the thrombotic event. Sie et al. studied 23 subjects in 17 families with protein S deficiency. Six had a history of arterial thrombosis, in three cases involving the cerebral vessels. In contrast, in a survey of 136 subjects from 12 kindreds, no case of symptomatic arterial occlusive disease was found, and in another series no case of deficiency of total protein S among 50 young survivors of stroke was detected. However, Sacco et al. found reduced plasma protein S in 21 of 103 stroke patients, but no follow up or family study was performed.

A similar picture has emerged in relation to protein C deficiency and stroke. In a study of 50 consecutive subjects suffering stroke at an age of 45 years or less, three had Type I familial protein C deficiency. In contrast, although cerebral venous thrombosis was recorded in three subjects, no case of arterial thrombosis was found in 53 protein C deficient individuals from 20 well-documented families with inherited deficiency. Stroke in Type II deficiency has also been reported, as has stroke in a child with the acquired protein C deficiency which may occur after high-dose chemotherapy. Again it is important to note that transient (acquired) protein C deficiency may be detected in the acute phase of stroke, and indeed this may be a marker of poor outcome.

Stroke in familial antithrombin deficiency has rarely been reported. Consumption of antithrombin during thrombosis results in a transient fall in the plasma level and such an abnormality was noted in three subjects in a survey of 45 consecutive episodes of stroke. Interestingly, there are two reports of stroke in young subjects with variant antithrombin with reduced heparin binding.

To settle the controversy on whether familial thrombophilia predisposes to cerebral arterial occlusive disease, more information is required on the prevalence of these deficiencies in the healthy population, as well as in those with stroke and non-vascular neurological disease. Although some well conducted surveys have suggested a high prevalence of deficiency of protein C and S when young stroke patients are screened, this has not been a consistent finding. At present it seems reasonable to conclude that deficiency of a natural anticoagulant, congenital or acquired, may add to the risk of arterial thrombosis, in the presence of other risk factors.

**Thrombocytosis and stroke**

Neurological manifestations are frequently noted in essential thrombocythaemia, which is a clonal marrow disorder, one of the myeloproliferative diseases, in which the predominantly affected cell type is the megakaryocyte. Peripheral blood platelet counts in excess of 1000 × 10^9/l are not uncommon, but extensive thrombotic disease can be associated with counts around 600 × 10^9/l in this disease. A total of 85% of affected individuals are over 50 years of age, although stroke in younger subjects may be a presenting event.

Neurological manifestations have included transient ischaemic episodes, visual disturbance, uncinate and focal epilepsy, and cerebellar ataxia, as well as hemiplegia. Slowly progressive stroke may occur. Thrombosis of dural sinuses and otherwise benign intracranial hypertension are other complications of this disorder.

Similar events may occur in another myeloproliferative disorder, polycythaemia rubra vera. Here, tissue hypoxia is often due to hyperviscosity secondary to a
raised haemotocrit, but megakaryocytic proliferation, with thrombocytosis, may contribute. In contrast, stroke is uncommon in non-myeloproliferative thrombocytosis. Raised blood platelet count is a reactive phenomenon in chronic inflammatory or neoplastic disease, as well as after tissue trauma, in the presence of chronic bleeding and after splenectomy. Intracranial vascular events have only occasionally been reported in this setting.99-103

Screening for coagulation abnormalities in thrombotic stroke

An automated full blood count will reliably detect the presence of essential thrombocytopenia in subjects presenting with stroke, although repeat testing and further investigation will be necessary to exclude a reactive thrombocytosis. An elevated red cell count and haemotocrit, often with a thrombocytosis, will alert to the possibility of polycythaemia rubra vera, confirmation being by exclusion of causes of secondary polycythaemia and demonstration of a raised body red cell mass.

More difficult is the decision to screen for antiphospholipid and for familial thrombophilia. Screening for the presence of antiphospholipid using the range of laboratory tests described above is justified in subjects presenting at an age of 50 years or less with thrombotic stroke, especially where other risk factors are absent. When stroke occurs against a background of recurrent thrombosis, thrombocytopenia, manifestations of collagen vascular disease or recurrent miscarriage, screening for antiphospholipid is particularly likely to be fruitful. The possible significance of positive tests should be confirmed by demonstration of reproducibility over a period of at least three months.

Assay of antithrombin, protein C and protein S, which is relatively expensive, is not justified at present in the routine investigation of cerebral arterial thrombosis, although the availability of further epidemiological data may allow the identification of subgroups where screening is likely to be productive. Performance of these assays may be justified in subjects with apparently spontaneous cerebral cortical venous thrombosis or in stroke where there is also a strong family history of venous thromboembolism.

Other tests of coagulation, such as platelet aggregation assays, fibrinogen concentration, coagulation factor assays and tests of fibrinolysis are not indicated, as the clinical significance, if any, of the often transient abnormalities which may occur is open to doubt.

Therapeutic considerations

In stroke due to essential thrombocythaemia, it is logical to recommend cytoreductive therapy, and usually also aspirin, as prophylaxis against further thrombotic events. Hydroxyurea has been increasingly favoured over alkylating agents and radiophosphorus, as the risk of transformation to a leukemoid state with long-term therapy appears to be lower. The role of α-interferon in this disorder remains controversial.

In subjects with antiphospholipid several therapeutic strategies have been adopted. Antiplatelet agents, anticoagulants, corticosteroids and other immunosuppressive drugs have been used. In the absence of non-thrombotic autoimmune manifestations, immunomodulatory therapy is not appropriate, at least as the initial therapeutic strategy, unless anticoagulant treatment has failed. Corticosteroids, immunosuppressant drugs, plasma exchange and high dose intravenous immunoglobulin have all been the subjects of anecdotal reports, not invariably with successful outcome.

In view of the high rate of recurrent stroke, aspirin or warfarin prophylaxis should be considered. Again, there is a lack of controlled trials to guide management. There are reports of successful use of aspirin or warfarin in individual subjects with cerebrovascular complications but recurrent events have occurred despite treatment.104-108 In the cases reported by the APA9 group 13 of 18 subjects treated with antiplatelet agents had further events. Propective studies are needed as a guide to the appropriate management of stroke in subjects with antiphospholipid. Until then most affected individuals will be given aspirin or warfarin in an attempt to influence the high risk of further stroke.

The diagnosis of inherited thrombophilia is not necessarily an indication for warfarin therapy in the absence of symptoms, but should lead to counselling and the use of prophylaxis during times of high risk, such as pregnancy and the post-partum period and peri-operatively. Long-term warfarin prophylaxis should, however, be considered after a life-threatening thromboembolic event, when the risks of such intervention must be weighed against the perceived risk of recurrence in an individual.

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9 McNeil HP, Simpson RJ, Chesterman CN, Ketia SA. Antiphospholipid antibodies are directed against a complex antigen that includes a lipid binding inhibitor of coagulation: β-glycoprotein I (apolipoprotein H). Proc Natl Acad Sci USA 1990;87:4120-4.


Neurological stamp

Karl Friedrich Hieronymus von Munchausen (1720–97)

Baron Munchausen served in the Russian army in the war against the Turks from 1763–72. After a distinguished military career he retired from the army to manage the family estate near Hanover where he amused and sometimes astounded his friends and relations with recollections of his adventures during the war. The tales were collected together by R E Raspe and first published in England in 1785 in the book Baron Munchausen’s narratives of his marvellous travels and campaigns in Russia. These were subsequently published in many languages and new editions appeared with more stories based on contemporary events. The name of Munchausen came to symbolise the preposterous and amusing stories containing grandiose but engaging lies.

In 1951 Richard Asher coined the term “Munchausen syndrome” to describe a syndrome of addiction to hospital in which adults invented false symptoms and signs. Professor Roy Meadows has used the term “Munchausen by Proxy” to describe the fabrication of an illness on behalf of someone else—usually a mother on behalf of her child.

This stamp was issued in 1970 by Germany on the 250th anniversary of the Baron’s birth (Stanley Gibbons 1522; Scott 1020).

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