

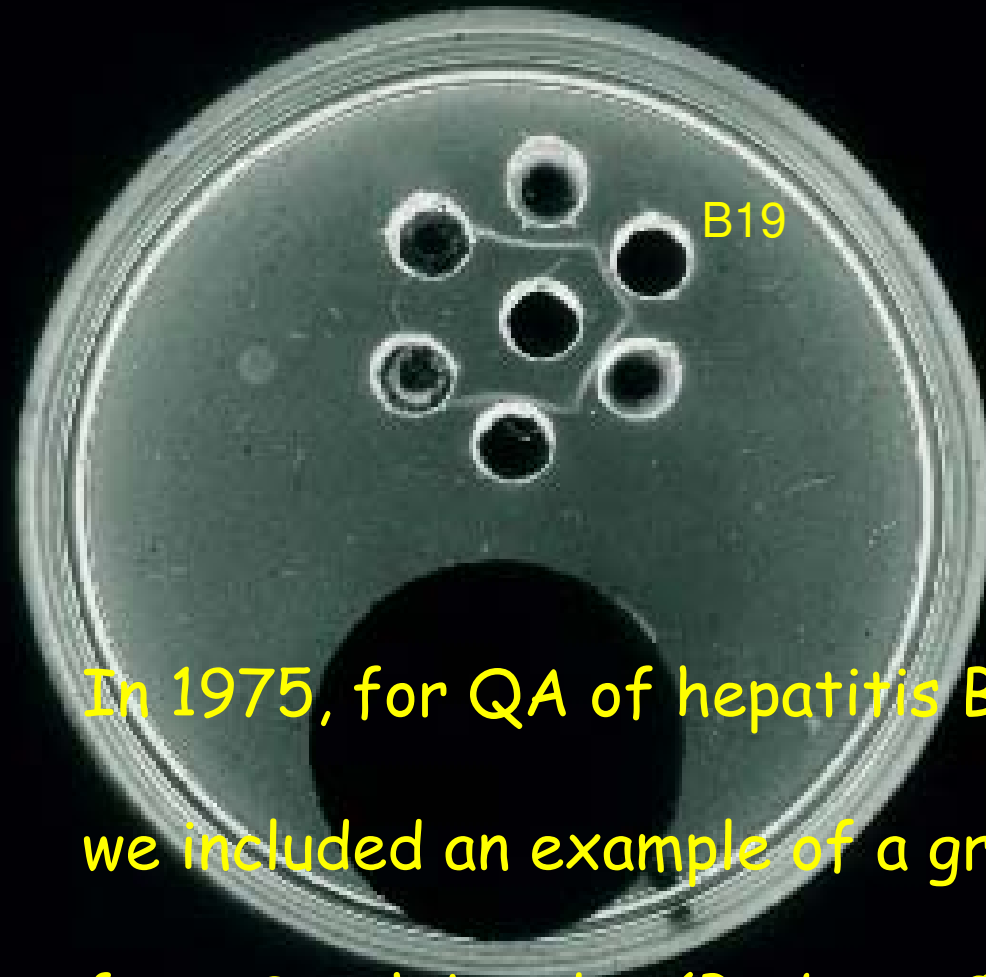
Human Parvovirus B19

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Retracing the history of B19 is a good way to appreciate its potential as a pathogen, and also for me to mention some of the many virologists who have been involved.

So, to begin at the beginning

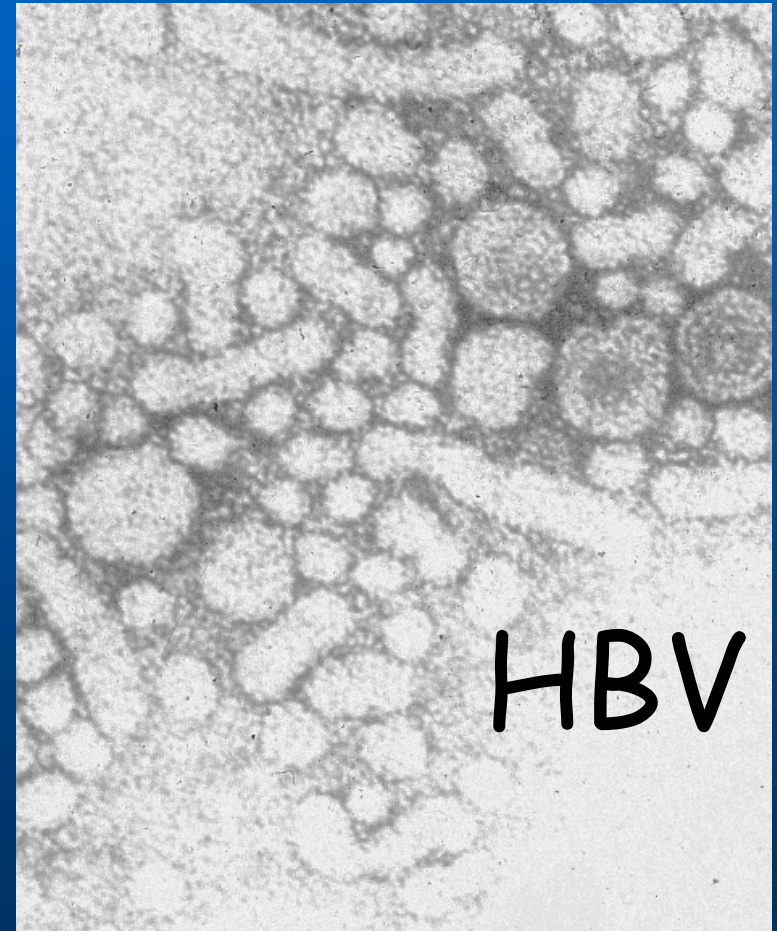
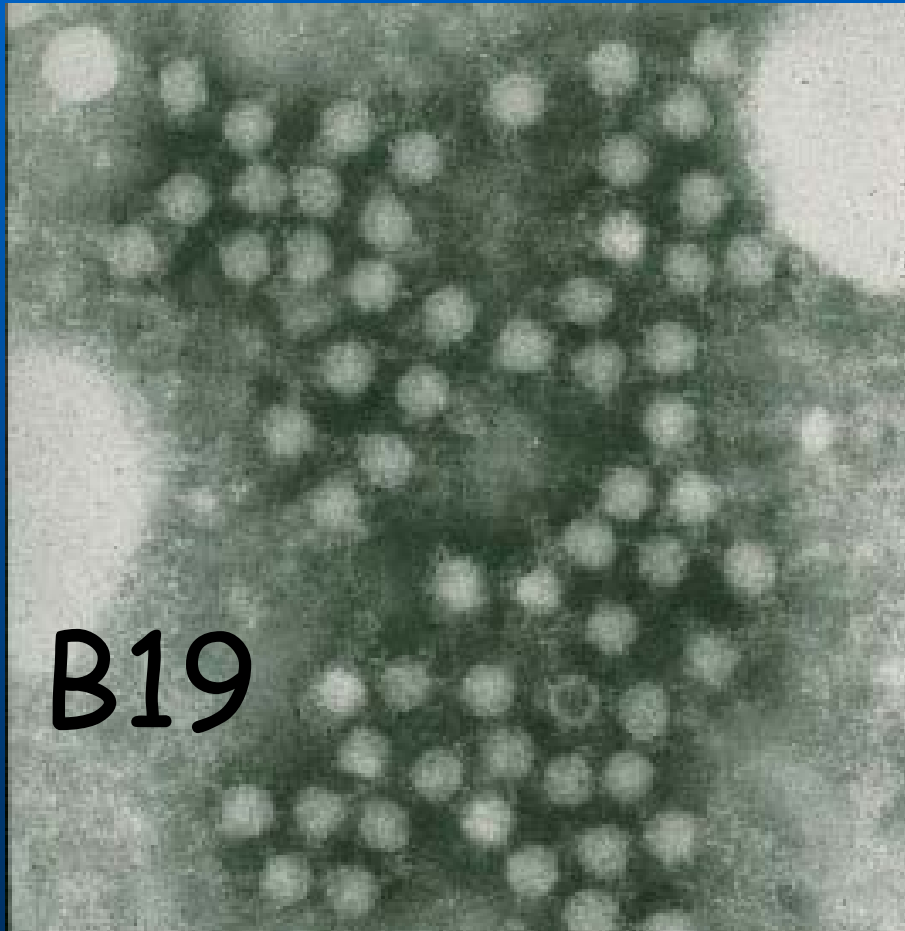


In 1975, for QA of hepatitis B testing in the BTS we included an example of a group of donor sera from South London (Barbara Cant and Dianne

Widdows) which gave anomalous results at the

Virus Reference Lab. It was sample 19 in panel B

To be positive in this gel diffusion test the antigen concentration had to be high, so we compared the appearance with HBV in the electron microscope



Similar, but.....

Anne Field saw some suggestive clues:



Some samples showed "empties" and fragmentation into half circles. The size was 20nm - both features of animal parvoviruses (HBV small rounds are 22nm)

Parvovirus taxonomy:

2 groups:

Adeno-associated viruses (AAV)

require helper virus

Autonomous parvoviruses

grow “only” in rapidly dividing cells

ANIMAL PARVOVIRUS DISEASE ASSOCIATIONS:

Kilham's rat virus - persistent asymptomatic

Canine/feline parvoviruses - diarrhoea, myocarditis

Porcine parvovirus - fetal loss

Minute mouse virus - ?

Bovine parvovirus - diarrhoea

Aleutian disease of mink - multisystem

Many animal parvoviruses cause asymptomatic long term infection in adults but acute disease in infants. Transplacental infection is common and often associated with fetal loss due to widespread virus growth in tissues

We tested the physical properties of B19 which were parvo-like: SG 1.40, resistant to ether.

Then we used antisera from the known AAV and animal parvoviruses in gel diffusion - all neg.

Finally we tested the sera of all the lab staff -40% positive so B19 was a common human infection.

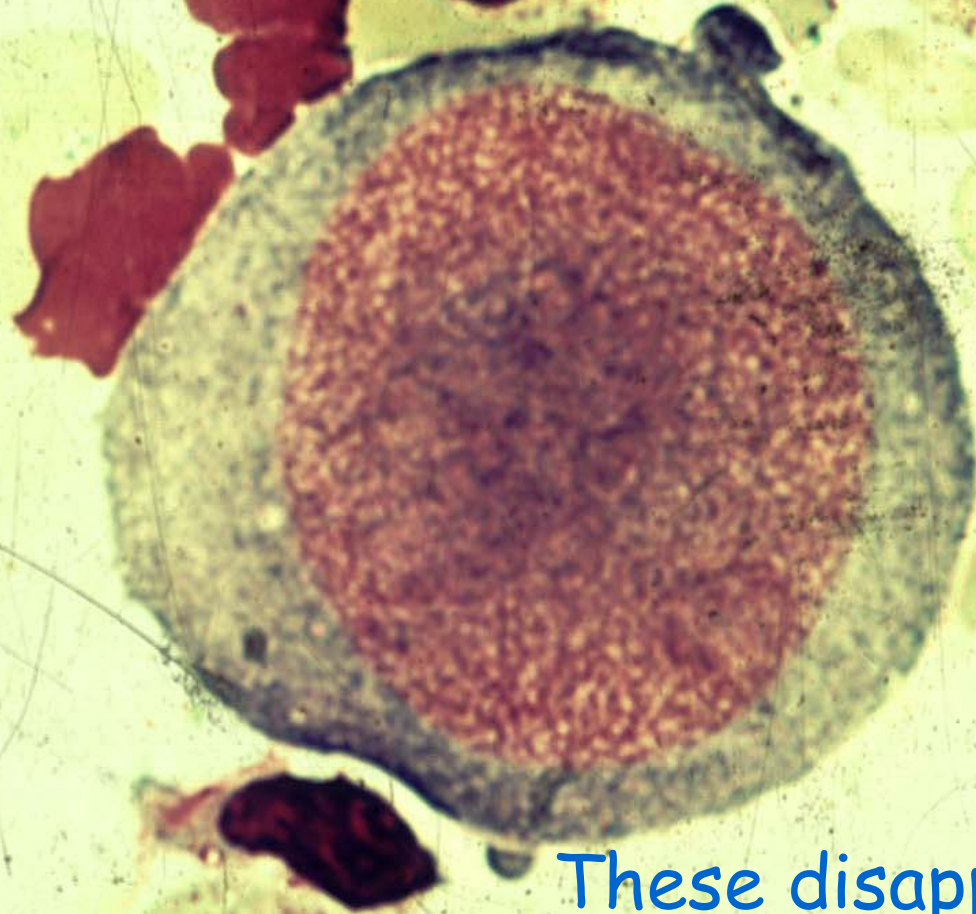
Then we published - but B19 was still an "orphan" with no known disease association - and nothing we did enabled us to culture it.

So in 1977 all our samples were frozen away.

The next clue also came from South London - this time the haematology clinic where over a few weeks a cluster of cases of aplastic anaemia was observed in children of an extended West Indian family with sickle cell disease. The children had been "off colour" and feverish, but serology for the common virus infections were negative. This prompted referral of the samples to the Virus Reference Lab where they were tested against a selection of "orphan" agents.

B19 was the only one positive.

The haematologists soon described giant pronormoblasts in the aplastic bone marrow



These disappear when antibody appears and haemopoiesis resumes

John Pattison and Mary Anderson, the clinical virologists from South London joined forces with Bernard Cohen at the VRL to develop B19 IgM and IgG ELISA assays. Though they had to purify virus from serum to use as antigen they were essentially the same as current kit tests.

B19 now had its first disease, and convenient tests. Its international career was about to take off:

Sickle cell clinics in Jamaica found that B19 was the "exclusive" cause of aplastic crisis there too (Sergeant et al). Cases were reported in patients with other forms of haemolytic anaemia

The French and Japanese BTS found that their "Aurillac" and "Nakatani" antigens were really B19.

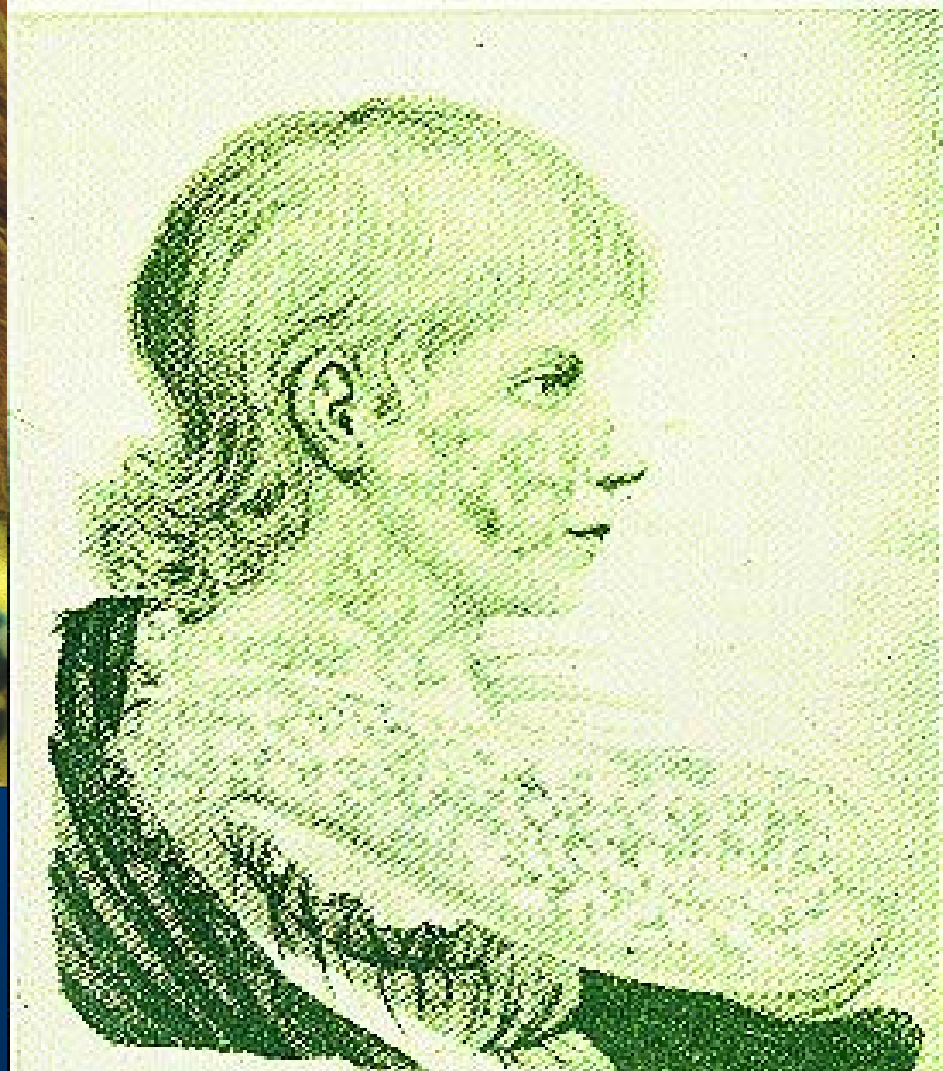
NIH got interested and grew B19 in bone marrow colony cultures (Neil Young).

Meanwhile a London school outbreak of "rubella" gave the clue to the second disease association.

Fifth disease

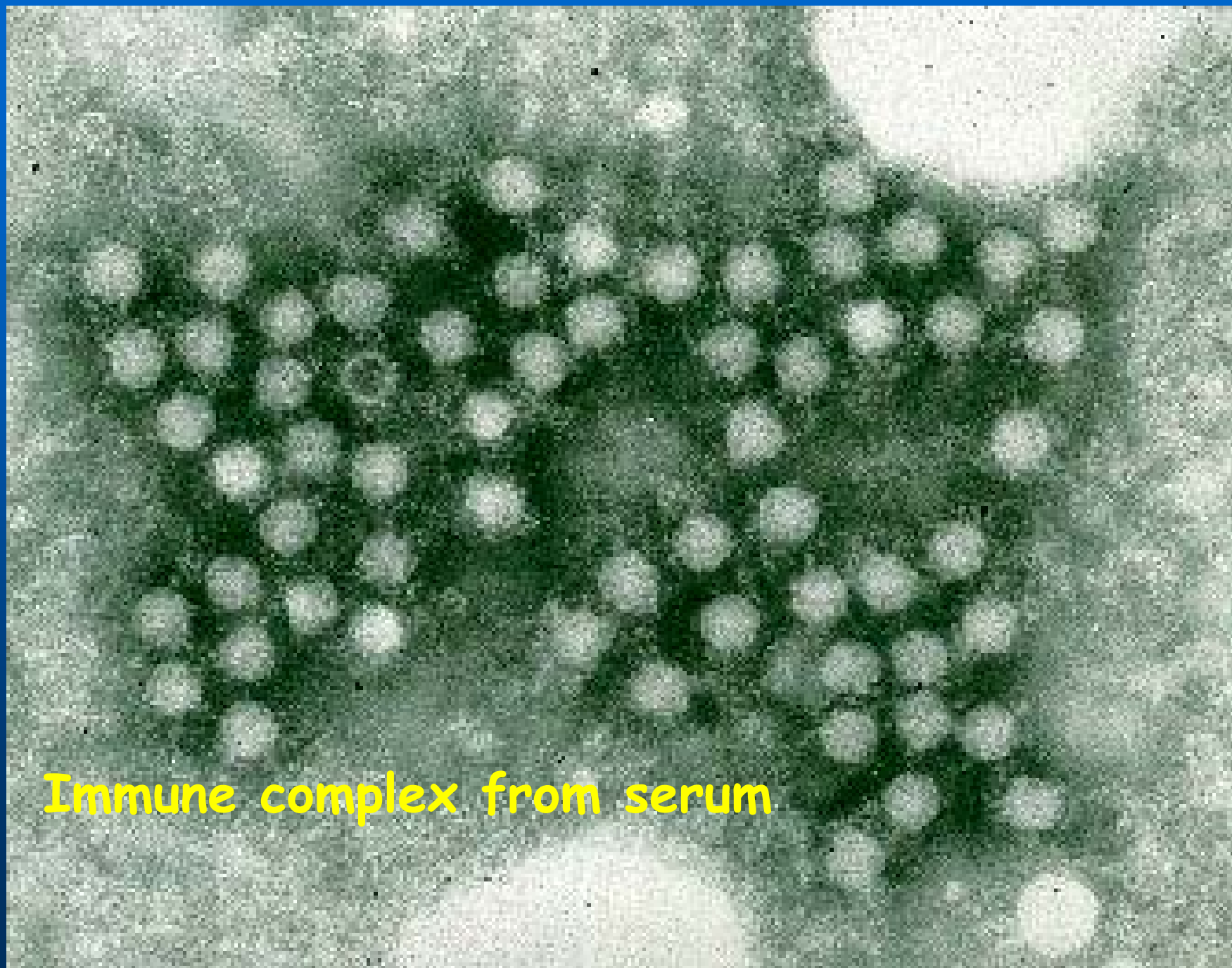


"Slapped cheek" syndrome









Immune complex from serum

Experimental transmission to humans:
(Mary Anderson and John Pattison)

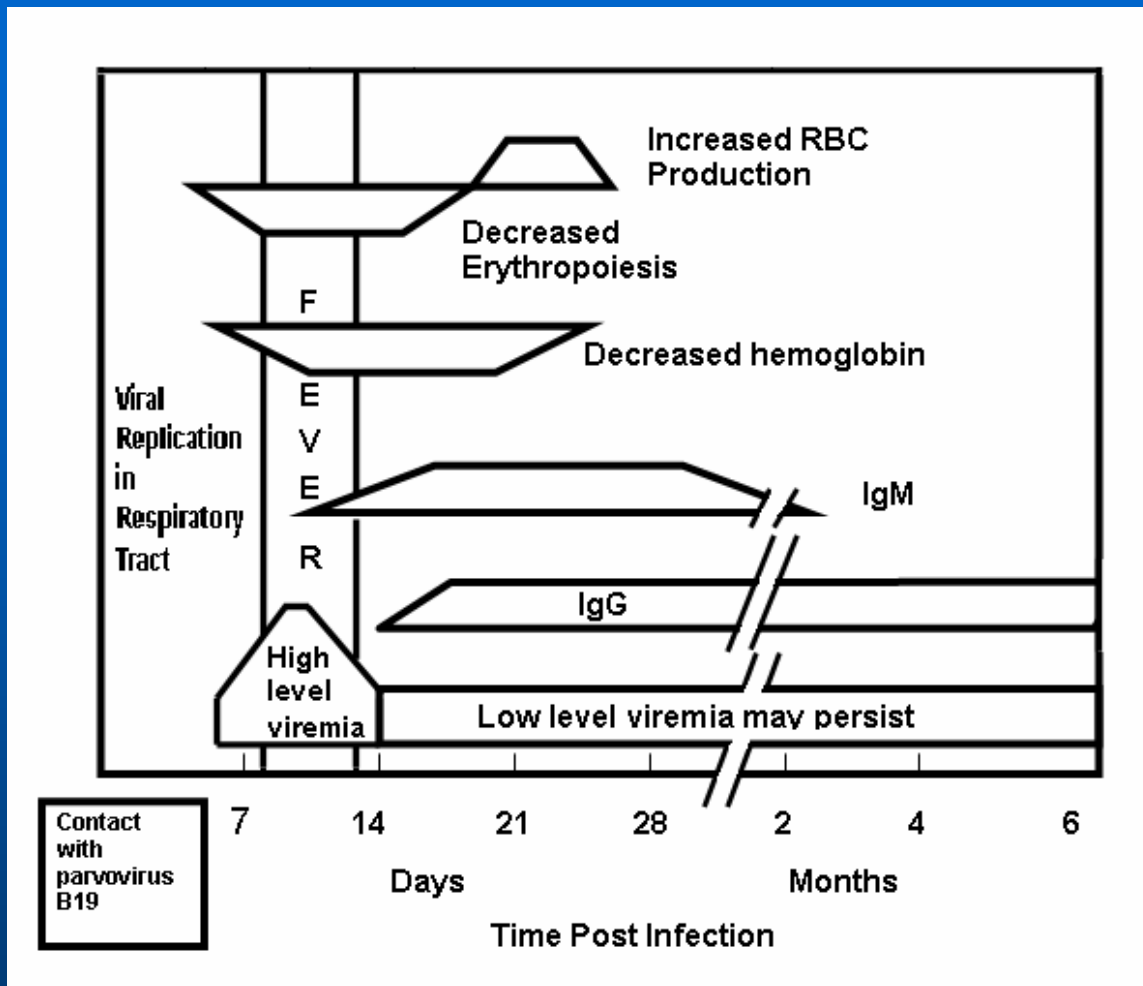
confirmed respiratory transmission

defined incubation period

showed depression of erythropoiesis

as well as rash and arthritis

Fifth disease is very like rubella



J Wildig et al 2006

Does B19 cross the placenta?

Timo Schwartz studied a hospital outbreak in Munich

Cross infection to nurses

Large number of cases in pregnant women -
some babies developed hydrops fetalis

Fetal loss an unresolved issue

B19 “early” in pregnancy crosses placenta

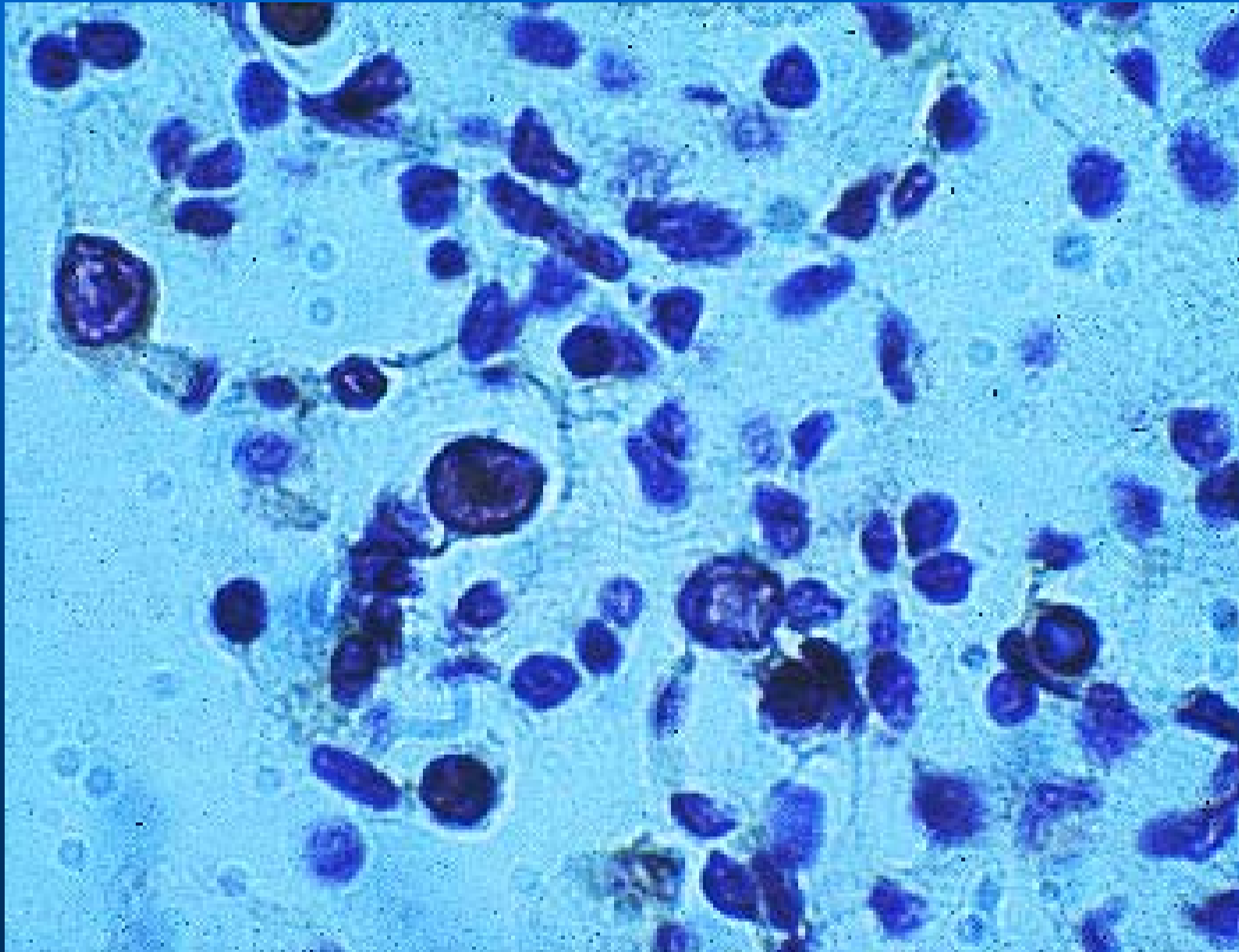
but baby cannot clear it – develops mid-timester

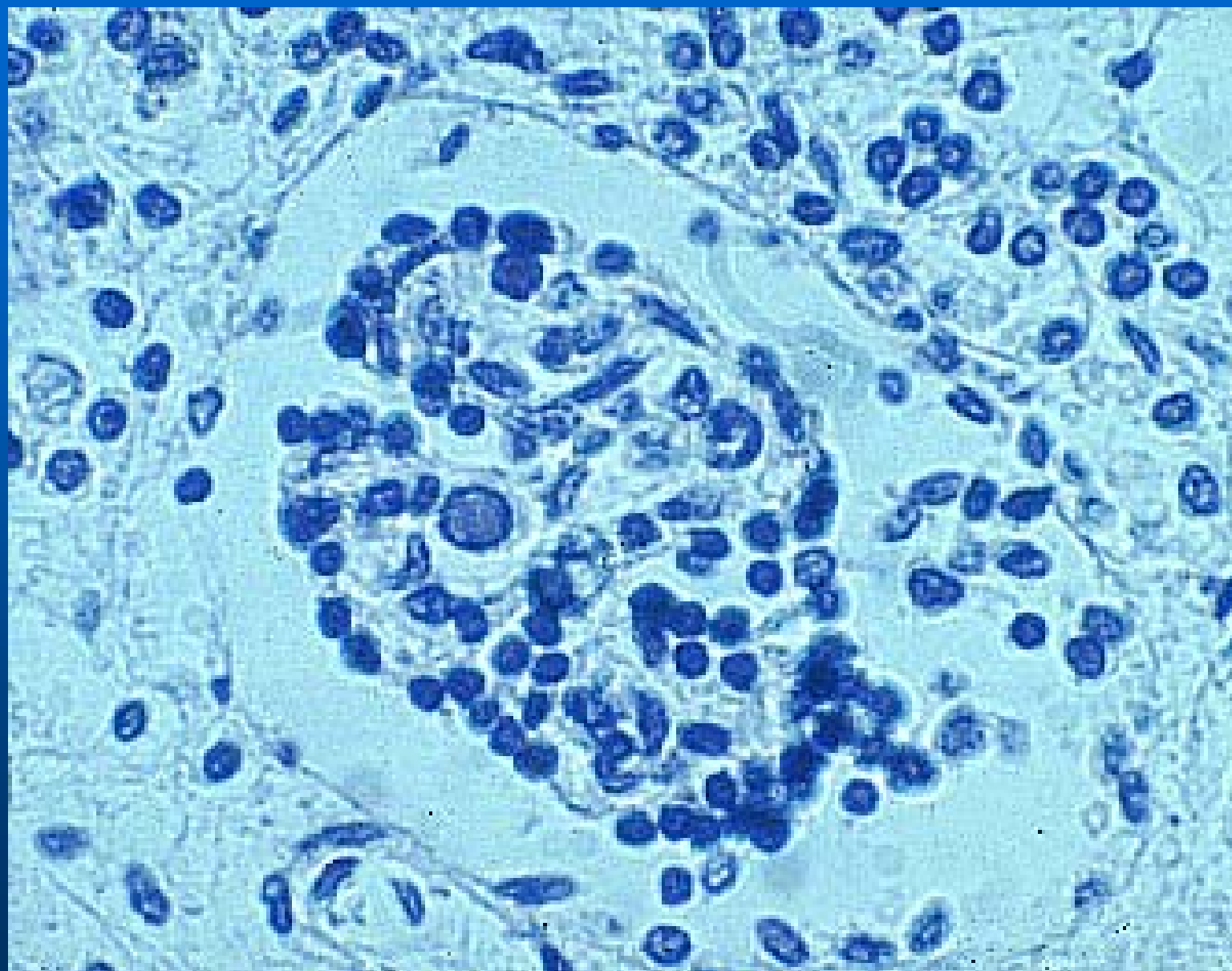
anaemia (hydrops)

Diagnosis requires fetal sample as mother may
be then by IgM neg

Worthwhile because intervention with fetal tx
of antibody possible

Other fetal tissues may be infected:





B19 has three very different pathogenic mechanisms:

arrest of the cell cycle in G2
(but which cells?)

immune complex formation

cytokine stimulation (IL-6) and apoptosis
? Trophoblast, myocardium

Immunosuppression prevents recovery
and anaemia may then be fatal:

AIDS
cancer chemo

but administration of immunoglobulin
(ie B19 antibody) "curative"

B19 is present in a significant number of blood donations , the figure varies from year to year. It can be transmitted even by heat treated products - there is no consensus re screening.

Which cells are infected?

erythroid series primary target

P blood group antigen the receptor
HA of human and baboon cells

Amish P neg people insusceptible

(Kevin Brown)

P antigen is necessary but not sufficient for B19 entry into cells

?in addition need $\alpha 5\beta$ integrins

?role of red cell adherence in viral dissemination

?? diagnostic application

Meanwhile John Clewley and Bernard Cohen developed PCR for B19 DNA;

Positive in immune suppressed patients with persistent anaemia, babies with B19 hydrops

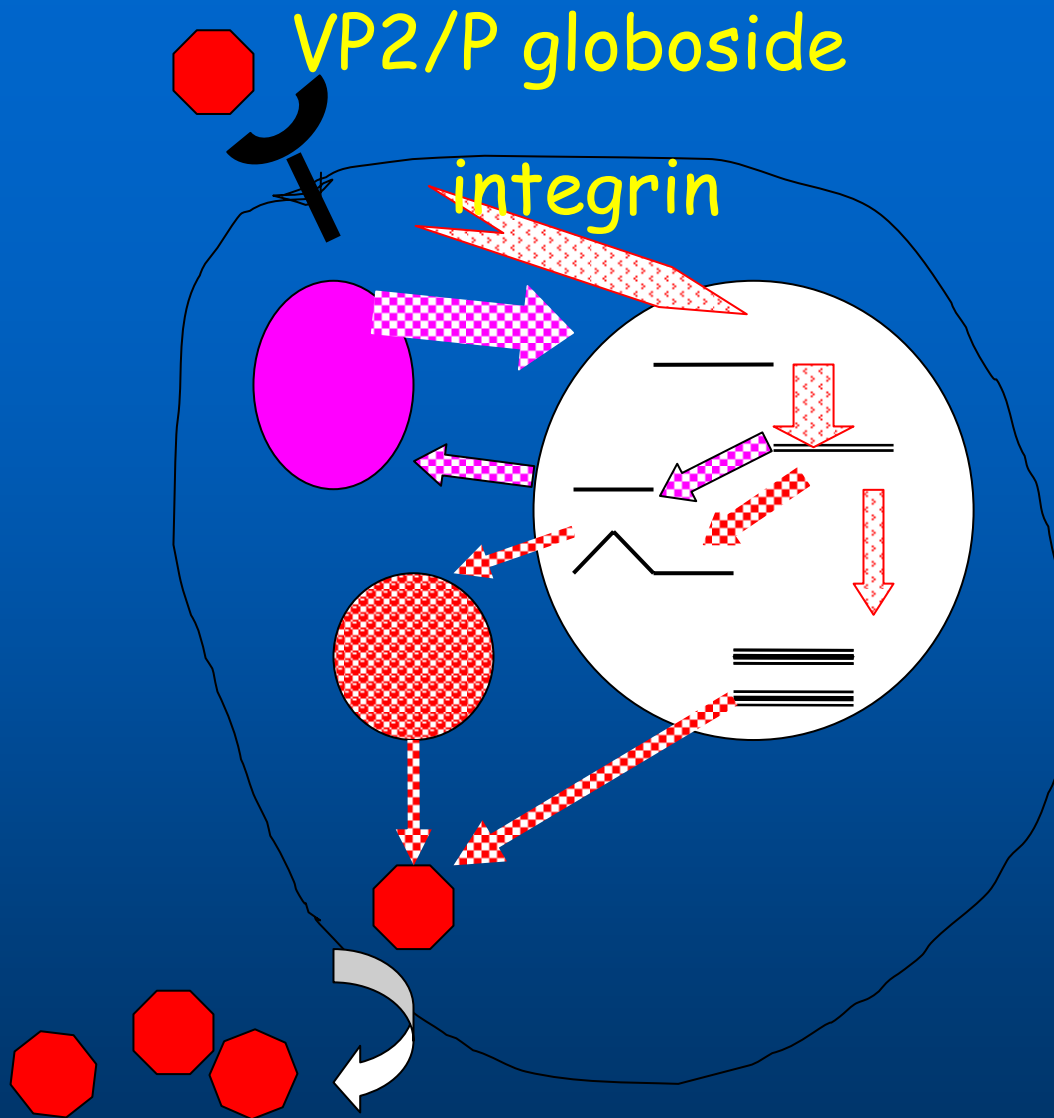
Sequencing showed worldwide distribution of prototype – with some variation

Recently some distinctive variants found

22 nm icosohedral virion
VP2 major antigen

Ss DNA genome
5600nt long palindromic LTRs at each end

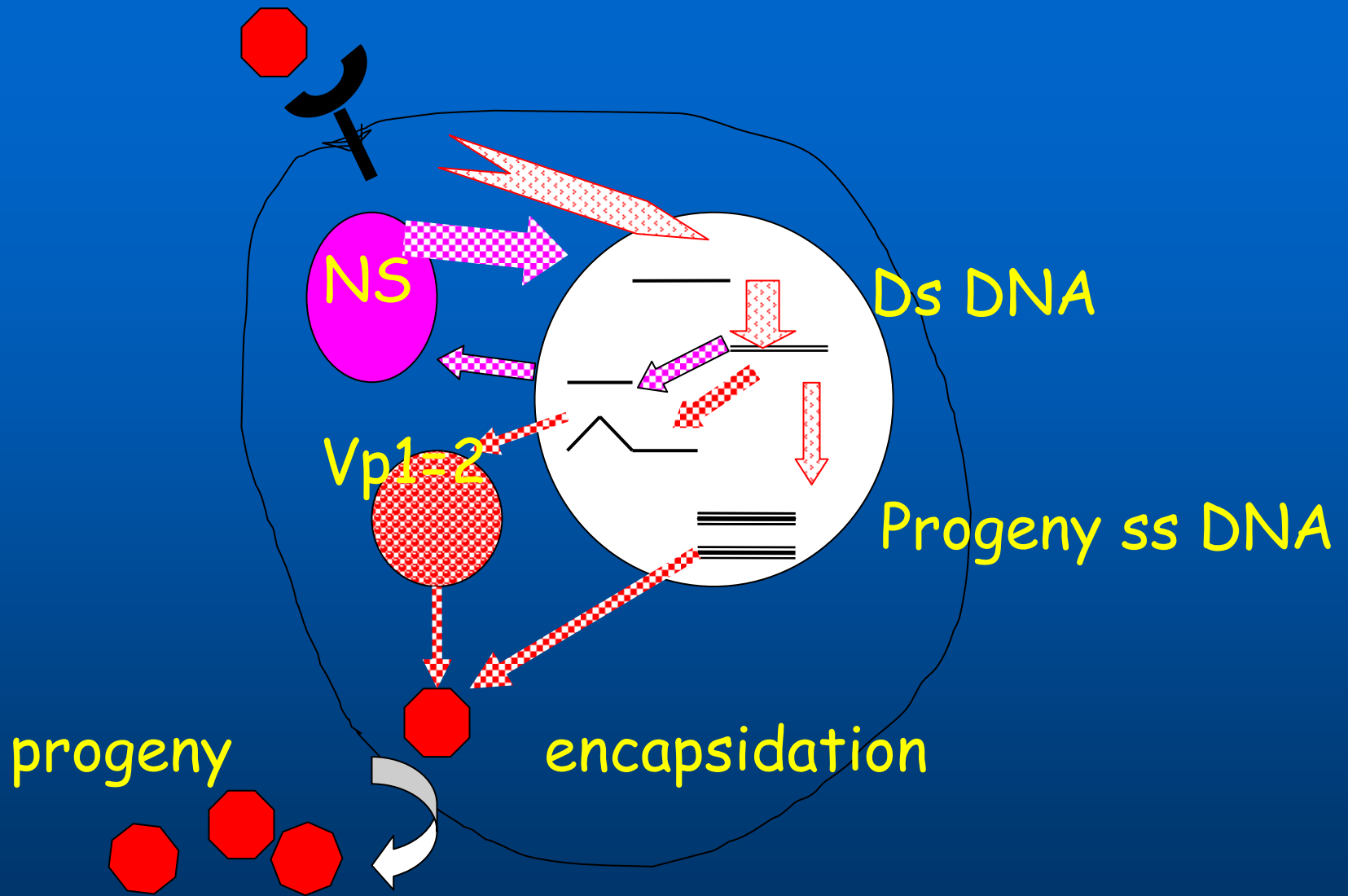
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nine transcripts
(NS is full length, other 8 spliced)

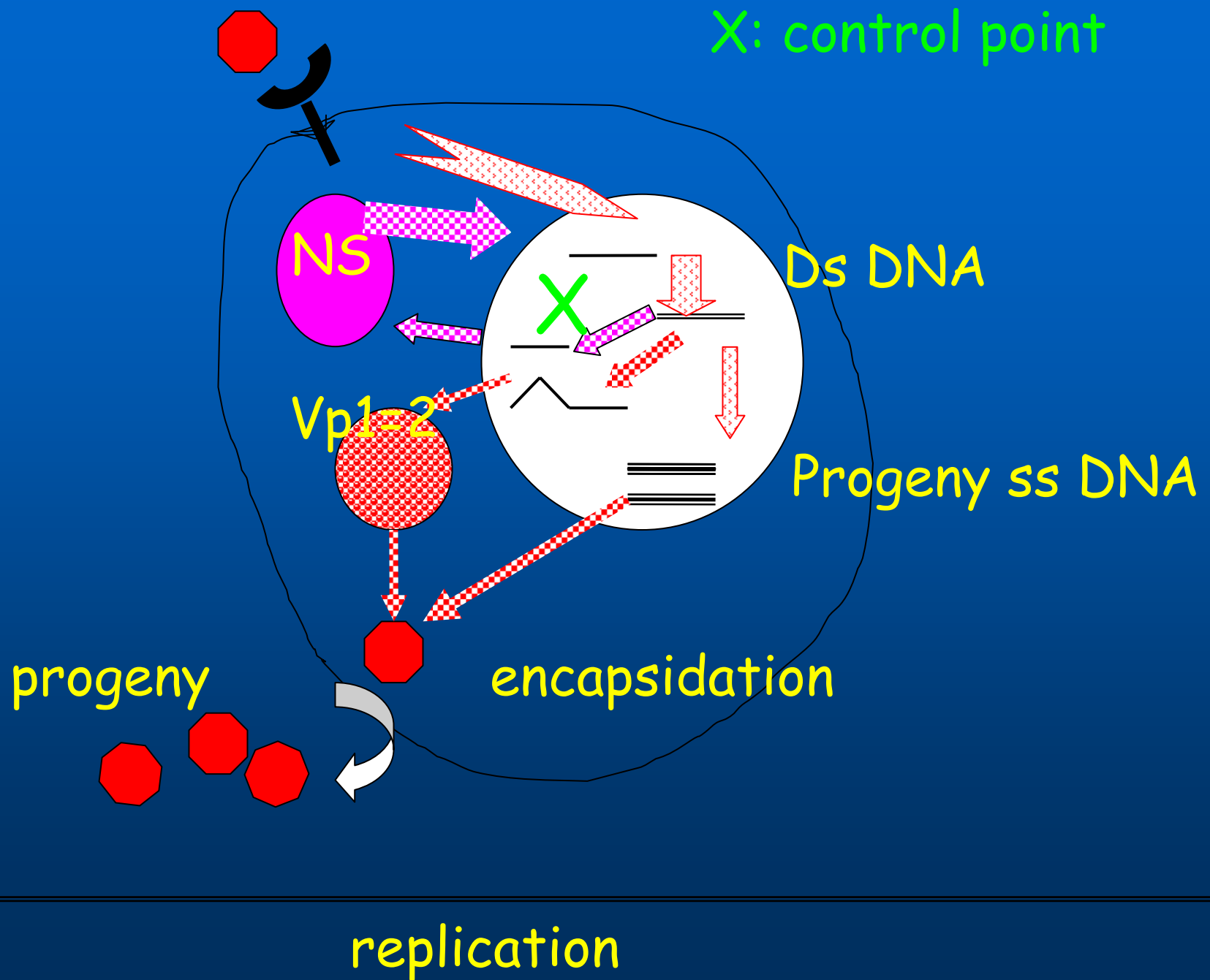


Entry and uncoating



Entry and uncoating





Cloning of B19 at NIH (Young and Kajigaya)

has made recombinant VP1 and 2 antigens available.

Recently a vaccine based on these antigens has also

been made and is beginning trials under the NIH

Orphan vaccine scheme.

? Correlation of anti-VP1 and VP2 with neut

NATURAL HISTORY OF B19:

In most countries a mild childhood disease with long intervals (< 10 years) between outbreaks.

Life threatening for patients with haemolytic anaemia or HIV. These the main candidates for vaccination

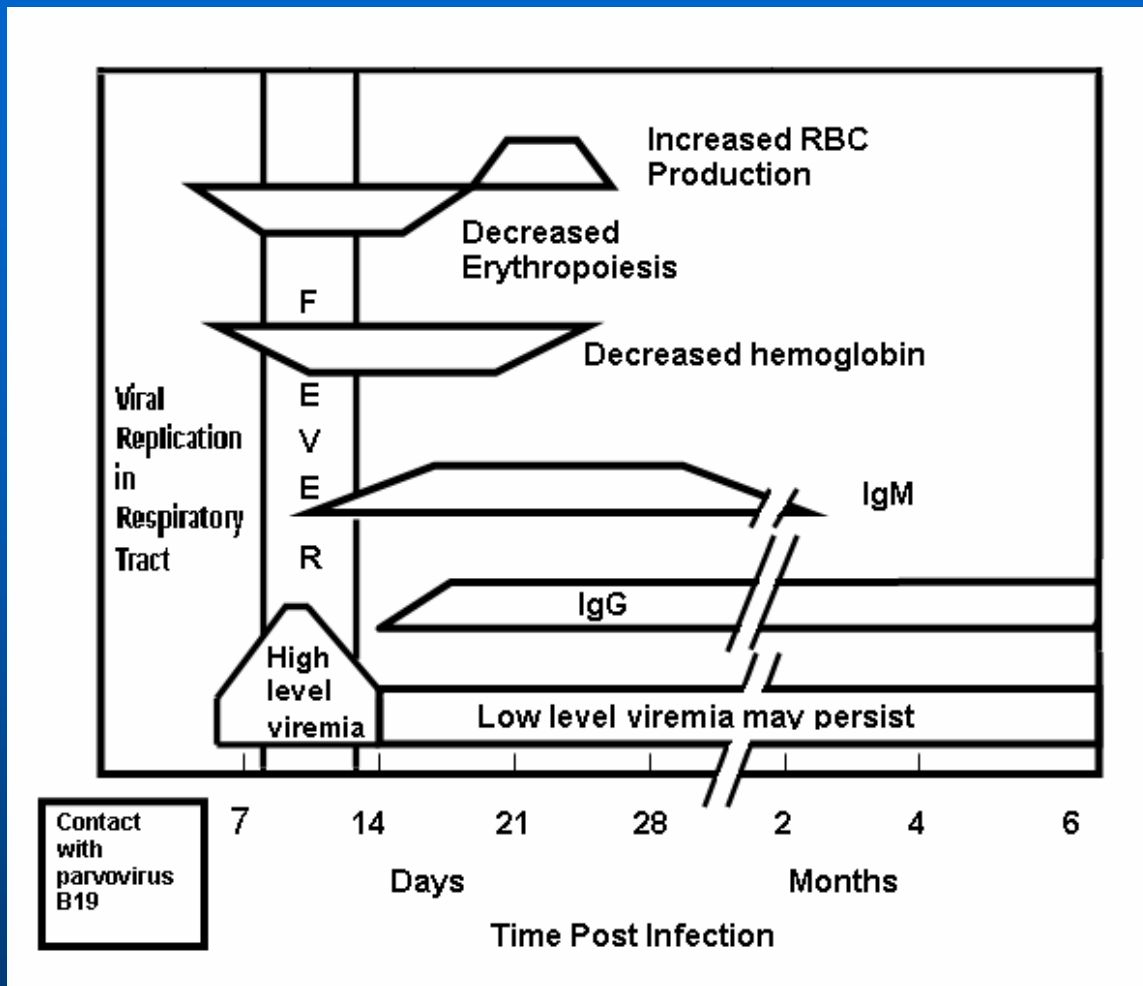
? Other roles possible eg in malaria

Maprik study

(J Wildig, Ivo Muller Y Cossart et al

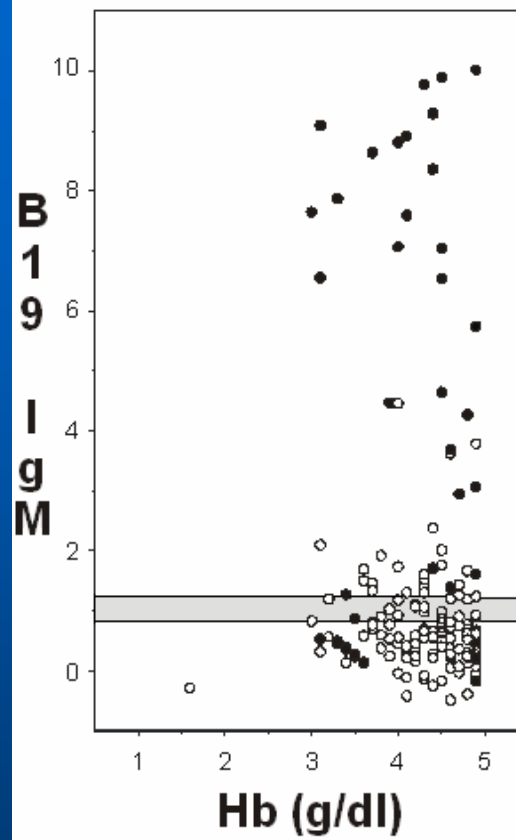
Does B19 contribute to anaemia in children with malaria?

A case/control study in PNG comparing children with Hb <50g/l with those >50g/l

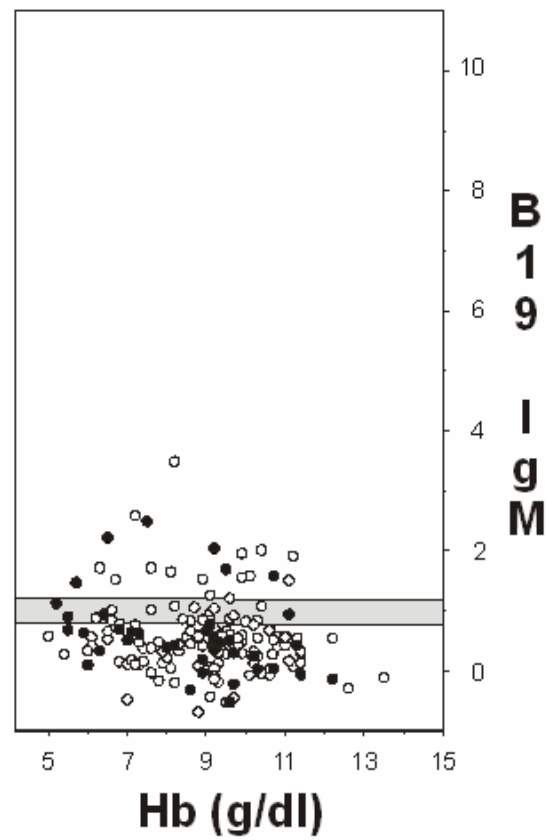


J Wildig et al 2006

Cases



Controls



ASSOCIATION OF PCR WITH IGM

	Cases *		Controls		Overall*	
IgM	+	-	+	-	+	-
PCR +	26	20	6	32	33	53
-	25	98	15	115	40	213

Odds ratio for severe anaemia in children with

B19 only		Falciparum and B19
B19 IgM only	1.89	1.89
B19 PCR only	0.61	0.50
B19 PCR and IgM	5.32	5.83

Plasmodium falciparum 5.84
ie b19 and malairia independent risks

