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Hosted By:

U.S. Department of Health and Human Services
National Institutes of Health

CPM and pregnancy outcome:
What we know and what we need to
know

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Problem of mosaicism and CPM

- How do we handle mosaicism and CPM in the prenatal diagnostic environment?
- How does mosaicism fit into the greater pattern of cytogenetic abnormality in humans?

History of CPM

- Pre CVS in 1984
- Amnios -sorting out artefacts from viable mosaics
- trisomy 2 - 'in the membranes'
- mosaic abnormality in villi from spontaneous losses
- not systematically studied

CVS - start of a systematic study

- Abnormalities in trophoblast which were not present in the fetus - immediate hazard to accurate 1st trimester PND
- 2 cases of CPM linked to IUGR - took a little longer to sink in and even longer to make sense of

Hazard to prenatal diagnosis

US	11.5K	Useful detail on most cases
UK	20.5K	Useful published detail on about 60% of cases
EUCROMIC	63K+	Data on mosaics only. Little published detail on most cases.

Hazard to prenatal diagnosis

- mosaicism in 1.5-2% of CVS
- trisomies (frequencies vary), sex chromosomes, structural, markers, ploidy
- huge variation in cell numbers
- different cell lineages
- some are real - many are CPM
- 5-10% of CPM cases have adverse outcomes

Adverse outcomes

- Most are corrected trisomies
 - altered placental function
 - UPD in fetus and placenta
 - recessive genes
-
- direct and culture
 - DNA studies
 - birthweight

Unfortunately.....

- Direct/culture incomplete
- direct/culture ?unrepresentative
- no birthweight data
- no DNA studies done and no material available
- not a good starting point, considering the amount of effort we had already put in!

Two approaches:

- Collect better series of data
- Collect sets of apparently problematical abnormalities
- Combined approach

UK data collection

- All UK CVS 1987-2000 (unbiased)
- 45,000+ procedures
- accessible and usable
- literature cases (publication bias)

- 6 months' money from Birth Defects Foundation - Sam(antha) Connors
- mostly unfunded

Potential database

- Further UK cases, 2001 onwards
- previous studies - EUCROMIC
- Australasian cases
- unpublished series - US, European, anywhere?
- Goodbye to the rest of my life!

Trisomy 18

- If you don't have fetal trisomy you don't have a problem
- placental trisomy has no associated clinical consequences?
- UPD is either not very common or has no associated clinical consequences?
- Little data on origin of mosaicism in prenatal cases

Trisomy 16 - what we know

- Mostly from case reports (DK) - biased
- trisomy 16 is common - mat MI
- mosaicism is almost all correction of this trisomy - almost all CPM (\pm UPD)
- severe IUGR and/or late pregnancy losses
- some normal outcomes, milder/no IUGR
- a problem of placental trisomy

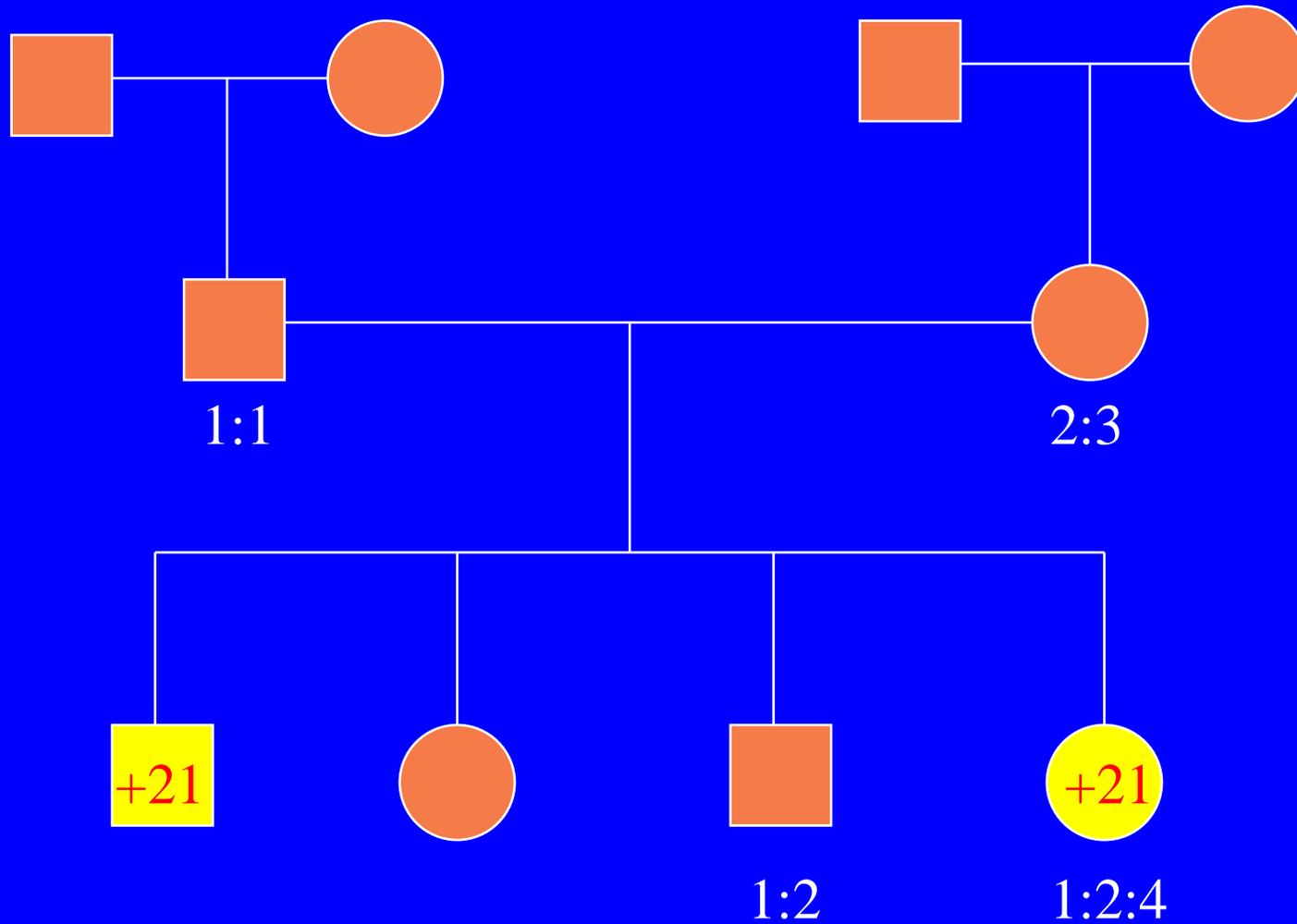
Trisomy 16 - what we don't know

- More severe outcomes with UPD?
- Interaction between UPD, levels of abnormal cells and their distribution
- Catch up growth - link to \pm UPD
- Long-term effects on health (malignancy?), life span, fertility.
- Further studies needed

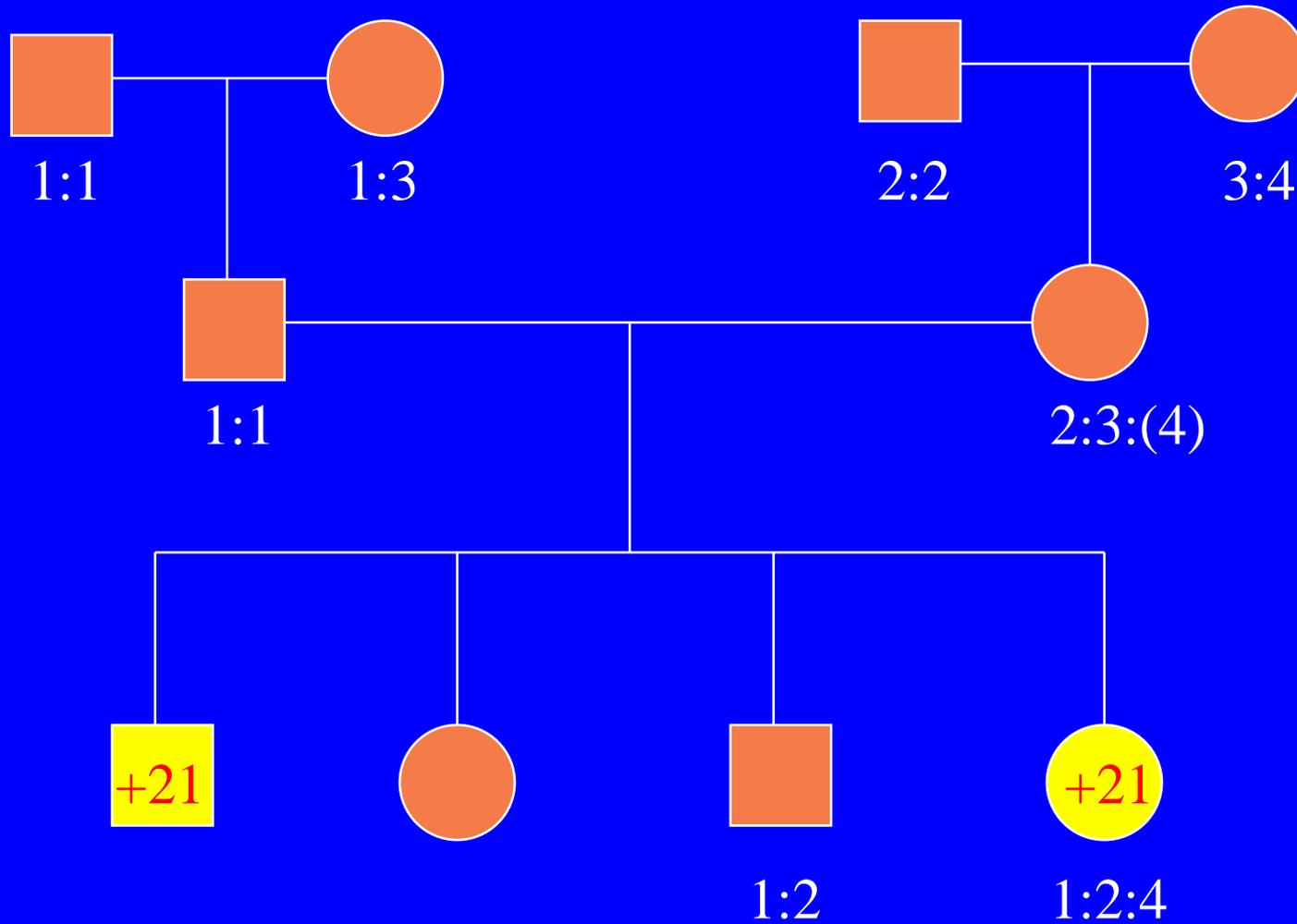
CPM and gonadal mosaicism

- DK trisomy 16 case
- grandmaternal age effect in trisomy 21

Parental gonadal mosaicism



Parental gonadal mosaicism



CPM and gonadal mosaicism

- DK trisomy 16 case
- grandmaternal age effect in trisomy 21
- risk of gonadal mosaicism in +13, +18, +21, XXX, XXY, XYY
- what about +2, +7, +9, +15, +22, all seen as CPM and spontaneous losses, many CPM cases are corrected trisomies
- fertility in males with X/XY CPM?

Trisomy 2 mosaics in CVS

- most somatic, in cultured cells
- some corrected trisomies, directs and cultures
- mat/pat, MI/MII (also seen in spont. losses)
- ? prognosis
- IUGR common in corrected trisomy group with or without UPD

Case 1: upd(2)mat (MII?)

- Mat age CVS
- trisomy 2 direct and culture
- oligohydramnios
- IUGR 765g at 31/52
- renal problems
- age 8
- very small, otherwise OK

Case 2: upd(2)mat - MI error

- abnormal AFP and hCG
- small during pregnancy
- oligohydramnios, but no other problems
- IUGR, 1300g at 35/52
- placental culture trisomy 2
- normal development
- age 3, small, otherwise normal

Case 3

- IUD at 38/52, 3270g, not IUGR
- hydronephrosis
- placental cultures 100% +2
- trophoblast 17% +2
- thrombosis of chorionic plate vessels
- cystic left kidney
- corrected maternal trisomy 2
- biparental ?MI/II

Case 4

- IUGR diagnosed at 21/52
- Stillbirth at 27/52, very small placenta
- IUGR, fetus 331 g, thin, reduced body measurements, organ development consistent with 27/52
- cultured placenta 25% +2
- trophoblast 5% +2
- correction of +2 of paternal origin
- biparental, ? MII error

Prognostic value

- Worst outcome in case 4 - biparental and lowest % of abnormal cells
- published data not much more help
- shows similar inconsistent patterns
- clearly a placental problem
- weak UPD syndrome - hypospadias
- ? Low levels of fetal mosaicism
- very little long-term follow-up

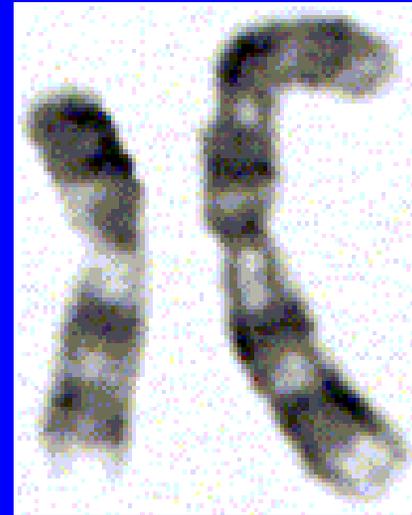
Structural abnormalities

- Most low level
- cell lineage restricted
- probably somatic in origin
- most of little consequence to pregnancy outcome

Case 1 - CVS

- Ventriculomegaly, talipes at 21 weeks'
- direct 46,XY

- culture



t(1;9) [30]

t(7;9) [27]

46,XY [1]

- parents normal

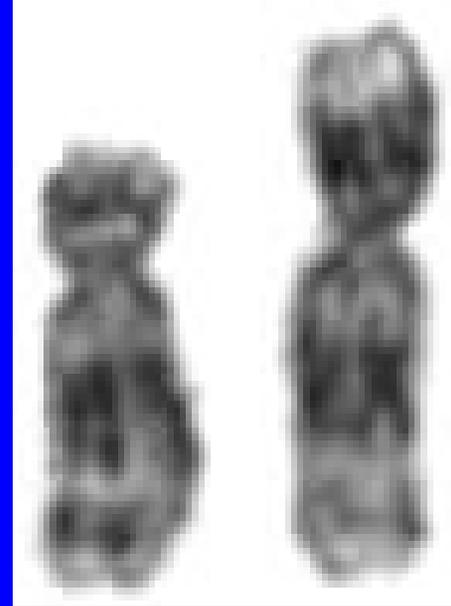
Case 1 - outcome

46,XY,der(9)t(7;9)(q22;q2?4)

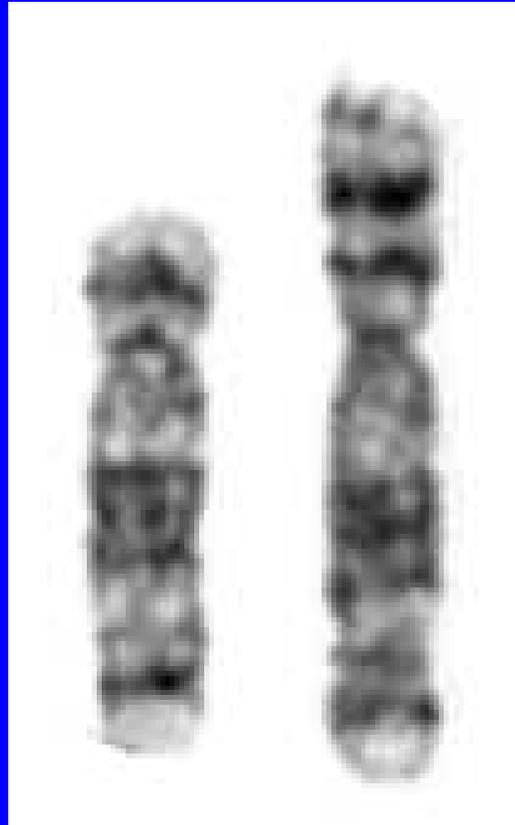
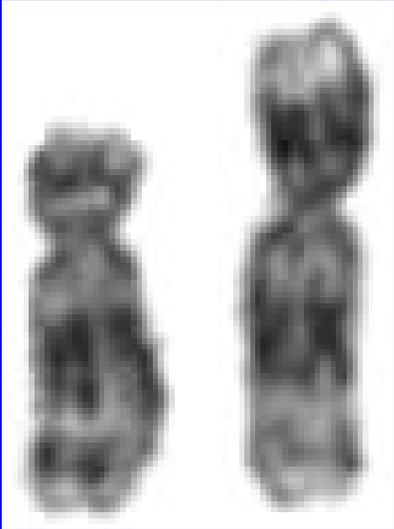
der(9)t(1;9) not seen in villi at follow-up

Case 2 - CVS directs

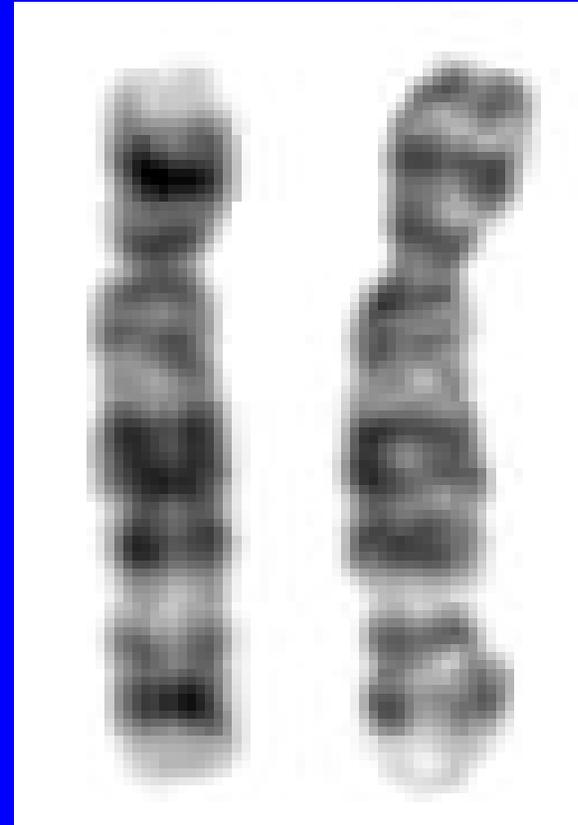
- Sickle cell disease
- normal scan
- CVS at 13 weeks
- all cells add(5)(p1?5)
- not 5 derived



CVS cultures

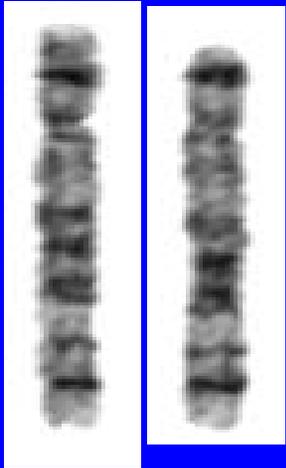


? origin

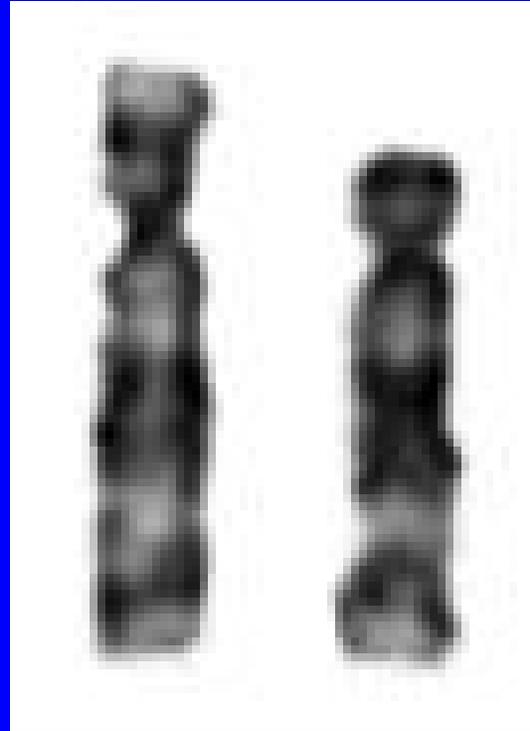


all 5 derived

CVS follow-up: fetus



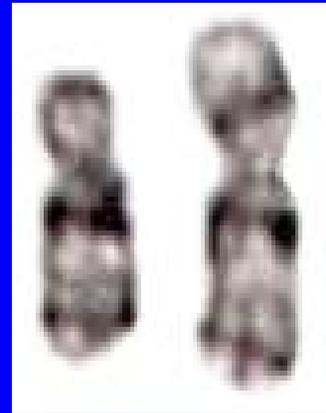
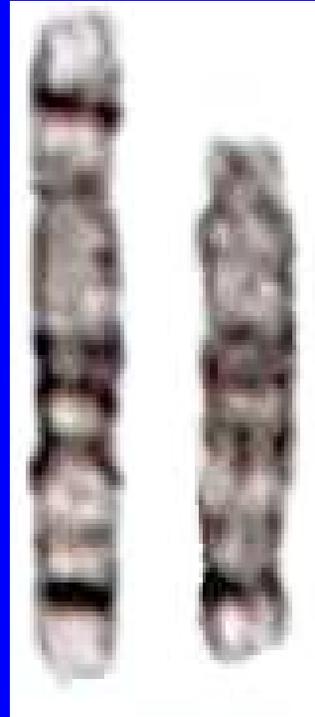
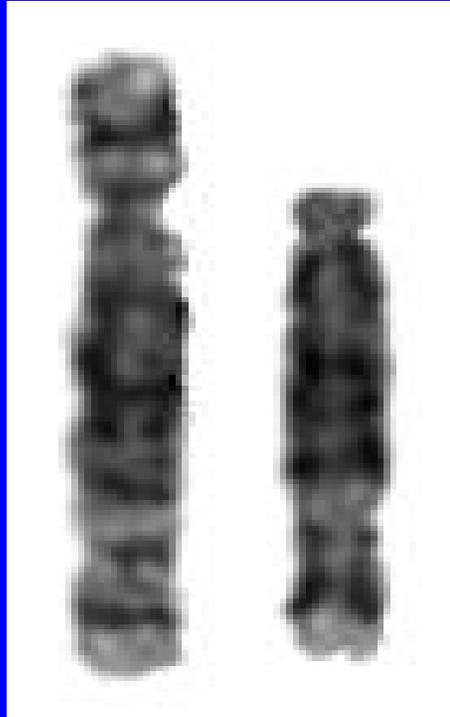
Cordocentesis
at 21 weeks'



Fetal
skin

del(5)(p15.2)

CVS follow-up: placenta



Case 2: post mortem

Low-set ears

pre-axial polydactyly

no internal abnormalities

Other structural mosaics

- Multiple abnormal cell lines with rearrangements involving 9p including a ring 9 - fetus affected
- multiple abnormal cell lines with rearrangements involving X - fetus affected

Structural abnormalities

- How to identify the small number of relevant cases
- effects of abnormality on placental function
- mitotic correction could (in theory) produce whole chromosome or segmental isoUPD
- most likely where a single chromosome is involved - deletions, duplications etc.
- 13q- in UK IUGR study

Conclusion

- Learned a lot over the last 20 years
- still a long way to go even to ascertain what is happening in early human development and its clinical consequences
- even further to go to understand the biology behind much of what we see.