

Fortnightly Review

Parvovirus B19: an expanding spectrum of disease

Bernard Cohen

See p 1542

Parvoviruses are small round viruses with a single stranded DNA genome that lack a lipid envelope (fig 1). They are widespread, and in veterinary medicine several are recognised as notable pathogens causing a range of diseases that includes reproductive failure. Animal parvoviruses are not, however, transmissible to humans, and pregnant women are not at risk. The first human parvoviruses to be recognised were adeno-associated viruses. These viruses replicate only in the presence of a helper virus, a function provided by adenoviruses or other large DNA viruses. Antibodies to adenoviruses are found in human populations, but the viruses are not pathogenic. They cause latent infection by integrating into the human chromosome and have attracted interest as potential vectors for human gene therapy.

The virus

Parvovirus B19, the first known pathogenic human parvovirus, was discovered by chance in healthy blood donors being screened for hepatitis B.¹ The name comes from the single isolate within a panel of hepatitis

Clinical presentations associated with parvovirus B19 infection

Most common	Rare
Asymptomatic infection	Vasculitis
Erythema infectiosum	Peripheral neuropathy
Acute arthritis	Nephritis
Hydrops fetalis	Myocarditis
Transient aplastic crisis	
Prolonged anaemia in immunocompromised patients	

sera in which the virus was discovered (panel B, serum 19). The virus's biochemical and biophysical properties put it into the family *Parvoviridae*, and because of its tropism for red blood cells it has been placed in the genus *Erythrovirus*, of which it is so far the sole member. It may, however, be joined by a simian parvovirus recently described in cynomolgus monkeys, which shares many of the properties of B19 and which may also provide an animal model for studies of B19 pathogenesis.¹⁴ We now know that the virus's tropism for red blood cells is mediated through the erythrocyte P antigen (globoside).² This is almost universally expressed on the surface of human erythrocytes and some other cell types. Rarely, individuals lack P antigen and, remarkably, are not susceptible to B19 infection.³

B19 was regarded at first as an "orphan" virus, unlinked to any disease; but subsequently a range of diseases caused by B19 infection has been described (box).

Infection in children

The first indication that the B19 virus caused disease in humans came from following up the viraemic donors who had been identified by chance.^{4,5} They were found to have had a non-specific febrile illness, sometimes combined with a rubella-like rash. In addition, two patients infected with B19 were reported to have had a minor febrile illness.⁶ The first disease to be definitely linked with B19 infection, however, was the transient aplastic crisis of sickle cell anaemia.⁷ The B19 virus was later shown to cause transient aplastic crisis in patients with other inherited haemolytic conditions, such as hereditary spherocytosis,⁸ as well as acquired forms of anaemia.^{9,10} Studies of the prevalence of antibodies to the virus, however, showed that B19 infection was often acquired in childhood and that 60% or more of adults in Britain are seropositive without evidence of haematological disease.¹¹ It therefore seemed likely that B19 might cause a common childhood illness, and in 1983 the link was made with

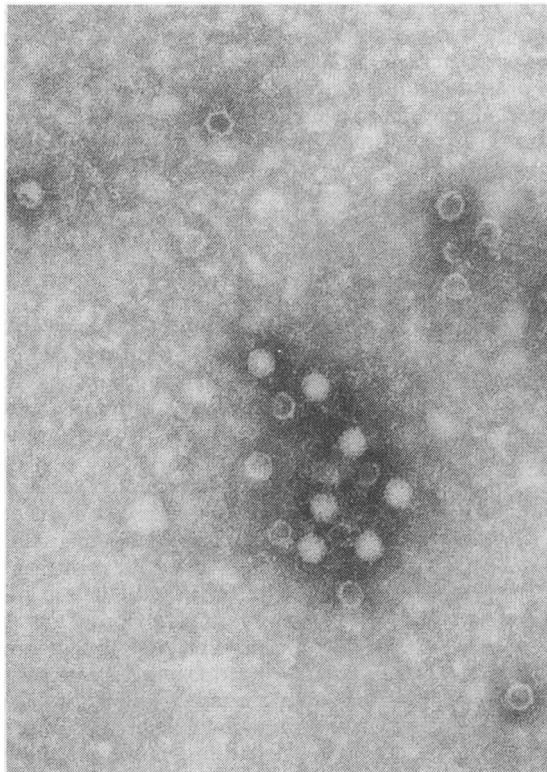


Fig 1—Electron micrograph of B19 isolate showing morphology typical of a parvovirus (final magnification $\times 157\,000$)

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Summary points

- Infection with parvovirus B19 is common and is usually spread by the respiratory route
- In immunocompetent individuals with normal red cells B19 infection is benign and self limiting, usually presenting as erythema infectiosum (the slapped cheek syndrome) in children
- In adults, especially women, B19 infection is often complicated by acute polyarthritis, which may persist in some cases
- Parvovirus B19 may also be transmitted across the placenta. Severe fetal B19 infection may result in hydrops fetalis and fetal death
- Parvovirus B19 causes transient aplastic crisis in patients with chronic haemolytic anaemia; such patients pose a risk of nosocomial transmission of the virus
- Severe anaemia, prolonged or relapsing, may develop in immunocompromised patients infected with parvovirus B19. This can be treated with normal immunoglobulin
- Parvovirus B19 may be transmitted by blood components or blood products

erythema infectiosum.¹² This mild illness, otherwise known as fifth disease or the slapped cheek syndrome (fig 2), is often mistaken for rubella or another exanthem. An accurate diagnosis is important for surveillance both of rubella and of measles. Fortunately, laboratory confirmation of erythema infectiosum, rubella, and measles is now possible with salivary diagnosis.¹³ Outbreaks of erythema infectiosum in schools usually occur in winter or spring. In Britain, April and May are the peak months, though cases may be recorded in any month. A pattern is emerging of two years of B19 epidemic followed by two years of low incidence. In 1993 and 1994 large B19 epidemics occurred, so 1997 will see the next upsurge of infection.

Infection in adults

B19 infection is a benign, self limiting illness in children, but in adults, especially women, it is often complicated by acute arthritis (fig 3). Indeed, arthritis without a rash is a common presentation of B19 infection in adults. In a study of acute arthropathy in adults, 19 of 24 cases attributed to infectious agents were associated with parvovirus B19.¹⁴ The study by



Fig 2—Child with slapped cheek syndrome (published with father's permission)

Jobanputra *et al* in this issue (p 1542) found that 6.7% (20/297) of serum samples submitted by general practitioners for rheumatoid factor tests were B19 positive on polymerase chain reaction.¹⁵ Most of them were also B19 IgM positive, indicating recent acute infection. This serves to remind us that, although B19 is a common cause of acute arthropathy, it is not often recognised.

B19 arthropathy usually resolves in a few weeks, but 10% of women with B19 infection develop joint symptoms lasting more than two months. In some cases the symptoms persist for years. We do not yet understand the pathogenesis of this chronic arthritis as histologically the joint shows no inflammatory response^{14,16} and evidence that B19 virus persists in the synovium¹⁷ has not been confirmed.¹⁸ None the less,

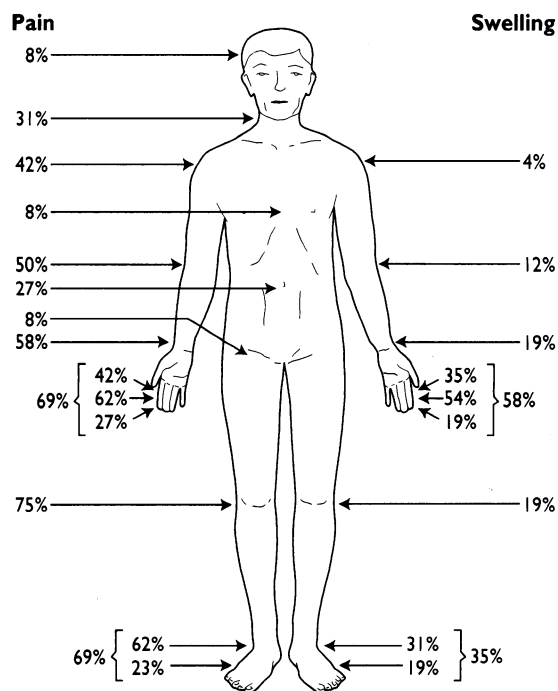


Fig 3—Distribution of joint involvement expressed as percentage of patients reporting pain or in whom joint swelling was observed (adapted with permission from Woolf AD *et al*, *Arch Intern Med* 1989;149:1153-6)

B19 infection should be considered in the differential diagnosis of early onset rheumatoid arthritis as some patients with B19 arthropathy fulfil the diagnostic criteria for this disease.¹⁴

Infection in pregnancy

The other important complication in women arises during pregnancy. Although most women who have had B19 infection in pregnancy deliver a healthy infant at term, B19 may cross the placenta, infect the fetus, and cause hydrops fetalis and fetal death. The fetus seems to be most susceptible during the first and second trimesters of pregnancy. The precise incidence of B19 embryopathy is not known, but about 10% of pregnancies complicated by B19 infection result in fetal loss.¹⁹ Pregnant women with asymptomatic B19 infection seem to be at greater risk than those reporting a rash. The clinical management of fetal B19 infection may include intrauterine blood transfusions. This treatment has been controversial, but a study conducted during the epidemic years of 1993 and 1994 found a higher rate of survival of fetuses that had had transfusion compared with those that had not.²⁰ A pregnancy does not need to be terminated when B19 infection occurs as no evidence exists of damage to fetuses that survive infection and are born alive.

Infection in immunocompromised people

The clinical manifestations considered so far result from the usually self limiting infection in those with normal immune responses. However, in immunocompromised patients B19 can persist, causing severe anaemia due to persistent destruction of red cell precursors in the bone marrow. White cell and platelet precursors may also be affected, and chronic bone marrow failure has been described in an infant with Nezelof syndrome, a rare combined immunodeficiency.²¹ Persistent B19 infection has also been recognised in children and adults with leukaemia,^{22, 23} in transplant recipients,²⁴ and in people with HIV infection.²⁵ Infection in these groups of patients is successfully treated with high doses of intravenous immunoglobulin. Prompt recognition of persistent B19 is important, not only because it can be treated in the affected individual but also to prevent nosocomial transmission to other compromised patients.²⁶

Other manifestations of B19 infection

In addition to the features of B19 infection outlined above, reports have linked B19 to several other diseases. These include vasculitis,²⁷ peripheral neuropathy²⁸ (numbness and tingling is sometimes a feature of outbreaks of erythema infectiosum²⁹), and myocarditis in infants³⁰ and in fetuses.³¹ Recently nephritis has been described in patients with B19 infection.³² This might have been predicted as extensive virus and antibody complexes form during B19 infection. Reports of B19 infection in patients with meningitis,³³ encephalitis,³⁴ Kawasaki disease,³⁵ hepatic dysfunction,³⁶ and heart failure³⁷ are less convincing as diagnosis involves unreliable antibody tests or uncontrolled polymerase chain reaction assays that can give misleading results. Even if B19 infection is proved, the aetiological importance of case reports should be confirmed by wider epidemiological studies.

B19 and blood transfusion

Though B19 causes a range of diseases, 20% to 50% of infections remain asymptomatic. The importance of asymptomatic B19 among blood donors should be considered. Its prevalence was initially estimated to be low, with 1 in 40 000 donors being viraemic.³⁸ More sensitive screening tests have now shown the prevalence to range from 1 in 3000 during non-epidemic periods³⁹ to as high as 1 in 167 during an epidemic.⁴⁰ Transmission of B19 has recently been documented in a thalassaemic patient receiving a single donor transfusion.⁴¹ The risks of B19 infection are greatly increased when thousands of donor plasma samples are pooled to manufacture blood products. Even with the lower prevalence of donors who are B19 positive, large pools made from thousands of plasma samples are likely to be contaminated. Moreover, the contamination will be at a significant level because a single donor plasma sample that is B19 positive contains as many as 10¹² virus particles/ml. Thus, although antibodies to B19 may also be present, patients receiving blood products are at risk of B19 infection. Transmissions of B19 to patients receiving clotting factor concentrates derived from plasma were first recognised in the early 1980s but only as asymptomatic infections.³⁸ The high seroprevalence of B19 in haemophilic patients showed that infection from blood products is common,³⁸ and symptomatic infections have since been described presenting with typical signs of erythema infectiosum⁴² or in more severe cases as hypoplastic anaemia⁴³ and pancytopenia.⁴⁴ The B19 virus continues to be transmitted by this route because, lacking a lipid envelope, it is not susceptible to the

solvent-detergent treatment used to inactivate HIV and the hepatitis B and C viruses in blood products. Moreover, B19 is stable in heat and remains infective even after treatment with dry heat at 80°C for 72 hours, which is used for some blood products.

An alternative to viral inactivation could be the screening of blood donors for the B19 virus. Donors could be selectively screened when unpooled blood or components were intended for patients at risk of developing severe B19 infections. Such patients would include those who are immunocompromised or have an underlying haemolytic anaemia, pregnant women, and probably neonates. The ultra sensitive polymerase chain reaction technique has recently been shown to be feasible for screening donors, by using a system in which donor plasma is pooled, thus reducing the number of tests needed.³⁹ Polymerase chain reaction, however, remains a complex and costly method, and simple antibody tests that can be automated are probably a more practical alternative. The presence of antibody to the B19 virus is assumed to show a resolved past infection and a donor free of the virus (unlike in cases of HIV or cytomegalovirus infections, in which the presence of antibody correlates with latent infection and infectivity). But before the microbiology departments of blood transfusion laboratories are burdened with yet another screening test, this assumption needs to be tested and the cost-benefit analysis of testing for B19 examined.

Prevention

A vaccine for parvovirus B19 infection is being developed.⁴⁵ Priority for the vaccine would go to patients with sickle cell anaemia, but in view of the important morbidity now known to accompany B19 infection, wider use of a B19 vaccine should be considered. If the vaccine proved safe and efficacious it could, for example, be given to infants at the same time as the triple vaccine (mumps, measles, and rubella).

Conclusion

It is apt that screening of blood donors for parvovirus is now in prospect. The virus was first found in healthy donors and is transmitted by blood components and blood products. B19 infection, however, is more usually transmitted by the respiratory route and is now known to cause several diseases. In immunocompetent people with healthy red blood cells the infection is relatively benign and self limiting. An exanthem (erythema infectiosum) in children or acute arthritis in adults are the most common clinical presentations. There are, however, vulnerable groups at risk of more severe disease. Both the acute anaemic episode (transient aplastic crisis) in patients with sickle cell anaemia and the prolonged anaemia in immunocompromised patients reflect the tropism of parvovirus B19 for erythroid progenitor cells. Finally, in pregnancy B19 may cross the placenta, causing severe fetal infections. The maternal immunity acquired from this event lasts for life, and subsequent pregnancies are unaffected by B19 infection.

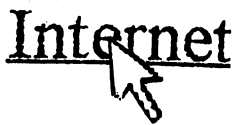
- 1 Cossart YE, Field AM, Cant B, Widdows D. Parvovirus-like particles in human sera. *Lancet* 1975;i:72-3.
- 1a O'Sullivan MG, Anderson DC, Fikes JD, Bain FT, Carlson CS, Green SW, et al. Identification of a novel simian parvovirus in cynomolgus monkeys with severe anemia. *J Clin Invest* 1994;93:1571-6.
- 2 Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 parvovirus. *Science* 1993;262:114-7.
- 3 Brown KE, Hibbs JR, Gallinella G, Anderson SM, Lehman ED, McCarthy P, et al. Resistance to parvovirus B19 infection due to lack of virus receptor (erythrocyte P antigen). *N Engl J Med* 1994;330:1192-6.
- 4 Paver WK, Clarke SKR. Comparison of human faecal and serum parvo-like viruses. *J Clin Microbiol* 1976;4:67-70.
- 5 Courouace AM, Ferchal F, Morinet F, Muller A, Drouet J, Soulier JP, et al. Human parvovirus infections in France. *Lancet* 1984;ii:160.

- 6 Shneerson JM, Mortimer PP, Vandervelde EM. Febrile illness due to a parvovirus. *BMJ* 1980;280:1580.
- 7 Pattison JR, Jones SE, Hodgson J, Davis LR, White JM, Stroud CE, et al. Parvovirus infections and hypoplastic crisis in sickle-cell anaemia. *Lancet* 1981;ii:664-5.
- 8 Kelleher JF, Luban NLC, Mortimer PP, Kamimura T. Human serum "parvovirus"; a specific cause of aplastic crisis in children with hereditary spherocytosis. *J Pediatr* 1983;102:720-2.
- 9 Frickhofen N, Raghavachar A, Heit W, Heimpel H, Cohen BJ. Human parvovirus infection. *N Engl J Med* 1986;314:646.
- 10 Lefrere JJ, Bourgois H. Human parvovirus associated with erythroblastopenia in iron deficiency anaemia. *J Clin Pathol* 1986;39:1277-8.
- 11 Cohen BJ, Buckley MM. The prevalence of antibody to human parvovirus B19 in England and Wales. *J Med Microbiol* 1988;25:151-3.
- 12 Anderson MJ, Jones SE, Fisher-Hoch SP, Lewis E, Hail SM, Bartlett CLR, et al. Human parvovirus, the cause of erythema infectiosum (fifth disease)? *Lancet* 1983;ii:1378.
- 13 Mortimer PP, Parry JV. Non-invasive virological diagnosis: are saliva and urine specimens adequate substitutes for blood? *Reviews in Medical Virology* 1991;1:73-8.
- 14 White DG, Woolf AD, Mortimer PP, Cohen BJ, Blake DR, Bacon PA. Human parvovirus arthropathy. *Lancet* 1985;ii:419-21.
- 15 Jobanputra P, Davidson F, Graham S, O'Neill S, Simmonds P, Yap PL. High frequency of parvovirus B19 in serum samples submitted for a rheumatoid factor test. *BMJ* 1995;311:1542.
- 16 Naides SJ, Foto F, Marsh JL, Scharosch LL, Howard EJ. Synovial tissue analysis in patients with chronic parvovirus B19 arthropathy. *Clin Res* 1991;39:733A.
- 17 Saal JG, Steile M, Einsele H, Muller C, Fritz P, Zacker J. Persistence of B19 parvovirus in synovial membranes in patients with rheumatoid arthritis. *Rheumatol Int* 1992;12:147-51.
- 18 Nikkari S, Roivainen A, Hannonen P, Mötönen T, Luukkainen R, Yli-Jama T, et al. Persistence of parvovirus B19 in synovial fluid and bone marrow. *Ann Rheum Dis* 1995;54:597-600.
- 19 Public Health Laboratory Service Working Party on Fifth Disease. Prospective study of human parvovirus B19 infection in pregnancy. *BMJ* 1990;300:1166-70.
- 20 Fairley CK, Smolencic JS, Caul OE, Miller E. An observational study of the effect of intrauterine transfusions on the outcome of fetal hydrops from parvovirus B19. *Lancet* 1995;346:1335-7.
- 21 Kurtzman GJ, Ozawa K, Cohen BJ, Hanson G, Oseas R, Young NS. Chronic bone marrow failure due to persistent B19 parvovirus infection. *N Engl J Med* 1987;317:287-94.
- 22 Kurtzman GJ, Cohen BJ, Meyers P, Amunullah A, Young NS. Persistent B19 parvovirus infection as a cause of severe chronic anaemia in children with acute lymphocytic leukaemia. *Lancet* 1988;ii:1159-62.
- 23 Weiland HT, Salimans MMM, Fibbe WE, Kluin PM, Cohen BJ. Prolonged parvovirus B19 infection with severe anaemia in a bone marrow transplant recipient. *Br J Haematol* 1989;71:300.
- 24 Ramage JK, Hale A, Gane E, Cohen BJ, Boyle M, Mufti G, et al. Parvovirus B19-induced red cell aplasia treated with plasmapheresis and immunoglobulin. *Lancet* 1994;343:667-8.
- 25 Frickhofen N, Abkowitz JL, Safford M, Berry JM, Antunez de Mayolo J, Astrow A, et al. Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anaemia in AIDS. *Ann Intern Med* 1990;113:926-33.
- 26 Evans JPM, Rossiter MA, Kumaran TO, Marsh GW, Mortimer, PP. Human parvovirus aplasia: case due to cross infection in a ward. *BMJ* 1984;288:681.
- 27 Li Loong TC, Coyle PV, Anderson MJ, Allen GE, Conolly JH. Human serum parvovirus associated vasculitis. *Postgrad Med J* 1986;72:493-4.
- 28 Denning DW, Amos A, Rudge P, Cohen BJ. Neuralgic amyotrophy due to parvovirus infection. *J Neurol Neurosurg Psychiatry* 1987;50:641-2.
- 29 Faden H, Gary WG, Korman M. Numbness and tingling of fingers associated with parvovirus B19 infection. *J Infect Dis* 1990;161:354-5.
- 30 Kinsely AS, O'Shea PA, Anderson LJ, Gary GW Jr. Parvovirus B19 infection, myocarditis and death in a 3-year-old boy. *Pediatric Pathology Abstracts* 1988;8:665.
- 31 Porter HJ, Quantrill AM, Fleming KA. B19 parvovirus infection of myocardial cells. *Lancet* 1988;ii:535-6.
- 32 Wierenga KJ, Pattison JR, Brink N, Griffiths M, Miller M, Shah DJ, et al. Glomerulonephritis after human parvovirus infection in homozygous sickle-cell disease. *Lancet* 1995;346:475-6.
- 33 Okumura A, Ichikawa T. Aseptic meningitis caused by human parvovirus B19. *Arch Dis Child* 1993;68:784-5.
- 34 Watanabe T, Sathoh M, Oda Y. Human parvovirus 1319 encephalopathy. *Arch Dis Child* 1994;70:71.
- 35 Nigro G, Zerbini M, Krzysztoskiak A, Gentilomi G, Porcaro MA, Mango T, Musiani M. Active or recent parvovirus B19 infection in children with Kawasaki disease. *Lancet* 1994;343:1260-1.
- 36 Yoto Y, Kudoh T, Asanuma H, Numazaki K, Tsutsumi Y, Nakata S, et al. Transient disturbance of consciousness and hepatic dysfunction with human parvovirus B19 infection. *Lancet* 1994;344:624-5.
- 37 Maim C, Fridell E, Jansson K. Heart failure after parvovirus B19 infection. *Lancet* 1993;341:1408.
- 38 Mortimer PP, Luban NLC, Kelleher JF, Cohen BJ. Transmission of serum parvovirus-like virus by clotting factor concentrates. *Lancet* 1983;ii:482-4.
- 39 McOmish F, Yap PL, Jordan A, Hart H, Cohen BJ, Simmonds P. Detection of parvovirus B19 in donated blood: a model system for screening by polymerase chain reaction. *J Clin Microbiol* 1993;31:323-8.
- 40 Yoto Y, Kudoh T, Haseyama K, Suzuki N, Chiba S. Detection of human parvovirus B19 DNA in clinical specimens by a nested polymerase chain reaction assay [abstract]. In: *Proceedings of Vth parvovirus workshop, Montpellier, 1995*:60.
- 41 Lyon DJ, Chapman CS, Martin C, Brown KE, Clewley JP, Flower AJE, et al. Symptomatic parvovirus B19 infection and heat treated factor IX concentrate. *Lancet* 1989;ii:1085.
- 42 Morfini M, Longo G, Rossi Ferrini P, Azzi A, Zakrewska K, Ciappi S, et al. Hypoplastic anaemia in a haemophilic first infused with a solvent/detergent treated factor VIII concentrate: the role of human B19 parvovirus. *Am J Hematol* 1992;39:149-50.
- 43 Yee TT, Lee CA, Pasi KJ. Life threatening human parvovirus B19 infection in immunocompetent haemophilia. *Lancet* 1995;345:794-5.
- 44 Zanella A, Rossi F, Cesana C, Foresti A, Nador F, Binda AS, et al. Transfusion-transmitted human parvovirus B19 infection in a thalassaemic patient. *Transfusion* 1995;35:769-72.
- 45 Bansall GP, Hatfield JA, Dunn FE, Kramer AA, Brady F, Riggan CH, et al. Candidate recombinant vaccine for human B19 parvovirus. *J Infect Dis* 1993;167:1034-44.

Guide to the Internet

The world wide web

Mark Pallen



This is the third in a short series of articles introducing the Internet to medical practitioners

The world wide web provides a uniform, user friendly interface to the Internet. Web pages can contain text and pictures and are interconnected by hypertext links. The addresses of web pages are recorded as uniform resource locators (URLs), transmitted by hypertext transfer protocol (HTTP), and written in hypertext markup language (HTML). Programs that allow you to use the web are available for most operating systems. Powerful on line search engines make it relatively easy to find information on the web. Browsing through the web—"net surfing"—is both easy and enjoyable. Contributing to the web is not difficult, and the web opens up new possibilities for electronic publishing and electronic journals.

The world wide web (WWW, W3, or simply "the web") is the crowning glory of the Internet, providing a uniform, user friendly interface to the net. It allows information to be presented in a sophisticated and attractive format, interlacing pictures with text. Simply by clicking on highlighted text, you can surf the net or search for information.

The web has fuelled such an explosion of interest in the Internet that it is easy to forget quite how new

it all is. Although Tim Berners-Lee and his coworkers first put forward proposals for the world wide web in 1989-90, the web was catapulted to success only with the release of Macintosh and Windows versions of Marc Andreessen's world wide web client program (or "web browser"), Mosaic, in the autumn of 1993. Since then, the web has shown astonishing exponential growth.

Anatomy of the web

The web page is the basic unit of information on the web. Four elements are needed for its creation, transmission, or retrieval: hypertext; uniform resource locators (URLs); hypertext transfer protocol (HTTP); and hypertext markup language (HTML).

HYPertext

Hypertext¹ underpins the web. The term "hypertext" was coined by Ted Nelson in the 1960s, although the concept was probably first proposed by Vannevar Bush in the 1940s.² The hypertext idea was later incorporated into the Macintosh program Hypercard and now also features in the help program built into the Windows operating system.

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