Practice Management Workshop

“What I Wish I Knew Before I Started Practice”

April 18, 2009

Coordinators:
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Presenters:
Solo Practice:
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Academic Practice:
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Group Pediatric Practice:
David Stager, Jr., Merrill Stass-Isern, Lance Siegel

Multispecialty Practice:
Charles Bock, Jeff Hunter, Marc Greenberg, & Robert Gold
Starting a solo practice in pediatric ophthalmology

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No financial relationship to disclose

Starting a solo practice

• A solo practice is feasible
  – Low start up costs and overhead
  – Minimal call

• May not be for everybody
  – Risk tolerance / desire to be an entrepreneur
  – Must enjoy business side of practice
  – Can be lonely

Starting a solo practice

• Evaluate market opportunities
  – Speak with pediatricians
  – Speak with pediatric ENTs
  – 1 pediatric ophthalmologist/250,000
  – 1 pediatric ophthalmologist/Toy’s R Us
  – Access to insurance contracts/fees

• Personal preferences
  – Location
  – Family considerations

Starting a solo practice

• Financing your new practice
  – Consider Hospital Support package
  – Financing needs
    – Build-out/equipment/start up expenses
    – Develop a business plan and projections of revenues and expenses
    – Working capital
    – Prepare a loan request
    – Finding a lender – commercial vs. SBA

Starting a solo practice

• Timeline for starting a practice
  – Highly recommend the AMA’s “Starting a medical practice”
  – Licensing and credentialing must start well in advance
  – Do a little of everything yourself at first
  – Develop a vision for your practice

Starting a solo practice

• Space procurement
  – Consider renting space from an existing practice or optometry office
  – Evaluate and select locations
  – Negotiate lease
  – Space planning and buildout

Starting a solo practice

• Hiring Personnel and Marketing Your Practice

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Financial Disclosure - I have no financial interest in the material presented today other than hopefully some of you will achieve your financial goals and other goals for your practice.

Starting a solo practice

• Sources of potential employees
  – Word of mouth
  – Agencies: many screen for you
  – Newspaper ad with resume
  – Hospital networks

• Medical Experience helpful, not mandatory
  – Manage site time for office, represents you and your practice
  – Interview directly: ask another to assist you if needed
Hiring An Office Manager

- CALL the references yourself
  - Check dates of consecutive employment (gaps often important)
  - Talk to their immediate superior or physician who worked with them

Employee Expectations

- Outline clearly what you expect from the employee
  - Clear benefits package
  - Ask what the employee expects
  - Give employee manual to every employee
    - General job description
    - Holidays
    - Benefits
    - Reasons for immediate termination
    - Hours of operation

Motivating Employees

- Bonus Structure: 30-40% of salary
- Discretionary: no formula
- Based on income, performance of employee and attitude
- Builds team spirit
- Movie: Miracle
- Teamwork is key

Marketing Your Practice

- Meet personally all potential referral sources:
  - Pediatricians
  - Ophthalmologists/optometrists
  - School nurses, vision screeners, Lion’s club screeners
  - Donate promotional items
  - Donate useful tools for vision screening

Website for Your Practice

Website Content

Power of a Logo

Advertising Planning

- Plan how to market your practice to the community
- Print Media: newspaper, magazines, postcards
- Radio
- Sponsorships
- Logo design: essential to give your practice an edge
Advertising Lingo
- Public Relations
  - Consider a PR agent to help you get an article printed in local paper/magazine OR a spot on TV
- Advertising
  - Graphic designer – creates logos, print ads, photo shoots, anything visual
  - Copy writer – writes the words for print and radio ads

Photo Shoot

Patient Information Booklets
- With Your Logo

Postcards for Short Notes

Controlling Expenses
- Billing and Collecting
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  - I have no financial relationships to disclose.

Net Collections – Expenses (Overhead) = Salary
- Salary – Taxes = Take Home $$$

Billing and Collecting
- $$\equiv \text{Gross Charges} \text{ – Collections}$$
  - Gross charges are limited by doctor productivity and Billing-Coding Knowledge
  - Collections = Gross Charges – Writeoff – Cost of Collections
  - Writeoff = Insurance acceptance + Bad debt
  - Collections cost = Computer charges + Staff Time + Cost of outstanding debt

Overhead
- Rent/Mortgage/Building Maintenance
  - Leasing vs. Ownership
  - Time and Tension = $$$
- Office Furniture and Equipment
  - New vs. Used
  - Depreciation
  - Income source
  - Supplies

Overhead
- Staff
  - Salary
  - Full-time, Part time
  - Ideal Employee: Productivity
  - How many employees?
  - Benefits
  - Training and Turnover Costs
  - Time and Tension = Money
Insurance Contracts
Ancillary Services

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• Dr. Laby is a paid lecturer for Alcon and a paid consultant for Vistakon

Young Pedi Ophths

• Contract with a teaching hospital one day a week
  – A good way to meet colleagues
  – A good way to build your practice – reputation
  – A good way to have a guaranteed income source as you start your practice
  – A good way to maintain an academic flavor to your practice
• Insurance carrier related issues
  • Ancillary Services

Insurance Carrier Related

• Types of Insurance
  – HMO: “Health Maintenance Organization”. Insured must use specific physicians and hospitals, referral from PCP necessary
  – PPO: “Preferred Provider Organization”. Insured can choose any physician, no “referral” needed
  – POS: “Point-of-Service”. A mix between an HMO and PPO. PCP can refer to physicians in plan and fully covered, if physician outside plan is used then partial coverage/deductible

• Reimbursement rates
  – Vary greatly from Insurer to insurer as well as within insurers
  – All CPT codes do not pay the same for all carriers (may be better to bill a 92004 in some and a 93204 with others)
  – Insurance company will pay you the smaller of what you charge or what they are willing to pay – must adjust fees to be slightly higher than best paying insurance company
  – Bill refraction (92015)

• Vision Plans
  – Many plans – largest are: EyeMed, VSP, Spectera, & Davis Vision
  – Can be unrelated to medical coverage or may be a part of medical coverage as added benefit
  – Often act as PPOs with plan physicians agreeing to significantly reduced reimbursement rates
  – Members can go out of network and be reimbursed but usually for less than full payment

• Negotiations
  – Must always be prepared to walk away
  – Often can negotiate increased reimbursement rates if you are only provider in the area and if you can show their payment is below norms
  – Be creative – e.g. quarterly bonus to make up for low patient payments
  – Contract terms that may be negotiable:
    • “Eligibility”: As long as you check a patient’s insurance at time of service and confirm – then you should be paid

Ancillary Services

• Legal – critical, look at AAOE for references
• Accounting/Payroll – identify partners early to insure proper planning
• Malpractice – OMIC vs. local carrier, types of surgery performed can affect premium
• Business liability/Umbrella – protects you if patient injured on premises, employee complaints
• Worker’s Comp – often required, protect against employee injury or disability
• Other insurances
1. Know What You Want (Goals)
- Patient Care
- Research
- Money
- Teaching

2. Know What You Are Willing to Give Up
- Money
- Time
- Control

3. Recognize Other Trade-Offs
- For example, compensation often inversely proportional to perceived:
  - "prestige" of institution
  - "desirability" of geographic location
  - percentage of "interesting" cases

4. Beware of Hidden Assumptions!
- Not necessarily true:
  - compensation higher in private practice than academic
  - best job for me is at most prestigious program
  - terms of an academic job offer are not negotiable
  - as an academician, I won’t need to concern myself with the “business” aspects of practice

5. Evaluate Opportunities
- Does the position fit with my goals?
- Realize there is no perfect “fit”
- Realize there are as many different types of academic practice as private practice

6. “Sub-Types” of Academic Practice
- Small department vs. large department
- Being the sole ped ophth vs. joining others (peers or more senior)
- If solo, established peds service vs. new service (or “resurrected” service)
- Full-time vs. part-time, “visiting” or consulting

Young Pediatric Ophthalmologists: Practice Management Workshop
Balancing the Academic Practice
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Balancing the Academic Practice

- Unique features of the Academic Practice
  - Indigent care
  - Research
  - Teaching
  - Reduced flexibility of the large institution
- Pediatric ophthalmology is critical
  - Department
  - Academic medical center (ex. ROP coverage)

Balancing the Academic Practice

- What is the source of your income?
  - Salary
  - Production (gross revenue – overhead)
- How is overhead calculated?
- Is overhead shared equally among partners?
- Grants and endowments
- Contracts
  - Hospitals
  - Non-profits

Balancing the Academic Practice

- What goals do you have in your academic practice?
  - Teach
  - Think
  - Travel
  - Save the world?
- You may need a strong salary, grant or endowed position (“sugar daddy”)

Balancing the Academic Practice

- As you become busier in the clinic and the OR, there is less time for other academic pursuits
- Salary based on production is a disincentive to do academic work
  - Not seeing patients
  - Overhead chugs along

Balancing the Academic Practice

- It is crucial to bargain for TIME and SPACE (clinical and research) as much as MONEY in the academic practice
  - Especially in Pediatrics, where reimbursement is relatively low (it’s not that bad!)
  - Often other specialties (retina, refractive) feel that they are subsidizing a pediatric practice

Before you negotiate:

- Know what you are worth to the practice, department, medical center, community and region

Summary

1) Academic Pediatric Ophthalmology is tremendously rewarding
2) Know what you want to achieve and focus upon in your academic career
3) Know your worth to the practice, department, medical center, community and region
4) Ask for time, research space, dedicated time and money in your contract
5) Lean toward a salaried position if you are going to spend a great deal of time outside of the clinic and OR

Practice Management Workshop

Developing an Academic Pediatric Ophthalmology Practice

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Issues to Consider

- Teaching
- Research
- Work
- Productivity

Expect to get compensated for the work you do

Do not look at residents and fellows as part of your “workforce”

Productivity

- Office
- Operating Room

Office Productivity

- Treat your clinic like a private practice
- Do not subject patients to a different standard than they would expect in an outside office
- Avoid “resident clinics”

Resident Clinics

- Send a mixed message to residents, staff, administrators and patients
- All patients should be YOUR patients
- Treat your hospital / university / academic clinic like you would your private practice clinic

Office Efficiency Tips

- Run on time
- If you run on time, you should expect your patients to run on time
- Do not tolerate “late shows” and “no shows” as part of an academic practice
- Keep track of patients as they go through the system

Do not count on referrals because of your practice type/location

- Do not allow your practice type/location to be an excuse to not get referrals

Strategies to Increase Productivity

- Open access scheduling
- Exit timing
- Review your performance
Open Access Scheduling
- What is it?
- What are the advantages?
  - Improved satisfaction
  - Less time on phone with triage
  - Less no shows

Misconceptions about Open Access
- It will bombard me with too many patients
- I can never catch up to my backlog
- I may not fill up my day

Exit Time Scheduling
- What is it?
- How is it done?
- Improves wait times especially when working with residents

Operating Room Efficiency
- Less control here with multiple trainees involved
- Try to move cases out of large hospital OR’s if possible
- Review turnover time data
- Stress value of improved time with OR, administration, etc.

The bottom line is.....
......treat your academic practice like a private practice for maximum efficiency and value

And......
If you want to be compensated like a private practice pediatric ophthalmologist, you need to work like one.

Young Pediatric Ophthalmologists: Practice Management Workshop
Compensation Considerations
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Disclosure

- I have no conflicts of interest to declare
- Also, this presentation will not involve any off-label use of approved drugs

Know your “worth”

- Department Chairs have a difficult balancing act
- They often are no different than any other US consumer – they want to get the best possible medical care providers as cheaply as possible
- Pediatric ophthalmologists are generally “nice” and often not aggressive in pursuing contracts

Consider some practical education

- The ACPE (American College of Physician Executives) have some excellent online programs and live programs (ALWAYS in great resort areas)
  - April Annual Meeting - Chicago
  - Fall - Tucson
  - Winter - Orlando
- Practice management and negotiations seminars

Salary “Arrangements”

- Straight salary
- Straight productivity (% of gross based on collections and overhead)
- Salary + incentive
- B + S + I
  - Base – Asst vs Assoc vs Prof
  - Specialty – based on medical specialty
  - Incentive

Before you negotiate:

- Know what you are worth to the practice, department, medical center, community and region
  - Rychwalski, MD
- Know what others are getting
  - Enzenauer, MD

Benchmarks are hard to find

- ACGME has data for
  - 1) Specialty (doesn’t subdivide eye surgery)
  - 2) Academic level
  - 3) Area of the US
- AUPO has some sub-specialty data
  - 1) “old” 2006-2007 time frame
  - 2) Was only available to AUPO members “for a price”
  - 3) Not specified by geographic area

Recognize the reality that your salary at an academic institution has to come from somewhere

- Generally a VERY SMALL contribution from a state budget for education – often linked to medical student education, where ophthalmologists are often not “big” players
- Your productivity
- Grants are very competitive
- Endowed chairs

Salary realities

- Often-times the hospitals and academic departments “need” you a lot more than they will admit
  - For RRC requirements
  - For competitive contract negotiations
  - ROP a special “challenge”
- More and more instances of salary support for pediatric ophthalmologist are being negotiated from the local children’s hospital

MY FAVORITE QUOTATION

- “It is not the critic who counts, not the man who points out how the strong man stumbled, or where the doer of deeds could have done better. The credit belongs to the man who is actually in the arena; whose face is marred by the dust and sweat and blood; who strives valiantly; who errs and comes short again and again; who knows the great enthusiasms, the great devotions and spends himself in a worthy course; who at the best, knows in the end the triumph of high achievement, and who, at worst, if he fails, at least fails while daring greatly; so that his place shall never be with those cold and timid souls who know neither victory or defeat.”
- TEDDY ROOSEVELT (Paris Sorbonne, 1910)
**Practice Management Workshop**

**Single Specialty Group Practice**

David Stager, Jr., M.D.
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**Practice Management Workshop**

**Single Specialty Group Practice**

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**POPACAS** (1968 Dr. Stager, Sr.)

- 7 pediatric ophthalmologists, 5 surgeons
- 4 offices Dallas, Plano, Grapevine
- 1 Ph.D.—Joost Felius with 6-10 papers published yearly, Pedig
- Overhead ranges 25 to 45%, avg ~40% (ASC/malpractice not incl)
- Monthly Journal club, office meeting

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**Choosing the Practice**

- Personality of the group
  - Reputation
  - Driven? Easy-going? Competitive?
  - Attitude towards outside activities e.g. family, philanthropy, etc.
  - Expectations?
- Location and offices
  - Drive time? Payer-mix of patients? Multiple office duty/opportunity?

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**Choosing the Practice**

- Attitude towards academic research and organizational/community involvement
- Call and coverage
- Vacation
- Marketing considerations — does the group promote itself? You?

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**Tips for Working in the Group**

- Always do what is best for patient
- Don’t be competitive
- It is not all about money
- It is all about the money
- Learn from each other - partners
- Monthly meeting, journal club?
- We are all human—we will make mistakes

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**Tips for Working in the Group**

- Never pass up the opportunity to do someone, especially a partner, a favor
- It’s not all about you

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**Compensation**

- Multiple arrangements exist
- Consider compensation that is a combination of production as well as shared
- Production rewards hard work
- Sharing encourages cooperation
- ASC ownership opportunity?

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**Overhead**

- Can be a huge source of contention
- Transparency best
- Production based for shared services (billing, collecting, etc)
- Physician specific (e.g. office furniture, number of techs, covered parking)
**Overhead**

- Be wary of fixed percent: ~40% of $100k vs 40% of $1 million
- Know what you are getting into!
  (Dr. Stass-Isern)

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**Single Specialty Group Practice**

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**Contract Negotiations**

- Approach your contract as you do the practice of medicine, be:
  - Knowledgeable
  - Informed
  - Patient

**Transparency**

- There must be 100% transparency regarding the practice and the contract
- Some physicians may be reluctant to “open their books” so you may need to sign a statement protecting their privacy

**The Contract**

- Must have a Buy In and a Buy Out
- You and your partner may have a clear vision when you buy into a practice, but LIFE HAPPENS....
- An exit strategy previously delineated avoids disappointment, resentment and misunderstood expectations

**Buy-Ins**

- How is it determined
  - % of production and/or AR?
  - Hard assets – most are depreciated within 5 years and have a small value
  - Goodwill should be eliminated

**Buy-Out**

- Reasons: death, disability, voluntary resignation, discharge, retirement
- If the buy-out is for anything besides death, is it treated as an adverse event and subject to a reduction in payment?
- What is included in the buy-out: assets, AR, liabilities, cash surrender value of life insurance, investment assets?

- Avoid non-competes
- Death of a partner - to solve a monetary problem if a partner dies - consider having life insurance (“Key-man insurance”)
- If you are buying into a practice and the other physician(s) are older - understand their timeline to retirement
Employee Contract

- If you have a probationary period before you buy into the practice - your employee contract may vary from the other physicians, otherwise it should be similar.

Employee Contract

Salary - income formula - understand this

- Is there a basic salary and then a % of net/gross AR reduced by a % of overhead expenses once a fixed amount of collections are reached
- Having the ability to earn above your base salary provides incentive

Key Points to Employee Contract

Overhead expense:
- First understand how the overhead expense for the practice is calculated and what the percentage is (40, 57% etc)
- Then understand how YOUR salary is calculated: Hours worked, Amount billed, AR gross or net

If one doctor requires more ancillary personnel - does this come out of his or her overhead? Is everyone’s overhead expense the same?

Key Points to Employee Contract

Disability insurance and overhead expense insurance:
- The expense of both these policies is high
- They are essential as the likelihood of a partner becoming disabled is much higher than a partner dying
- For the non-disabled partner this could be a financial disaster, as all the overhead expense remains minus the productivity of the disabled partner

Key Points to Employee Contract

Benefits:
- Health Care - if there is health care coverage for the office employees, do the physicians also receive coverage?
- If there is an age difference or family size difference that considerably increases the premium for a specific physician(s) - does the practice cover this or does the difference get paid by the individual physician

Key Points to Employee Contract

Expenses:
- Maximization of expenses is important
- However one physician should not end up paying for the other expenses
- Understand what they include and what the limits are

Key Points to Employee Contract

401k and profit share:
- Does the practice have one?
- When are you eligible to participate?
- Does the practice also have a non tax deductible plan to maximize your retirement funding?

Finally

- A partnership can be wonderful and rewarding, but just like any other long term agreement you have:
  - READ the small print and understand it
  - Prevention of misunderstandings is the best remedy

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Single Specialty Group Practice

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I have no financial interest to disclose.
**Reimbursement Equation**

Percentage billed for 3 months + percentage collected for 3 months divided by 2 =
Doctor percentage of net
(net = gross - overhead)

**Using the group to increase contract rates**

- Not general ophthalmologist
  (different codes, more consults)

- How to be considered a group
  (e.g. usually need 10 providers)
Practice Management Workshop
Multispecialty Practice
Robert S. Gold, M.D.
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Compensation Formulas
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Compensation Formulas
- Depends on the structure of the practice
- Equal share per partner
  - Now rare
  - Unlikely to include a pediatrics partner, you must educate them

Compensation Formulas
- Production-based
  - Most likely
  - Look for a percentage of shared compensation
  - Recognizes that you add value to the practice that can not be measured financially

Compensation Formulas
- Production-based
  - Based on dollars produced or RVUs
    - RVU-based formulas help to smooth out the effects of a higher Medicaid population, but are uncommon
    - Dollars produced more common, and here is where local payor distributions and expense allocation are very important

Compensation Formulas
- How are expenses allocated?
  - This is crucial
  - Some expenses should be shared equally, regardless of usage--phones, electric, etc.
  - Some expenses can be user-dependent--technician allocation, equipment usage
  - If you will be doing some general, you must expect more equal allocation (you’ll have to help pay for the IOL Master)

Compensation Formulas
- Hybrid
  - A percentage is shared
  - A percentage is based on production
  - Recognizes that you contribute in a way that cannot be measured in dollars (call sharing, bringing in patients to other physicians)
  - Gives incentive to high producers, does not punish lower producers as severely, helps even out inequities of expense allocation

Compensation Formulas
- Points to remember:
  - Do not go into negotiation with guns blazing
  - Ask questions thoughtfully--confrontation is seen as very threatening, filter anything an attorney suggests you ask

Compensation Formulas
- Points to remember:
  - It is hard as a new hire to change the structure, so decide if you can live with it as it stands, and hope to change it later (but don’t count on it)
  - Ask people you know about their experiences
**What is a Pediatric Ophthalmologist Worth?**

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I have no financial relationships to disclose

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**What types of practices do we serve in?**

- SOLO PRACTITIONERS  
- SINGLE SPECIALTY GROUPS  
- MULTISPECIALTY GROUPS  
- ACADEMIC  
- MILITARY  
- MANAGED CARE

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**PRACTICE A**  
SOLO PRACTICE

- PAYOR MIX  
  - MEDICAID - 40%  
  - MEDICARE - 16%  
  - COMM. INS. - 36%  
  - SELF-PAY - 8%

- PRACTICE MIX  
  - PEDI - 60%  
  - ADULT STRAB - 15%  
  - GEN - 25%

- 7 FTE staff  
  - 1 MD  
  - OVERHEAD COST - 42%

- MD PAYS OTHER EXPENSES PERSONALLY

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**PRACTICE B**  
SOLO PRACTICE

- PAYOR MIX  
  - MEDICAID - 30%  
  - MEDICARE - 2%

- COMM. INS. - 68%

- PRACTICE MIX  
  - PEDI - 95%  
  - ADULT STRAB - 5%

- 8 FTE  
  - FOR 1 MD  
  - OVERHEAD COSTS - 45-50%

- TAKE HOME 40% WITH 10% IN RESERVE FUND  
  - MOST EXPENSES PAID BY PRACTICE

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**PRACTICE C**  
GROUP SINGLE-SPECIALTY

- PAYOR MIX  
  - MEDICAID - 50%  
  - MEDICARE - <5%

- COMM. INS. - 45%

- PRACTICE MIX  
  - PEDI - 95%  
  - ADULT STRAB - 5%

- 19 FTE  
  - OVERHEAD COSTS - 45%

- SHARED AMONG ALL MDs

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**PRACTICE D**  
GROUP SINGLE-SPECIALTY

- PAYOR MIX  
  - MEDICAID - 6.5-10%  
  - MEDICARE - 6%

- COMM. INS. - 82-87%

- PRACTICE MIX  
  - VARED - 75-100% PEDI, 0-25% ADULTS

- 18+ FTE  
  - FOR 7 MDs  
  - OVERHEAD PER MD - 25% - 40%

- VERY FEW EXPENSES PAID BY PRACTICE’S PA

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**PRACTICE E**  
ACADEMIC

- PAYOR MIX  
  - MEDICAID - 60%

- COMM. INS. - 40%

- PRACTICE MIX  
  - 100% PEDI TERTIARY CARE SETTING

- 8-10 FTE  
  - FOR 1 MD (includes trainees)

- OVERHEAD 64% THOUGH $5 EARNED FROM OTHER HATS

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**PRACTICE F**  
GROUP MULTI-SPECIALTY

- PAYOR MIX  
  - MEDICAID - 33%  
  - MEDICARE - 7%

- COMM. INS. - 57%

- PRACTICE MIX  
  - 85-90% PEDI AND 10-15% ADULT STRAB

- OVERHEAD - 56% OF PEDI COLLECTIONS

- PEDI OPH GETS 10% OVER OTHERS

- NET COLLECTION % (“Delta Factor”)

- PRACTICE COVERS ALL EXPENSES, INSURANCE, CME, ETC.

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**SURVEY OF OTHER NATIONAL PRACTICES**

- LARGE MIXED GROUP  
  - SOUTHWESTERN USA

- 50+ MDs w/ 6 PEDs

- PROFIT CENTERS MODEL  
  - PRACTICE OWNS 30% ASC

- PEDI OVERHEAD APPROX. - 45-50%
SURVEY OF OTHER NATIONAL PRACTICES

- NORTHWEST USA
  - 11 MDs (1 PEDI)
  - ASC AND OPTICAL
  - PEDI OVERHEAD 60%

- SOUTHEASTERN USA
  - 18 MDs w/ 4 PEDI's
  - COLLECTIONS RANGED FROM $540-1,110K
  - ASC, OPTICAL, OTHER PROFIT CENTERS
  - PEDI OVERHEAD 42%-48%

- SOUTHWESTERN LARGE MULTI-SPEC
  - 30 MDs (1 PEDI)
  - PEDI OVERHEAD 58%

- MIDWESTERN GROUP
  - (14 MDs, 40 ODs, 1 PEDI)
  - 300+ FTEs,
  - PEDI OVERHEAD 68%

SUMMARY

- PURE PEDIATRICS SEEMS TO BE MOST PROFITABLE
- OWNERSHIP MAY BE OVERRATED
- ON AVERAGE, A PEDI OPH. SHOULD EXPECT TO TAKE HOME 50-55% OF COLLECTIONS
- "TAKE HOME %" RANGED FROM 32% TO 70%
- PAYOR MIX HIGHLY INFLUENCED THE BOTTOM LINE
- MOST INDIVIDUALS GENERATED $750K-$1 MILLION RANGE WITH A FEW OUTLIERS

SUMMARY

- PEDI OPH’s IN LARGE GROUPS GET THE SHORT STICK.......ALTHOUGH WE ARE NOT GENERALLY HIGH PRODUCERS, WE ARE VERY LOW OVERHEAD USERS, BUT OFTEN ARE SUBJECT TO HIGHER COSTS THAN WE ACTUALLY INCUR. "THE BEAST"
- DON'T BELIEVE EVERYTHING YOU ARE TOLD......TRUST YOUR INSTINCTS
- AS A TREND, ACTUAL INCOME(W-2) WAS ABOUT DOUBLE THE REPORTED INCOME THAT A NATIONAL CONSULTANT WOULD QUOTE FOR PEDI. OPH.

RECOMMENDATIONS

- NEGOTIATE A DEAL THAT MAKES EVERYONE REASONABLY HAPPY
- BIRDS OF THE SAME FEATHERS DO BETTER
- DON'T BE AFRAID TO LIMIT POOR PAYORS ...... THEY PULL YOU DOWN
- YOU ARE NEEDED....YOU ARE RARE

Ambulatory Surgery Centers (ASC’s)

Marc F. Greenberg, MD
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Children’s Healthcare of Atlanta at Scottish Rite
Eye Consultants of Atlanta, PC

ASC’s Populations Served

- Multispecialty
- Single Specialty-Ophthalmology
- Adult
- Pediatric
- Mixed
ASC’s Ownership

• National Hospital Corporation
• Local Hospital
• Physician-Multiple Groups
• Physician-Single Group
• Mixed

ASC’s Surgical Advantages

• Surgeon control
• Outpatient procedure focused
  – Instrumentation
  – Nursing mentality
• Healthy patients
• Quicker turnover times
• Predictable start/finish times
• Manageable setting
• Patient satisfaction

ASC’s Surgical Disadvantages

• Medically complex patients
  – Rejected
  – Limited resources increase surgeon liability
• Uncommon procedures
• Long procedures
• Expensive equipment
• Surgeon individuality/inflexibility
• Limited hours/emergencies
• Insurance/Medicaid

ASC’s Financial and Other Advantages

• Ownership
  – Income
  – Equity
• Efficiency
• No call?

ASC’s Financial and Other Disadvantages

• Ownership
  – Investment risk
  – Liability risk
• Drain on hospital resources
  – Revenue and nurses
  – On-call physicians
  – Divert complex, expensive, and underfunded cases to hospitals, yet...
  – Require hospitals for emergencies in ASC, as well as after hours (and your relatives).

ASC’s Summary

• Efficient, pleasant surgical environment with opportunity for financial reward. May keep some health care costs down.
• Cannot handle all cases at all times. Increased medical and liability risk.
  “Cherry-picks” resources from hospitals.

ROP Contracting

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Financial Disclosures for Robert Gold:
- Medical Advisory Board for Pediavision
- Consultant for Quest Medical
- Speakers bureau for Alcon

ROP Contracting

• Consultant to NICU
• Positive relationship with neonatologists
• Educate hospital executives
• Negotiate
  – Reimbursement - # of exams, time factor, “on call stipend”, billing
  – Indemnification
  – ROP coordinator / tracking
  – NICU vs. non-NICU coverage

General Ophthalmology
Requirements and Optical

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- Speakers bureau for Alcon
General Ophthalmology Requirements

- Will you need to do general ophthalmology when you join a new practice?
  - Overflow patients
  - Do you want to do general ophthalmology as well as pediatric ophthalmology?
  - Surgical—depends on practice setting/volume
    - Limit to pediatric ophthalmology/adult strabismus
    - Cataract/glaucoma surgery—peds ↔ adults

- Office emergencies
  - Pediatric and adult?
  - On call
  - Emergency room
  - Office
    - Equitable
    - Willingness to “split up” major holidays

Optical

- Important part of a multispecialty practice
- Importance of pediatric optical contribution to the multispecialty practice
- During employment period, productivity vs. “good will”—contract negotiating avenue??
- Can lead to significant financial reward as progress with practice
Electronic Health Records for Pediatric Ophthalmology: Practical Comparison
Robert W. Arnold, MD and panel

AAPOS Workshop

Spurred by the "Economic Stimulus Plan," may physicians are turning to electronic medical record (EMR) adoption, while others are considering switching from their prior purchases. Adopting an EMR is NOT simple. It is expensive in terms of money and time. It represents a major change in communication for both doctor and staff. The individual pediatric ophthalmologist might be selecting software and hardware. On the other hand, selection of a package might be "forced" by a large group practice, or medical institution.

Pediatric ophthalmology and strabismus represents one of the most complex exams in all of medicine with respect to reporting. Development of efficient software for ophthalmology is related to the number of professionals covering various aspects of the general and specific eye exam. Pediatric ophthalmologists and orthoptist represent a minority in terms of users, and also in terms of income. Refraction and motility are often relegated to "a tech" report for general ophthalmology, whereas these components are paramount to the pediatric exam, requiring a high level of professional experience. The diagnoses and coding for pediatric ophthalmology often differ from general ophthalmology.

One important aspect of an electronic medical record is work flow. How efficiently can an experienced pediatric ophthalmology input typical exams and output reports with various dominant systems today? With three test cases representing typical pediatric ophthalmology patients, prevailing software packages on modern computer systems will be compared by leaders in the field of pediatric ophthalmology EMR.

The typical cases follow:
Case Number 1: Infant with NLD-consult and pre-op
Name Ei Pifora
Gender Female
Birthdate 2/28/08
Referred by Pediatrician Ima Bratman, MD
Chief Complaint non-clearing mucopurulent discharge left eye
HPI both eyes "goopy" by age 1 month. Attempted hygiene, gentle massage and right eye cleared by age 3 months. Left exacerbated with URI age 5 months. Improved on oral Augmentin age 6 months for otitis media right. Persists despite one trial week of Polytrim 1 qtt OS tid, and a second with Vigamox one drop TID x 5 days.
PMH Normal vaginal delivery after normal pregnancy. Normal growth and development. One healthy 3-year-old brother, had NLD right eye cleared spontaneously age 3 months. Otitis media x 1; only time oral antibiotics given.
Immunizations up to date. No smokers in home
Medications none currently
Allergies None
Past Surgery None
EXAM
Constitutional Alert and interactive, no distress except with drop instillation
External mild erythema over lateral canthal tendon left and left lower lid, crusting collarettes left lashes. Both right puncta present, left lower puncta present, left upper not visualized.
Acuity active fixation, steady, centered and maintained OU
Pupils round, reactive to direct light
Fields accurate saccades at times to peripheral objects
Motility ortho on cover test near, full comitant versions. Bruckner Test normal
Conjunctiva right clear, left grade 1 injected, moderate whitish mucopurulent discharge with massage over left medial canthal tendon.
Cornea clear
Anterior Chamber formed and grossly clear
Iris blue, normal
Lens clear
IOP tactile- low teens
Refraction-manifest
Refraction-cycloplegic +1.25 +0.25 x 95 R, +1.50 +0.25 x 80 L
Retina optic nerves 0.2 C/D ou with normal vessels and RPE
Impression
Plan
Case Number 2: Mixed amblyopia and accommodative esotropia-prior BMR elsewhere, with OAIO, schedule surgery and prescribe atropine
Name Eazo Troap
Gender Male
Birthdate 12/31/2004
Referred by Pediatrician Whyp A. Snaught
Chief Complaint Left eye still goes up and in
HPI Left eye started crossing about age 1 year. Saw eyedoctor Kham Preehens who started glasses and recommended patch right eye. Eazo pulled patch off. Had surgery on inside muscle each eye just before 2nd birthday. Initially "it worked" but then he needed glasses again, and now left eye goes up and in last three months.
PMH Healthy, normal birth, normal development
Medications Vitamins
Allergies Peanuts, Penicillin
Past Surgery Eye muscle surgery, medial rectus recessions 4mm each.
EXAM
Constitutional Alert, no syndrome or obvious delays
External Normal
Acuity Patched HOTV 20/63 R and 20/25 L
Pupils Normal, round, reactive no Marcus Gunn
Fields Normal to confrontation
Motility With glasses (+2.75+0.25 x 90 R and + 2.25+0.50 x 85 L) 25 PD ET distance and 30 PD ET near. Without glasses 35 PD ET distance and 45 PD ET near. 3+ inferior oblique overaction right and 2+ left with V pattern (glasses distance 15 PD ET up and 35 PD ET downgaze. Minimal evidence of nystagmus. Stereo: no Fly.
Conjunctiva Medial conjunctival limbal incision scars- minimal
Cornea Clear
Anterior Chamber Clear and deep
Iris Brown
Lens Clear
IOP Tactile mid teens
Refraction-manifest +2.75 sphere R and +2.50+0.25x90 L
Refraction-cycloplegic +3.00 sphere R and +2.50 + 0.50 x 90 L
Retina Normal with 0.3 C/D colorful nerves and moderate excyclotorsion R>L
Impression
Plan
Case Number 3 Neurofibromatosis with asymmetric optic nerve cupping and s-shaped ptosis with anisometropic astigmatism
Name Vonnie Wrek
Gender Female
Birthdate 1/1/2007
Referred by Pediatric neurologist Lokuz Seroolyuz, MD
Chief Complaint 5 café-au-lait spots
HPI New pediatrician Latta Eenzite, MD noticed several flat, coffee-colored patches including axillary. Pediatric neurologist exam unremarkable but poor view of eyes.
PMH 3 weeks premature but on growth curve height and weight. Didn't walk until 14 months. No seizures. Father has thick glasses- not at exam.
Medications None
Allergies None
Past Surgery None
EXAM
Constitutional Alert, interactive
External Slight ptosis more temporal left worse in downgaze, café-au-lait over left zygoma 1.0 x 0.8 cm faint, No globe dystopia
Acuity Patched HOTV 20/25 R and 20/40 L
Pupils Round, reactive, grade 1 Marcus Gunn L
Fields Full to confrontation
Motility Comitant 5 PD exophoria distance and near, no nystagmus, Stereo: detects fly wings
Conjunctiva Clear
Cornea Clear
Anterior Chamber Clear, deep
Iris Brown, no Lisch but dark 0.5 mm nevus L periphery at 5:00-
Lens Clear
IOP Tactile mid-high teens, Attempt with Tonopen unsuccessful
Refraction-manifest +1.25 +0.50 x 105 R +2.00+0.75 x 70 L
Refraction-cycloplegic +1.75+0.50 x 105 R and +2.75 +0.50 x 72 L (20/32)
Retina Normal RPE and vessels, Optic nerves good color 0.2x0.2 C/D r and 0.4x0.4 C/D left rim a bit larger
Impression
Plan
Leber Congenital Amaurosis: Clinical Course, Genotype-Phenotype Correlations, Clinical Trials Update and Future Directions

Elias I. Traboulsi and Daniel C. Chung

LCA occurs in 1/81,000 to 1/40,000 live births in occidental countries but may be much more common in countries where consanguineous marriages are common and in genetically isolated communities. This genetically heterogeneous group of diseases is characterized by severe visual loss from birth, pendular nystagmus, sluggish pupillary reactions and no particular characteristic fundus appearance.

Photopic and scotopic ERG recordings are generally severely attenuated. In patients with RPE65 mutations for example, early in the course of the disease process scotopic waveforms are severely attenuated while photopic ones are reduced but still recordable.

Patients with LCA have been described as having high hypermetropia, but while this is true for many patients, it is not a universal finding. In fact many are myopic, and some have no significant refractive errors.

Photoaversion is not uncommon in patients with LCA and is particularly severe in patients with GUCY2D mutations. This has led to a confusion of LCA with achromatopsia in some. ERG differentiates the two disorders.

More than half of the patients with LCA have an eye-poking behavior called the oculo-digital sign. The exact cause for this behavior is unclear. It is thought to result in phosphenes and cause some satisfaction for the patients who perpetuate it. This sign is not unique to patients with LCA and has been observed in many children with early or congenital blindness from a variety of causes such as retinopathy of prematurity or cataracts.

Keratoconus develops in an unknown proportion of patients with LCA. Its etiology is unknown but constant eye rubbing from the oculo-digital behavior may be causative. It does not appear to be more prevalent in one or the other genetic subtypes of LCA. Cataracts develop in some patients with LCA in their teens and twenties and may be more common in those with RDH12 mutations.

Neurodevelopmental abnormalities are also more prevalent in patients with LCA and some may be secondary to the blindness, while others are co-existent. It is beyond the scope of this lecture to discuss these abnormalities but it is possible that some may be secondary to the underlying genetic defects as some of these genes are expressed in the brain.

The retina may appear almost completely normal in some patients with LCA, especially those with GUCY2D mutations or may show a variety of non-specific or characteristic changes (vide infra).
Phenotype – Genotype Assignment

It is possible to predict the underlying genetic defect in some patients with LCA on the basis of clinical characteristics. In the following section I will describe the clinical distinguishing features of some subgroups of patients with LCA. I will assign each to a category of *(difficult), **(easier), or *** (easiest to guess), depending on ease of prediction with increasing number of stars. It is easier to prioritize genetic testing, if possible or probable molecular diagnoses are suggested by the clinician to the testing laboratory.

LCA1 and Guanylate Cyclase (*GUCY2D, OMIM 204000, ***)

LCA patients with mutations in GUCY2D have very poor vision in the range of hand movements (HM) to no perception of light (NLP). They are light sensitive and have no night blindness. There is a variable degree of hypermetropia. The fundus is generally normal in appearance (Figure 1) and may not show any pigmentary or atrophic changes for years.

LCA4 and Aryl Hydrocarbon Receptor Interacting Protein-Like 1 (*AIPL1, OMIM 604393, *)

The *AIPL1* gene consists of 6 exons and encodes a protein of 384 amino acids that may have a protein folding function. The protein may also be involved in photoreceptor differentiation and survival. Mutations in AIPL1 cause a severe LCA phenotype with very poor vision (LP to 20/400), variable hypermetropia, light sensitivity and night blindness. Although the fundus may initially be normal, progressive retinal changes occur including pigmentary changes and maculopathy in the form of a bull’s eye lesion or atrophic lesion. One-fourth of patients develop keratoconus or cataracts. Rod ERG abnormalities may be present in carriers of single gene mutations. In one study of 26 patients with AIPL1-related LCA the W278X mutation constituted 48% of mutant alleles.

RP12 and Crumbs homologue of Drosophila (*CRB1, OMIM 604010, ***)

Patients with CRB1 mutations are in general highly hypermetropic. Their vision varies from 0.05 to 0.15. They are night blind. Some have a peculiar ophthalmoscopic sign consisting of preservation of the para-arteriolar retinal pigment epithelium (PPRPE). Others have perivascular sheathing, nummular pigmentary changes, macular dysplasia, and occasional hemorrhages. The OCT is characteristic and shows retinal thickening with obliteration of the normal retinal architecture.

LCA2 and Retinal Pigment Epithelium-specific protein, 65 kd (*RPE65, OMIM 180069, ***)

Night blindness is universal in patients with *RPE65* mutations. Patients have poor vision very early in life with nystagmus. ERG recordings obtained early in life show relative preservation of cone function. Visual function improves over the first few years of life and vision may be relatively fair through teen-age years, with later deterioration as patients reach their third to fifth decades. There is diffuse retinal degeneration with fundus depigmentation, especially in the posterior pole. Patients may be myopic or hypermetropic. As the
degeneration progresses, vision decreases and the ERG shows deterioration of cone function. Gene therapy has been performed in animals and humans with RPE65-related retinal degenerations with restoration of visual function. It is beyond the scope of this paper to discuss the details of gene therapy.

**LCA3 and Retinol Dehydrogenase 12, (RDH12, OMIM 604232, **)**

Night blindness is predominant symptom of this type of LCA. Patients are not photophobic. They have hypermetropia with progressive fundus pigmentary changes in a fishnet pattern that accompany progressive vision loss. Some patients develop cataracts and others have a Coats’-like response. The ERG responses are relatively preserved early in the course of the disease but progress to flat tracings.

**LCA10, Centrosomal Protein, 290-KD (CEP290, OMIM 611755, **)**

This is the most common cause of LCA in Northern Europeans, accounting for up to 25% of cases with the Cys998X in 20% of all patients. There is a severe but stable phenotype with vision of light perception or hand movements, possible cataracts and keratoconus in some patients as disease progresses. There is no heavy pigmentary retinopathy. A Coats-like response has been described in some. Heterozygotes may have olfactory defects. CEP290-related LCA is one of a number of retinal dystrophies grouped under the category of retinal ciliopathies because the abnormal proteins are important in the structure or function of ciliated cells that include photoreceptors. These disorders include among others Usher syndrome and the Bardet-Biedl syndromes.

**LCA5, LCA5 Protein (Lebercilin, OMIM 604537, *)**

Lebercilin mutations are a rare cause of LCA. They result in one of the most severe forms with LP or NLP vision. There have only been a few reported cases.

**LCA in Adults**

The diagnosis of LCA in adults is challenging. These patients are most often labeled as having RP. Clues to the accurate diagnosis include nystagmus, poor vision since birth and the presence of severe vision loss with keratoconus. RPE65 disease should be considered in patients who have had some preservation in vision in childhood with predominant night blindness and a fundus appearance as described in the RPE65 section above. Most systemic diseases associated with a retinal degeneration would have manifested themselves by adulthood, making their diagnosis unlikely; Bardet-Biedl syndrome however always needs to be considered and its multisystem manifestations should be looked for. Testing is tailored to the individual patient.

**Does the Genotype Determine Clinical Course and Visual Outcome?**

Vision inevitably worsens in all genotypes of LCA. Patients with better visual acuity/visual function early in life (not necessarily in 1st year of life) tend to have better preservation of vision, and for a longer period of time. A meta-analysis of the literature and actual data is needed to determine natural history and rate of vision loss in different genetics types of
LCA. It is uncertain if there is intrafamilial consistency in the severity of the LCA phenotype. Additional studies are needed in this respect also.

**Gene Therapy in LCA**

One of the most exciting advances in the management of inherited retinal diseases has been the successful treatment of animals and humans with RPE65-related retinal degenerations using virus-mediated gene transfer. This has paved the way to the exploration of similar and other therapies for other forms of retinal dystrophies. Additional modalities that hold promise in the management of patients with retinal dystrophies include neurotrophic factors and encapsulated cell technology, photoreceptor and RPE transplantation, nanoparticle-mediated gene therapy, pharmacotherapy, and artificial retina and retinal prosthetic devices. The role of dietary modification and vitamin supplementation in retinal degenerations is still under investigation.

**RPE65**

Defects in the gene, RPE65, cause vision loss at infancy with progression to blindness by early adulthood. Labeled as LCA2, RPE65 gene normally encodes a retinal isomerase responsible for the regeneration of visual pigment after light exposure. Although the absence of this protein causes early profound visual impairment in humans and animal models, the degeneration of the retinal cells themselves is delayed. Differing from other forms of retinal degenerative disease, the cells remain present, though not functioning, even after blindness has set in and electrophysiologic response is all but absent.

This pathophysiologic characteristic of LCA2 proved to be a promising disease for investigation of gene targeted therapies. The beginning hypothesis was, that by the insertion of the wild type RPE65 gene, the function of the targeted retinal cells, in this case retinal pigment epithelial cells, could be repaired before structural degeneration occurs. Outcome measures could also be rapidly measured for any therapeutic effect that may occur.

**Pre-clinical Animal Studies**

This hypothesis was applied to two animal models, the Briard dog, a canine species with a spontaneously occurring RPE65 mutation, and the *RPE65*-/− transgenic mouse. In the canine model of LCA2, an attenuated adeno-associated virus (AAV) vector containing RPE65 complementary DNA (cDNA) was injected into the subretinal space of one eye. Functional analysis was undertaken by electroretinography, pupillometry and visual behavior studies. The electroretinogram (ERG) revealed a marked restoration of ERG wave levels, when compared to wild type animals and the contralateral control eye. To demonstrate visual function at a higher order, pupillometry was performed and showed a 50% increase in pupillary response, along with lower light threshold levels over the non-injected control eye. Animals were also evaluated for restored visual behavior by their ability to ambulate through an obstacle course at different light levels. Post injected animals exhibited a faster transit time through the obstacle course with fewer errors than baseline measurements. Further histological and biochemical analysis confirmed the presence of the protein and its expression. Ongoing observation of these animals has now exceeded 7.5 years, and long-term restoration of visual function continues.
An engineered murine model, Rpe65-/-, was also investigated for efficacy of gene based visual restoration. Due to the early onset of visual demise, intervention was initiated prior to birth, in utero, and within the first post-partum month. Similarly to the canine model, murine transgenic animals received a unilateral, subretinal injection of an AAV vector encoding the wild type RPE65 cDNA. Post injection analysis revealed a restored ERG, RPE65 expression by immunohistochemistry and biochemical verification of 11-cis retinal.

Based on these results, groups from University College London/Moorfield Eye Hospital in the United Kingdom (UK), the University of Florida/University of Pennsylvania (UF) and the Children’s Hospital of Philadelphia/University of Pennsylvania (CHOP) planned investigations into the safety and efficacy of this approach in humans. All three groups initiated human gene therapy trials for LCA2 in the past two years, and reports of their findings have been published in 2008.

**Trial Design**

Although there were three independent groups, they all had very similar approaches, using an AAV vector carrying the wild type RPE65 cDNA targeting retinal pigment epithelial cells with a subretinal injection. Differences in the vector were mainly seen in viral transgene promoters and modifiers. Each group initially injected 3 individuals ranging in ages from 17-24 years of age, all three groups reported some level of efficacy.

A standard three-port pars plana vitrectomy was performed, and the posterior cortical vitreous was removed to allow injection into the subretinal space of the vector in a volume of 150 µL (UF/CHOP) to 1000 µl (UK) of buffered saline, volumes were different among the different groups. The injections created localized dome-shaped retinal detachments in the treated eyes of the patients without significant complications. Preoperatively and at intervals postoperatively the patients underwent complete ophthalmic and physical examinations, serum and tear collections for biodistribution assessments of the vector and potential immune response.

Efficacy was evaluated using both subjective and objective measures performed preoperatively and at regular intervals postoperatively. Objective measures included pupillary light reflex, nystagmus testing, and ERGs. Subjective methods involved visual acuity, dark adaptation threshold sensitivity, visual fields and mobility.

**Safety and Efficacy Results**

In all, nine adult patients were reported on this past year, all but one having vision worse than 20/200. After receiving subretinal injections of their respective AAV.RPE65 vector, three patients reported statistically significant visual acuity improvement and 7 of 9 patients reporting increased light sensitivity. All three clinical trial sites reported light sensitivity improvement in at least one subject. None of the groups reported any significant changes in the ERGs of their participants, however this global retinal test is relatively insensitive. Postoperative examinations were unremarkable, except for two patients; one developed a macular hole that was considered visually insignificant due to the extremely poor baseline vision and a second patient who had documented foveal thinning after surgery. No
significant adverse events postoperatively were reported. Extensive evaluation for a mounted immune response to vector or transgene showed minimal reaction, as well as biodistribution assays being largely negative.

One of the most dramatic objective results was seen by pupillometry. At baseline, in all patients tested by pupillometry, pupillary light reflex to alternating stimulation of the left and right eyes showed much less sensitivity to light than in control subjects. Baseline responses to stimulation with 0.04 lux in dark-adapted patients were negligible, and responses to 10 lux, which is 250 times brighter, were weak. Following injection, pupillary response in patients’ treated eyes was significantly greater than in the untreated eyes. The vector-injected eyes became approximately three times more sensitive to light than at baseline and surpassed the sensitivity of the previously better, untreated eye. This appears as an acquired relative afferent pupillary defect, with the treated eye responding to the light stimulus and the untreated eye remaining defective.

It is encouraging that all groups report some form of efficacy with this approach, with no reported adverse safety issues. It is the slight differences in approach that may give clues to optimize delivery, heighten efficacy and maintain safety for future LCA2 trials and other trials for retinal degenerative disease.

**Future Directions**

These early human clinical trials treating the genetic disease LCA2 with subretinal injections using a gene-therapy delivery system appears to be safe and in the short term, there is significant evidence of efficacy in terms of improvement in retinal and visual function. Although these are short-term results, it is incredibly encouraging to see that gene replacement therapy for LCA2 can be effective in some measures. In considering the next step for these trials, preclinical studies suggest that earlier intervention may be more efficacious in restoration of retinal and visual function.

It may prove that results in LCA2 may be further improved by applying the gene treatment to the pediatric populations. This would also present with a new and different set of issues than in adult clinical trials. These studies have not only laid the ground work for further investigations in LCA2, but also allows for the applications of methods to other retinal degenerative disease such as LCA CEP290, Stargardt disease, Usher disease and other forms of retinitis pigmentosa.
Table 1 - List of genes that have been identified to date as causative of a phenotype of LCA.
Case mix varies depending on ethnic background and the prevalence of consanguinity in various countries.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Locus</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCA1</td>
<td>17p13.1</td>
<td>GUCY2D</td>
</tr>
<tr>
<td>LCA2</td>
<td>1p31</td>
<td>RPE65</td>
</tr>
<tr>
<td>LCA3</td>
<td>14q24</td>
<td>RDH12</td>
</tr>
<tr>
<td>LCA4</td>
<td>17p13.1</td>
<td>AIPL1</td>
</tr>
<tr>
<td>LCA5</td>
<td>6q11-q16</td>
<td>Lebercilin</td>
</tr>
<tr>
<td>LCA6</td>
<td>14q11</td>
<td>RPGRIP1</td>
</tr>
<tr>
<td>LCA7</td>
<td>19q13.3</td>
<td>CRX</td>
</tr>
<tr>
<td>LCA8</td>
<td>1q31-q32</td>
<td>CRB1</td>
</tr>
<tr>
<td>LCA9</td>
<td>1p36</td>
<td>Unknown</td>
</tr>
<tr>
<td>LCA10</td>
<td>6q21.3</td>
<td>TULP1</td>
</tr>
<tr>
<td>LCA11</td>
<td>7q31.3-q32</td>
<td>IMPDH1</td>
</tr>
<tr>
<td>LCA12</td>
<td>1q32.3</td>
<td>RD3</td>
</tr>
<tr>
<td></td>
<td>14p</td>
<td>SPAT4A7</td>
</tr>
</tbody>
</table>
Understanding skew deviation and differentiating it from trochlear nerve palsy

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Skew Deviation & Ocular Tilt Reaction

- A vertical strabismus caused by supranuclear lesions in the brainstem and cerebellum
- Ocular tilt reaction:
  1. Skew deviation
  2. Ocular torsion
  3. Head tilt
- Associated with tilt of the subjective vertical
## Skew deviation vs 4th nerve palsy

<table>
<thead>
<tr>
<th>Fourth Nerve Palsy</th>
<th>Skew Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypertropia in primary position</td>
<td>1. Hypertropia in primary position</td>
</tr>
<tr>
<td>2. Incomitant (acute): Hypertropia worse on gaze to opposite side; may become comitant with time</td>
<td>2. Incomitant, comitant, or alternating</td>
</tr>
<tr>
<td>3. Hypertropia worse on ipsilateral head tilt</td>
<td>3. Hypertropia may or may not change with head tilt</td>
</tr>
<tr>
<td>4. Compensatory head tilt contralateral to the hypertropic eye</td>
<td>4. Pathologic head tilt contralateral to the hypertropic eye</td>
</tr>
<tr>
<td>5. <strong>Ex</strong>cyclotorsion of the hypertropic eye</td>
<td>5. <strong>Inc</strong>yclotorsion of the hypertropic eye (and excyclotorsion of the hypotropic eye)</td>
</tr>
</tbody>
</table>
Skew Deviation & Ocular Tilt Reaction

- Believed to be due to imbalance of the VOR projections from the utricles in the inner ears to ocular motoneurons (i.e. the utriculo-ocular reflex)
1. Detect head translation and mediate the translational or linear VOR (LVOR)
2. Detect static head tilt and mediate the ocular-counterroll reflex
Connections from the utricle to extraocular muscles

To horizontal rectus muscles

Head Translation to the Left

To oblique muscles

Static Head Tilt to the Right Shoulder

Disynaptic pathway — weak contribution
Polysynaptic pathway (possibly via cerebellum) — strong contribution

Otoconia movement

Hair cells in lateral utricle inhibited
Hair cells in medial utricle activated

Hair cells in medial utricle inhibited
Hair cells in lateral utricle activated

Hair cells in lateral utricle inhibited
Hair cells in medial utricle activated

Hair cells in medial utricle inhibited
Hair cells in lateral utricle activated

Hair cells in lateral utricle inhibited
Hair cells in medial utricle activated
Stimulation of Right Utricular Nerve

**Otolith: perception of earth vertical**

**A. Normal:**
Head upright

**B. Normal:**
e.g. Left head tilt

**C. Abnormal:**
Right otolith lesion

Perception of earth vertical

Also pathologic head tilt to the right
Subjective visual vertical & OTR

- SVV Tilt 94%
- OT 83%
- SD 31%
- OTR 20%

Patients with acute unilateral brainstem lesions 100%

Gaps in our understanding of skew deviation

1. Although brainstem or cerebellar lesions have been purported to cause skew deviation, there is no direct evidence that skew deviation can be caused by isolated lesion in the **cerebellum**

2. Although imbalance of the utriculo-ocular reflex has been purported to cause skew deviation, there is no direct evidence that skew deviation is associated with **abnormal utriculo-ocular responses**
Brainstem lesions causing skew deviation

Examples:

Dorsal midbrain (pretectal) syndrome

Internuclear ophthalmoplegia (INO)

Lateral medullary syndrome
Lack of clinical evidence:

- Skew deviation was induced in cats by sectioning the middle cerebellar peduncle, but adjacent tegmental structures in the brainstem may have also been damaged (Magendie and Hertwig 1826)
- Skew deviation is seen in patients with spinocerebellar degenerations / dysgenesis or developmental malformations of the cervicomedullary junction, but the brainstem is usually involved in these conditions
Cerebellar skew deviation and the torsional vestibuloocular reflex

Agnes M.F. Wong, MD, PhD, FRCS; and James A. Sharpe, MD, FRCPC

Abstract—Background: Skew deviation is typically caused by lesionation damage, and has not been identified with focal cerebellar lesions. This vertical strabismus has been attributed to asymmetric disruption of vestibuloocular reflex (VOR) projections from otolithic receptors of the utricle to scalar motoneurons, but asymmetry of the utriculo-scallar counter roll reflex has not been detected. Methods: Lesions localized to the cerebellum were identified by MRI in five patients with vertical strabismus. Their skew deviation was measured by prism cover test in all patients and by search coils in three patients. The angular VOR was tested in patients and 10 controls during sinusoidal ±10 degree torsional, vertical, and horizontal head-on-body rotations at 0.5, 1, and 2 Hz. Static torsional VOR gain was measured by the change in torsional eye position divided by change in head position during maintained head tilt. Results: Static torsional VOR gains were asymmetric in each patient. Three patterns of asymmetry were identified: 1) decreased static gain in one eye in both directions; 2) decreased gains in both eyes in one direction; and 3) asymmetric gain in one direction in one eye alone. Dynamic torsional VOR gains were symmetrically reduced in both directions in both eyes in all patients. Conclusions: Focal cerebellar lesions can cause skew deviation. The static torsional vestibuloocular reflex (VOR) is linked to cerebellar control of vertical vergence. Asymmetry between the eyes or in direction of the static torsional VOR provides evidence that monocular or binocular imbalance of the utriculo-scallar reflex leads to cerebellar skew deviation.
Gaps in our understanding of skew deviation

1. Although brainstem or cerebellar lesions have been purported to cause skew deviation, there is no direct evidence that skew deviation can be caused by isolated lesion in the cerebellum.

2. Although imbalance of the utriculo-ocular reflex has been purported to cause skew deviation, there is no direct evidence that skew deviation is associated with abnormal utriculo-ocular responses.
Functions of the Utricles

1. Detect head translation and mediate the translational or linear VOR (LVOR)
2. Detect static head tilt and mediate the ocular-counterroll reflex
Hypotheses

- If skew deviation is caused by imbalance of utricular-ocular pathway, then:
  1. The ocular counterroll (OCR) would be abnormal
  2. The translational or linear vestibular ocular reflex (LVOR) would be abnormal
  3. The abnormal torsion and vertical strabismus seen in skew deviation might be head position-dependent
Hypothesis 1: Is the OCR abnormal?

- Skew deviation (n=3)
  - Negative three-step test
  - Presence of other neurologic symptoms and signs
  - MRI confirmed cerebellar lesions

- Ten normal subjects
Methods

- Scleral search coils
- Head tilt 30 deg toward the right shoulder (CW) and left shoulder (CCW)
- OCR gain = change in torsional eye position divided by change in head position
Results

CCW-CW Asymmetry

OCR Gain Asymmetry

Upper 95% CI
Normal Mean
Lower 95% CI

P1
P2
P3

Hyper Eye
Hypo Eye
The asymmetric reduction in OCR gains (CW vs CCW) supports that skew deviation is caused by damage to the utricular-ocular reflex pathway (Wong AM, Sharpe JA. *Neurology* 2005;65:412-419)
If skew deviation is caused by imbalance of utricular-ocular pathway, then:

1. The ocular counterroll (OCR) would be abnormal
2. The translational or linear vestibular ocular reflex (LVOR) would be abnormal
3. The abnormal torsion and vertical strabismus seen in skew deviation might be head position-dependent
Hypothesis 2: Is the LVOR abnormal?

- **Skew deviation** (n=6)
  - Negative three-step test
  - Presence of other neurologic symptoms and signs
  - MRI confirmed brainstem or cerebellar lesions

- **Age-matched normal subjects** (n=12)
Methods

- Subjects fixated at a target monocularly at 15 and 20 cm
- Lateral head translation impulses delivered manually along interaural axis
  - Unpredictable in direction and timing
- Eye movements measured by scleral search coils
- Head translation measured by accelerometer and linear potentiometer
Normal subjects:
• LVOR sensitivity decreased as viewing distance increased

Patients:
• All six patients had significantly diminished LVOR responses (mean reduction = 58%)
• LVOR sensitivity did not modulate with viewing distance

Sensitivity = ratio of peak eye velocity to peak head velocity
The reduction of LVOR in patients was asymmetric by eye, with no pattern identified.
If skew deviation is caused by imbalance of utricular-ocular pathway, then:

1. The ocular counterroll (OCR) would be abnormal
2. The translational or linear vestibular ocular reflex (LVOR) would be abnormal
3. The abnormal torsion and vertical strabismus seen in skew deviation might be head position-dependent
Hypothesis 3: Clinical Observation

Upright

Supine

Otolith Hair Cell Polarization

- Saccule
- Utricle
- Striola
- Anterior
- Dorsal
- Lateral
Hypothesis 3: Objective

To investigate whether torsion and vertical strabismus differs in upright vs supine position in skew deviation, and to compare the findings in fourth nerve palsy, and normal subjects

Predictions:
- Skew - Marked reduction of torsion and vertical misalignment from upright to supine
- CN IV palsy - No change in torsion and vertical misalignment from upright to supine
- Normal subjects – No change in torsion and vertical alignment from upright to supine
Methods

- **Skew deviation** (n=10)
  - Negative three-step test
  - Presence of other neurologic symptoms and signs
  - MRI confirmed brainstem or cerebellar lesions

- **Fourth nerve palsy** (unilateral) (n=13)
  - Positive three-step test
  - No other neurologic symptoms and signs
  - Negative MRI

- **Normal subjects** (n=12)
Methods

- Double Maddox rods to measure torsion
- Prism and alternate cover test to measure vertical deviation
Skew: Marked reduction of torsion from upright to supine
CN IV palsy: Minimal change in torsion from upright to supine
Normal subjects: No change of torsional phoria from upright to supine
Torsion Change Index (TCI)

\[ TCI = \frac{(T_{\text{up}} - T_{\text{supine}})}{(T_{\text{up}} + T_{\text{supine}})} \]

ANOVA, \( p < 0.001 \)
Skew: Marked reduction of vertical misalignment from upright to supine
CN IV palsy: Minimal change in vertical misalignment from upright to supine
Normal subjects: No change of vertical phoria from upright to supine
Vertical misalignment: Marked reduction in skew, but not in CN IV palsy or normal subjects

\[ VCI = \frac{(V_{up} - V_{supine})}{(V_{up} + V_{supine})} \]

ANOVA (p<0.001)
In skew deviation, there was a marked reduction of torsion and vertical misalignment from upright to supine position, whereas no change was seen in CN IV palsy or normal subjects (Parulekar MV, Dai S, Buncic JR, Wong AM. Arch Ophthalmol 2008;126:899-905)

Head position-dependent change in torsion provides objective evidence that skew deviation is caused by dysfunction of the utriculo-ocular reflex
When changing from an upright to supine position, the orientation of the utricles changes from earth-horizontal to earth-vertical.

This new orientation of the utricle leads to a saturation in the overall activities of the utriculo-ocular reflex, such that any asymmetry of the reflex is minimized.

This, in turn, leads to a reduction in torsion and vertical misalignment in skew deviation.
In CN IV palsy, the utriculo-ocular pathway is intact; thus there is no change in torsion or vertical deviation in different head positions.

The contralateral head tilt commonly seen in CN IV palsy is a compensatory mechanism that utilizes the normal intact utriculo-ocular reflex to minimize the magnitude of vertical diplopia.
To differentiate between fourth nerve palsy and skew deviation:

- Ocular torsion and vertical misalignment that decrease from upright to supine position → skew deviation
- Torsion and vertical misalignment that do not change significantly between upright and supine position → CN IV palsy
# Skew deviation vs 4th nerve palsy

<table>
<thead>
<tr>
<th>Fourth Nerve Palsy</th>
<th>Skew Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypertropia in primary position</td>
<td>1. Hypertropia in primary position</td>
</tr>
<tr>
<td>2. Incomitant (acute): Hypertropia worse on gaze to opposite side; may become comitant with time</td>
<td>2. Incomitant, comitant, or alternating</td>
</tr>
<tr>
<td>3. Hypertropia worse on ipsilateral head tilt</td>
<td>3. Hypertropia may or may not change with head tilt</td>
</tr>
<tr>
<td>4. Compensatory head tilt contralateral to the hypertropic eye</td>
<td>4. Pathologic head tilt contralateral to the hypertropic eye</td>
</tr>
<tr>
<td>5. <strong>Ex</strong>cyclotorsion of the hypertropic eye</td>
<td>5. <strong>Inc</strong>yclotorsion of the hypertropic eye (and excyclotorsion of the hypotropic eye)</td>
</tr>
<tr>
<td>6. Hypertropia and abnormal torsion <strong>persist</strong> in upright and supine position</td>
<td>6. Hypertropia and abnormal torsion <strong>disappear</strong> when changing from upright to supine position</td>
</tr>
</tbody>
</table>
Summary

- Skew deviation can be caused by brainstem or cerebellar lesions
- Skew deviation is caused by imbalance of the utriculo-ocular pathway:
  - Asymmetric and abnormal OCR responses
  - Asymmetric and abnormal LVOR responses
  - Head-position dependent changes in torsion and vertical misalignment
- A new clinical test to differentiate between skew deviation and 4\textsuperscript{th} nerve palsy
Graves’ Orbitopathy: Honing Your Skills to Improve Outcome

AAPOS WORKSHOP – San Francisco, California 2009

Linda Dagi, MD Gill Roper-Hall, DBOT, CO Oscar A. Cruz, MD Alexa Elliott, MD

I INTRODUCTION: PATHOPHYSIOLOGY, PRESENTATION, AND TREATMENT CONSIDERATIONS

1. Pathophysiology
   a. Loss of homeostatic control of T3 and T4 on an autoimmune basis

2. The Endocrinologist
   a. Thyroid suppression
   b. Thyroid ablation
   c. B blockers

3. The Ophthalmologist
   a. TSHr AB levels
   b. Absence of blood test to predict clinical course

4. The Role of the Fibroblast

5. The cascade producing glucosaminoglycans

6. Graves’ Orbitopathy: Expansion of the fat pads around the eyes and inflammatory changes

7. Graves’ Orbitopathy: Expansion of the orbital fat compartment; proptosis,

8. Tendon sparing enlargement and fibrosis of the extra-ocular muscles
   a. Secondary restrictive, incomitant strabismus, arching brow, compressive optic neuropathy
   b. Ocular hypertension

9. Best Imaging
   a. CT
   b. MR T1 and T2 STIR or FSEIR: fat suppression

10. Compressive optic neuropathy
   a. Risk greater in absence of proptosis

11. Lid Retraction:
    a. B adrenergic stimulation
    b. Infiltration of retractors
    c. Proptosis
    d. Fixation duress

12. Copy Cat Syndrome: Positive three step test in 20% of patients with GO

13. Demographics: Orbitopathy present in 20-35% of adult patients with Graves hyperthyroidism
    a. Radiographically apparent in 80-90%
    b. 8:1 female:male incidence
    c. Under 40 typically proptosis, over 50 EOM, over 70 compressive ophthalmopathy
    d. Smoking, hypoxia increase risk and severity of orbitopathy
    e. Radiation independent risk factor

14. Steroids for inflammatory orbitopathy:
    a. High dose IV pulse dosing more effective, fewer side effects with less rebound after discontinuation
    b. Absolute indications: acute inflammatory compressive optic neuropathy and at onset of treatment with I-131
    c. Consideration in case of significant inflammatory presentation; will reduce same and modest reduction in proptosis and vertical strabismus

15. New Immune-modulators to consider

16. Orbital Irradiation
    a. Possible benefit in reducing inflammatory proptosis, vertical strabismus and compressive optic neuropathy; Lack of definitive evidence based work.
    b. Risk: radiation retinopathy
    c. Youth, diabetes, and vasculopathic diseases are contraindications
17. Graves’ in Children
   a. 0.1 per 100,000 pre-pubertal, 3.0:100,000 post pubertal.
   b. Females predominate post-pubertal

18. The Children’s Hospital Experience
   a. Pre-pubertal proptosis, lid retraction
   b. Post pubertal: proptosis, lid retraction, inflammatory signs, strabismus
   c. No cases of compressive optic neuropathy
   d. Higher initial levels of TSH receptor antibodies (TBII) and a lesser rate of decline with thyroid suppression therapy correlate with severity
   e. Oligoclonal TSH receptor antibodies (secreted by a limited number of B-cell clones) - more severe disease.

II MOTILITY EVALUATION AND DIPLOPIA MANAGEMENT IN DYSTHYROID OPHTHALMOPATHY

1. Role of Orthoptist
   a. Documents extent of EOM involvement
   b. Provides quantitative measurements
   c. Provides relief of diplopia
   d. Watchdog for complications

2. Initial Evaluation
   a. Prior history of endocrine dysfunction
   b. No prior history
   c. Associated features (lid retraction, lag, proptosis)
   d. Restriction vs. paresis
   e. Typical vs. atypical presentation
   f. Correlate with ocular deviation

3. Ocular Misalignment
   a. Diplopia
   b. Vertical deviation
      1. Hypo- vs. hyperdeviation
      2. Secondary deviation
      3. Consecutive deviation (spontaneous, post-op)
   c. Horizontal deviation
   d. Combined
   e. Compensatory head posture

4. Common EOM Findings
   a. Restricted upgaze
      1. Unilateral, bilateral, asymmetric
      2. Hypotropia, worse in lateral upgaze
      3. Chin elevation
   b. Restricted abduction
      1. Unilateral, bilateral, asymmetric
      2. Esotropia
   c. Combined
      1. Effect of tight inferior vs. tight medial recti
   d. Other
      1. Exotropia, hypertropia (restriction of adduction or downgaze rare)
      2. Ortho (restricted IR + SR, equal upgaze restriction)
      3. Variable (MG)
5. Concurrent Visual/Optical Problems
   a. Decreased visual acuity
   b. Change in refractive error
   c. Bifocal position

6. Evaluation Methods
   a. Cover test/prism measurements
   b. EOMs/Hess or Lancaster chart
   c. Hertel/lid fissures
   d. Photographs
   e. Head tilt and torsion testing non-localizing

7. Management of Diplopia
   a. Concurrent with medical treatment
      1. Temporize until stable
      2. Discourage smoking
   b. Compensatory head postures
      1. Presbyopes vs. driving
      2. Adjust bifocal or progressive add height
      3. Single focus glasses (dist/near)
   c. Prisms
      1. Restore BSV in primary gaze
      2. Reduce a head posture
      3. Select optimal prism
      4. Incomitance/reasonable range of BSV
      5. Fresnels ideal, incorporate later (apply to ONE lens in adults)
      6. Use oblique prism to combine vert and horiz amounts
      7. Apply different prism top and bottom
   d. Occlusion
      1. Blenderm (3M) occlusive tape
      2. Not necessary to alternate occlusion
      3. Most prefer to occlude hypotropic eye
      4. Distance only/near only
   e. Post-operative AXT
      1. Raise bifocal height/nose pads
      2. Base in prisms
      3. Single focus readers/prism readers

III STRABISMUS SURGERY IN DYSTHYROID OPHTHALMOPATHY

1. General Principles
   a. Surgical Rehabilitation
   b. Motility Evaluation
   c. Bilateral, asymmetric disease
      1. Forced ductions
      2. Upper eyelid retraction
      3. Fixation duress
      4. Increased sympathetic tone
   d. Realistic goals and expectations
      1. Restoration of single binocular vision
         -at least in primary and downward gaze
2. **General Surgical Principles**
   
a. Recession, recession, recession!
   b. Surgical design to correct limitation of ductions
      1. Nguyen (Feldon)
      2. Thomas (Cruz)
      3. Dal Canto (Traboulsi)

3. **Surgery for Horizontal Strabismus**

4. **Surgery for Vertical Strabismus**
   
a. Restrictive hypotropia
      1. Progressive overcorrection
      2. Measurements in downgaze
      3. Role of adjustable surgery
   b. Other Vertical Deviations

5. **Surgical Complications**
   
a. Progressive overcorrection
   b. A-pattern exotropia
   c. P.I.T.S. (Pulled In Two Syndrome)
   d. Lower lid retraction
   e. Torsional diplopia

**IV OCULOPLASTIC CONSIDERATIONS:**

**Absolute Indications** for Oculoplastic referral
1. Optic neuropathy
2. Corneal decompensation.

Active disease phase may respond to radiation, longer standing disease requires decompression.

**Bone vs. Fat Decompression**

1. In selected cases, fat decompression alone has been demonstrated to reverse optic neuropathy. Gold standard is still bone decompression for vision threatening disease.

Complications of bone decompression:

1. In some studies, bone decompression has from 30-50% incidence of new onset or worsened strabismus so patients must be counseled appropriately.

2. CSF leak. Preop CT scan on everybody CT to clarify boney landmarks. ie relative height of cribiform plate. This also gives you useful information about fat to muscle ratio.

3. Cheek numbness usually temporary

**Surgical Pearls:**

1. Where possible, remove some fat as well as bone in decompression.
2. Leave more floor to decrease likelihood of diplopia
3. Include ENT colleague to endoscopically release medial fat into ethmoids
Graves' Orbitopathy: Honing Your Skills/ Dagi, Roper-Hall, Cruz, Elliott

**Relative Indications** for Oculoplastic referral

1. Subjective orbital tension and objective proptosis

Cosmetic Proptosis: Offer fat decompression to patients with proptotic “tense” orbits if CT shows enlarged orbital fat compartment rather than enlarged muscles. Surprising subjective relief. Approach opens septum of upper lid which is often thickened in these patients, as well as being tense with enlarged fat compartment. Fat itself often is somewhat fibrotic. On average I remove 2 cc per eye. Overnight stay and one eye at a time. Can be tedious but minimal diplopia risk.

An already diplopic patient with significant bothersome proptosis may benefit from bone decompression as well. Will require muscle surgery in the future regardless. Many oculoplastics specialists offer boney decompression for proptosis alone.

**Lids, Upper**

Retraction upper –
Lid crease incision with release of levator and Muellers from tarsus. Essentially approach like a congenital ptosis levator resection without any resection or re-attachment. Usually does not require spacer or suture.

**Surgical Pearls:**
1. Sharp wescotts
2. Use left hand to dissect under Muellers of left eye and right for right eye
3. Q-tips great for identifying strands of Muellers
4. Patient participation useful

**Retraction Lower**-
Transconjunctival incision between lower lid retractors and base of tarsus with placement of spacer.

**Surgical Pearls:**
1. Spacer. My favorite spacer material is ear cartilage graft - good contour and stiffness. Other options are hard palate, which can be more painful but does not require conjunctival dissection and covering. May reabsorb. AlloDerm notorious for this. Synthetic spacers like Porex may rotate and have to be removed. Most recent material on the market is multiple-layered pig intestine.
2. Take care to leave nice rim of cartilage along outer ear to avoid ear deformity.
3. Complications: suture granuloma. Treat with topical steroids or excision.
4. Leave Frost sutures post op up to 1 week

**Timing:** The typical cascade of orbit surgery first, then strabismus repair, then lids. A change in the position of the former can change the position of the latter. I have had one case where I did lids and muscles at same time with a very good result. Every case is different.

**BIBLIOGRAPHY**


Chen VM and Dagi LR. Ocular alignment in Graves’ disease may mimic that of superior oblique palsy. *J Neuro-Ophthalmol* 2008 Dec 28(4)302-4
Graves' Orbitopathy: Honing Your Skills/ Dagi, Roper-Hall, Cruz, Elliott


Thomas SM, Cruz OA. Comparison of Two Different Surgical Techniques for the Treatment of Strabismus in Dysthyroid Ophthalmopathy. *JAAPPOS* 2007;11:258-261
I. Introduction and Basic review of glaucoma presentation
   A. Infants and young children
      1. Signs and symptoms of ocular stretching
      2. Most cases are surgical once diagnosed
      3. Limited role for technology in assessment
   B. Older children
      1. More subtle clinical evidence
      2. Larger role for medical therapy if diagnosed
      3. Emerging role for technology in diagnosis/management
   C. The Glaucoma Suspect
      1. Suspect by optic nerve appearance
      2. Suspect by intraocular pressure
      3. Suspect by accompanying features
   A. Objective measurements in children with glaucoma
      1. Vision, Refraction
      2. Corneal Diameter, Intraocular Pressure (IOP)
      3. Axial length
      4. Optic nerve head assessment (cupping and more)
      5. Visual field testing

II. Toolbox for the Glaucoma Suspect
   A. The Optic Nerve Head
   C. Visual Fields
   D. OCT - Imaging of the optic nerve, macula, nerve fiber layer
   E. Visual field testing
   F. Future new methodologies

III. The Optic Nerve Head
   A. Methods of Evaluation
      1. Stereoviewing
      2. Photography
      3. Other methods (later)
   B. Considerations
      1. Nerve head size
      2. Cupping
      3. Symmetry
      4. Other factors

III. Visual Fields
   C. When to use them
   D. What algorithm to use
   E. How often to do them in children
   F. When is it useless to try?
Does this child have glaucoma?
Sharon Freedman, Allen Beck, Alex Levin

IV. Optical Coherence Tomography and other Imaging modalities
A. What does OCT measure?
1. Peripapillary retinal nerve fiber layer
2. Macular parameters
3. Optic nerve head parameters
B. What do we know about normal values (OCT-3)?
1. Effects of refractive error
2. Effects of age
3. Effects of race/ethnicity
4. Other possible factors?
C. How do OCT measurements change in glaucoma?
D. How should we use OCT?
1. Departure from normal
2. Symmetry or lack thereof
3. Changes over time
A. Other imaging technologies
B. Ultrasound
C. Photographs – are they still useful?

V. Central Corneal thickness and Measured IOP
A. Relationship to measured IOP – why do we care?
B. Normal CCT values
C. Abnormal values and categories of diagnosis
   1. Aniridia, anterior segment dysgeneses, other…
   2. Aphakia
   3. Congenital glaucoma
D. When to “adjust” measured IOP and when NOT to…
E. Future / best ways to measure IOP in children
   Putting the puzzle together – its more than just CCT
F. Role of the diurnal curve and setting Target pressures

VI. Genetics and Glaucoma
A. Where are we now?
B. What should we be doing about genetics in clinic now?
C. What is around the corner?
D. What might the future hold?

VII. Questions and Discussion
Does this child have glaucoma?
Sharon Freedman, Allen Beck, Alex Levin

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SELECTED REFERENCES:

OUTLINE

1. OVERVIEW, EPIDEMIOLOGY
   Dr. Tina Rutar

- Childhood blindness is rare, with a prevalence ranging from 0.03% to 0.15% of children depending on the geographic area sampled. However, the public health impact is immense due to the fact that children live with blindness for many years. The number of “blind years” due to childhood blindness nearly equals that of “blind years” due to adult cataracts.

- Many conditions associated with childhood blindness, such as premature birth, vitamin A deficiency and congenital rubella syndrome, also impact childhood mortality. Thus, efforts to control blindness often decrease childhood mortality.

- The causes of childhood blindness vary greatly by geographic region and by socioeconomic level. Note that although retinal disorders predominate overall, blindness due to corneal disease becomes progressively more important as socioeconomic level declines.

<table>
<thead>
<tr>
<th>Site of abnormality (%)</th>
<th>Developed</th>
<th>Former Socialist</th>
<th>Latin Am. &amp; Carib.</th>
<th>Middle East</th>
<th>China</th>
<th>India</th>
<th>Other Asia</th>
<th>Sub-Saharan Africa</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retina</td>
<td>25</td>
<td>44</td>
<td>47</td>
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<td>25</td>
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<td>21</td>
<td>24</td>
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<tr>
<td>Cornea</td>
<td>1</td>
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<td>8</td>
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<td>4</td>
<td>28</td>
<td>21</td>
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<td>Whole globe</td>
<td>10</td>
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<td>15</td>
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<td>Lens</td>
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<td>Uvea</td>
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<td>1</td>
<td>5</td>
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<td>Other (e.g. CNS)</td>
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<td>2</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>


2. TRACHOMA
   Dr. Tom Lietman

- Trachoma is the leading cause of infectious blindness, and is most prevalent in poor, dry regions.

- Children harbor most of the infection in an endemic community, and may form a core group for trachoma transmission.
- Mass antibiotic distributions can eliminate infection from the most severely affected communities, allowing hope for elimination from large areas even without an effective vaccine.

3. **PEDIATRIC CORNEAL BLINDNESS**
   **Dr. Ken Nischal**

- Acquired causes of corneal blindness include vitamin A deficiency, neglected/late presenting glaucoma, infectious keratitis and metabolic diseases. Corneal grafting may not be the best treatment option for corneal opacification due to vitamin A deficiency. Deep anterior lamellar keratoplasty is an option for treating corneal opacification due to metabolic disorders. In the developing world, infectious keratitis is primarily caused by bacteria and fungi, whereas herpes simplex virus keratitis predominates in the developed world.

- Corneal blindness also occurs due to congenital and developmental anomalies. The prognosis in anterior segment dysgenesis and Peters anomaly depends on the ability to accurately diagnose the extent of malformation and to plan the appropriate surgery. In the developing world, think of options other than penetrating keratoplasty, such as optical iridectomy. Corneal opacification due to corneal dystrophies and dermoids carries a better visual prognosis. Descemet’s stripping endothelial keratoplasty can be used to treat congenital hereditary endothelial dystrophy.

- Given the inherent difficulties in treating corneal disease surgically in developing countries, efforts to decrease the factors predisposing to corneal blindness are of utmost importance. These include vitamin A supplementation, control of trachoma, ophthalmia neonatorum prophylaxis, treatment of corneal abrasions with safe and inexpensive antimicrobial agents, and stopping the use of harmful traditional ocular medications.

4. **PEDIATRIC CATARACTS IN LOW AND MIDDLE-INCOME NATIONS**
   **Dr. Ed Wilson**

- In some parts of Africa and Asia, cataract is now the leading cause of new cases of avoidable blindness in children due to the reduction in corneal blindness.

- The previously poor outcomes of surgery for pediatric cataract in the developing world have now improved with the increasing utilization of IOLs in conjunction with capsulectomy and vitrectomy.

- The Vision 2020 Cataract Plan calls for “suitably equipped specialist centers” for the performance of childhood cataract surgery. Equipment and training for safe pediatric general anesthesia is a major unmet need in many parts of the developing world.

- In many poor countries, more boys present for surgery than girls, despite there being no evidence of a gender difference in incidence.
- Many general physicians and primary eye care workers still communicate to families that children cannot be operated at a young age or cannot have surgery unless the cataract is “mature.”

- A majority of children presenting for surgery with mature bilateral cataracts in poor countries do not have nystagmus. This may indicate a high early death rate among babies born with bilateral nuclear cataracts.

- Surgery for monocular infantile cataracts remains controversial in poor and middle income countries owing to the poor visual outcome in the presence of scarce resources.

5. PEDIATRIC OCULAR TRAUMA IN LOW AND MIDDLE-INCOME NATIONS
   Dr. Tony Murray

- Epidemiological data for ocular trauma are still rare or totally lacking in low and middle-income countries.

- Of children who sustain eye injuries, approximately 27% become unilaterally blind or severely visually impaired, 8% become bilaterally visually impaired, and 3% become blind.

- The types and prognosis of injuries differ from those in developed countries.

- Non-existent or inadequate safety measures, the lack of proper eye health facilities, the use of traditional medicines, poor education and lack of awareness are contributing factors.

6. PEDIATRIC GLAUCOMA IN LOW AND MIDDLE-INCOME NATIONS
   Dr. Robert Stamper

- Glaucoma in neonates and children is uncommon, yet glaucoma accounts for 10-20% of childhood blindness.

- In low and middle-income nations, glaucoma is often the end-stage of secondary diseases, but congenital (infantile) glaucoma has higher rates due to consanguinity.

- Early detection is helpful in management.

- Goniotomy is still an important and relatively inexpensive tool. Newer management techniques include Schlemm's canal surgery (360 degree trabeculotomy) and tube-shunt procedures (Ahmed, Baerveldt, Molteno).

- Management is often difficult and even with modern surgical technology, poor vision is a common outcome.
7. **PEDIATRIC RETINAL BLINDNESS IN LOW AND MIDDLE-INCOME NATIONS**
   Dr. Bill Good

- Pediatric retinal disease in low and middle-income countries has been neglected because many conditions can’t be treated, there is a lack of trained personnel to manage retinal disease, and equipment is too expensive for many regions.

- Retinopathy of prematurity is the most common cause of preventable blindness. In middle-income countries, it occurs in larger birth weight infants than in the West, and it may have a more florid, rapidly advancing presentation. The disease still tends to reach the point where treatment is indicated at approximately 36 weeks gestational age.

- Toxoplasmosis is the second leading cause of preventable retinal blindness in low and middle-income countries.

- Hereditary retinal disorders are also common, probably more so than in the West due to consanguinity. These can be screened and diagnosed by refraction, which usually shows significant hyperopia, or significant myopia.

8. **GENETIC DISORDERS AND OCULAR MALFORMATIONS**
   Dr. Elias Traboulsi

1. Retinal dystrophies and degenerations, including Leber congenital amaurosis, are the leading cause of severe visual impairment in children in developing countries.

2. Ocular malformations are next and include microphthalmia, optic nerve malformations, and anterior segment dysgenesis and Peters anomaly.

3. The lack of modern genetic services in developing countries is an impediment to the diagnosis, counseling for, and treatment of these rare but severe conditions.
The human genome contains 3 billion chemical base pairs (A, T, G, and C). Approximately 16% of these base pairs encode a gene. About 85% of the base pairs in a gene are in a highly accurate "folded" state. The remaining 15% of the base pairs in a gene are less accurately folded. The average gene size in the human genome is approximately 3,000 base pairs. Almost all (99.9%) nucleotide bases are exactly the same in all people. The functions are unknown for over 50% of discovered genes.

April 2003: HGP sequencing is completed and Project is declared finished two years ahead of schedule.

1990: Project initiated as joint effort of U.S. Department of Energy and the National Institutes of Health

February 2001: Analyses of the working draft are published

June 2000: Completion of a working draft of the entire human genome

1903 --Sutton noted parallels between biological sex and the sex of chromosomes.

Biol Bull 1903)

1903 1903 --Sutton noted parallels between Sutton noted parallels between

DNA base pairs (A, T, G, and C). Number of human DNA pairs of human DNA


Sequence pairs of human DNApairs of human DNA

DNA base pairs (A, T, G, and C). Number of human DNA pairs of human DNA

bases) 2.6 billion bases (largest-chromosome at 2.4 million bases)

• match organ donors with recipients in transplant programs
• detect bacteria and other organisms that may pollute air, water, soil, and food
• identify endangered and protected species as an aid to wildlife officials (could be used for prosecuting poachers)
• identify crime and catastrophe victims
• exonerate persons wrongly accused of crimes
• identify potential suspects whose DNA may match evidence left at crime scenes

DNA Identification (Forensics)

Laboratory mouse (Laboratory mouse (Mus musculus) Mus musculus

Human (Human (Homo sapiens) Homo sapiens

Yeast (Yeast (Saccharomyces cerevisiae) Saccharomyces cerevisiae

Bacterium (Bacterium (Escherichia coli) Escherichia coli

Organism Genome Size (Bases)Genome Size (Bases) Estimated GenesEstimated Genes

Homo sapiens Homo sapiens 2.6 billion 30,000

Mus musculus Mus musculus 2.6 billion 30,000

Saccharomyces cerevisiae Saccharomyces cerevisiae 12.1 million 6,000

Escherichia coli Escherichia coli 4.6 million 3,200

Drosophila melanogaster Drosophila melanogaster 97 million 19,000

Caenorhabditis elegans Caenorhabditis elegans 137 million 13,000

Anticipated Benefits of Anticipated Benefits of

Genome ResearchGenome Research

DNA Identification (Forensics)

• identify potential suspects whose DNA may match evidence left at crime scenes
• exonerate persons wrongly accused of crimes
• identify criminals and catalytic enzymes
• exonerate persons wrongly accused of crimes
• identify criminals and catalytic enzymes
• evaluate the health risks faced by individuals who may be exposed to radiation (including low levels in industrial areas) and to cancer-causing chemicals and foods
• study evolution through genealogical mutations in lineages
• study migration of different population groups based on maternal inheritance
• study mutations on the Y chromosome to trace lineage and migration of males
• compare breakpoints in the evolution of mutations with ages of populations and historical events

Anticipated Benefits of Anticipated Benefits of

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Anticipated Benefits of Anticipated Benefits of

Genome Research-cont.

DNA Identification (Forensics)
Disease types

Mendelian disorder: Due to defect in a single gene
- Color of Mendel's peas
Example: Huntington's disease, certain retinal and corneal dystrophies, various types of cataracts

Complex disease: Risk influenced by many genes, environmental factors, and other interactions
- Example: Alzheimer disease, progressive open angle glaucoma, age-related macular degeneration, myopia

Monogenic Diseases
- Stargardt Disease
- Ocular Albinism
- Congenital Glaucoma
- Retinitis Pigmentosa

Complex Diseases
- AMD
- POAG
- Cardiovascular Disease
- Alzheimer Disease
- Myopia

Genes and Disease

- Genes
- Environment

Is there correlation in inheritance of certain DNA stretches and disease?

Clinical data
Genotype data

Is there correlation in inheritance of certain DNA stretches and disease?

Linked Marker
- If a genetic marker is segregating with the disease in a family, the marker is "linked" to the disease
- Single nucleotide polymorphism (SNP): .CCAGTTTACCTAGCA, (allele A)
- .CCAGTTTACCTAGCA, (allele G)
Unlinked Marker

- If a genetic marker is NOT segregating with the disease in a family, the marker is "unlinked" to the disease

LOD SCORE
(or p-value)

LOD score > 3 means that data are > 1000 times more likely under linkage than no linkage
P-value < 0.05 means that data would occur with <5% probability under no linkage

Types of families

- A few large families with three or more generations
- Typical for "Mendelian diseases"

Many smaller families – more typical for "complex diseases"

Types of families

LINKAGE = PROPERTY OF LOCI: Same marker, different allele
ASSOCIATION = PROPERTY OF ALLELES: Same marker, same allele

For association analysis, we can also use families with only one affected person ("singleton", "simplex" families)

Human Genome Project

- Helps us identify "candidate genes" in regions of linkage
- Genes that "make sense" to be involved in the disease of interest
- Bioinformatics folks help us navigate all these web sites and find plausible candidate genes
- Is sequence variation in these genes related to disease - eg, more frequently seen in affected than unaffected individuals?

What about non-genetic risk factors?

- Study participants fill out questionnaires about their lifestyle, diet, smoking, drinking habits etc
- Analyze jointly with genetic factors, eg, in "case-control studies"
- Ultimately, hope to identify both genetic and non-genetic factors that will help reduce risk of disease or develop more targeted treatment

Genome screen: Glaucoma

(Wiggs et al. 2000)
**What's next?**
- Genome screen: Identifying a region "(forest)"
- Fine mapping: Identifying the gene "(house)"
- Genotype more markers in the region
- Use additional analysis tools

---

**Gene identification: Alzheimer disease**

- **Genome screen**
  - Identifying a region
- **Fine mapping**
  - Identifying the gene

---

**Genotype more markers in the region**

---

**Use additional analysis tools**

---

**Progress in Genotyping Technology**

- **Cost per genotype (Cents (USD))**
- **Nb of SNPs**
- **Technological advances**
  - **Sequencing**
    - ABI Sequencing platforms
    - Massively Parallel Signature Sequencing (Massive Parallel Sequencing)
  - **Genotyping**
    - Microsatellite Scoring
    - Single Nucleotide Polymorphism (SNP) arrays
      - Ion Torrent S1/S5/S150/multiple/individual
    - Whole genome genotyping
      - Affymetrix 10K, 100K, 100K individual/chip
      - Illumina 517K, 1M, 5M, 317K individual/chip
  - **Sequencing**
    - ABI sequencing platforms
    - Illumina Chelex Parallel Sequencing

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**2007: The year of GWAS**

- **Increase in Data Density**
- **Decrease in Genotype cost**

---

**Gene Wide Association Studies (GWAS)**

- **Unbiased genome wide approach interrogating DNA of 1000's of individuals with high density SNP chip arrays**

---

**In vitro Microarray**

- **Increase in Data Density**
- **Decrease in Genotype cost**

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**Whole Genome Association Studies (GWAS)**

- **A haplotype map of the human genome**

---

**Unbiased genome wide approach interrogating DNA of 1000's of individuals with high density SNP chip arrays**

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**Increase in Data Density**

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**Technology for Genotyping**

- **Sequencing**
- **Genotyping**
- **Microsatellite Scoring**
- **Single Nucleotide Polymorphism (SNP) arrays**
  - Ion Torrent S1/S5/S150/multiple/individual
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- **Unbiased genome wide approach interrogating DNA of 1000's of individuals with high density SNP chip arrays**

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**In vitro Microarray**

- **Increase in Data Density**
- **Decrease in Genotype cost**

---

**Whole Genome Association Studies (GWAS)**

- **A haplotype map of the human genome**

---

**Unbiased genome wide approach interrogating DNA of 1000's of individuals with high density SNP chip arrays**

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**Increase in Data Density**

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**Technology for Genotyping**

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GWAS Accelerating Discovery

Type 2 diabetes (T2D)

P Values of GWA Scan for Age-Related Macular Degeneration (Complement Factor H)

The 11 Step Program to Disease Gene Discovery

Pathway to Success
- New Technology and Resources
- Whole genome association studies.
- New Approaches
- Whole genome association studies.
- New Analytical Approaches
- High resolution follow-up mapping of linkage peaks.
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Familial Adenomatous Polyposis

- Autosomal dominant disease characterized by >100 polyps of the colon and rectum, predisposing these patients to colon CA.
- Gardner syndrome involves the development of extracolonic manifestations, and consists of intestinal polyps, characteristic patches of CHRPE, skeletal hamartomas, and soft tissue tumors.
- Adenomatous polyposis coli (APC) gene transmembrane tumor-suppressor gene.

Association of CHRPE with Gardner Syndrome and FAP

- Ocular lesions in FAP are bilateral in 86% of cases.
- Ocular lesions are observed in the presence or absence of other systemic manifestations of Gardner syndrome.
- Presence of multiple fundus lesions is a highly specific and sensitive phenotypic marker for Gardner syndrome.
- CHRPE lesions present in 2/3 of families with FAP.

Case Study

- 4 Year Old: Routine Exam
- 20/30 OU
- Presence of multiple fundus lesions is a highly specific and sensitive phenotypic marker for Gardner Syndrome and FAP.

Gene Screening Test Results

- Homozygous for a 16 bp duplication in exon 15 in the HPS1 gene — encodes a novel inner membrane protein that is thought to be a component of multiple cytoplasmic organelles and is apparently crucial for their normal development and function.

- Diagnostic for Hermansky-Pudlak syndrome (OMIM 604982)
  - Oculocutaneous albinism
  - Platelet defects, cerebral accumulation in body tissues (pulmonary interstitial fibrosis, granulomatous colitis)
- Frequency in Puerto Rico is 1:800
Infantile Glaucoma

- Developmental abnormality in the iris-lens angle, that leads to impaired aqueous outflow and increased intraocular pressure.
- Symptoms: Photophobia, Blepharospasm, Epiphora
- Ocular Features: Corneal enlargement and edema, Optic nerve cupping

Infantile Glaucoma: Incidence

- 80% by one year
- 70% by 6 months
- Saudi Arabia: 1 in 2500
- Western Europe: 1 in 12,500

Infantile Glaucoma: Late Changes

- Corneal edema, enlargement
- Enlarged ciliary root-lens dislocation
- Horizontally oriented Descemet's membrane, corneal edema
- Trauma increased susceptibility to rupture of globe
- Myopia, antimongoloid, anhiplopia
- Optic nerve cupping
- Often reversible with normalization of intraocular pressure
- Ganglion cell loss

Infantile Glaucoma Heredity

- Most cases are sporadic
- Major locus on short arm of chromosome 2 (2q22)
- Juvenile glaucoma long arm of chromosome 1
- Not associated with adult onset glaucoma
- With no family history of glaucoma, affected parent has 5% chance of having an affected child

National Ophthalmic Disease Genotyping Network (eyeGENETM)

- NEI /vision community collaboration
- Immediate access to existing CLIA certified research diagnostic and clinical laboratories, and use of existing infrastructure and resources
- Interoperability with clinical and pathogenic data
- Enhanced accuracy of patient phenotyping, diagnosis, clinical and research participation
- Genetic disease
- Gene/phenotype database
- Enhanced ability to recruit patients

Mendelian Glaucoma Genes

<table>
<thead>
<tr>
<th>Chromosomal Loci of Glaucoma Genes</th>
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<tbody>
<tr>
<td>GLC3A 2p21 CYP1B1/P450 GLC3A 2p21 CYP1B1/P450</td>
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<td>Rieger RIEG1 4q25 PITX2 PITX2</td>
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<td>Phenotype Name Locus</td>
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<tr>
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<tr>
<td>sydney 1 in 2500</td>
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<td>Onset</td>
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<td>juvenile: AD</td>
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Hermansky-Pudlak Syndrome

- HPS1 gene: chromosome 22q13 (13% non-PR)
- HPS2 gene: chromosome 1q22-23 (8% non-PR)
- HPS4 gene: chromosome 11p15-p13 (4% non-PR)
- HPS5 gene: chromosome 2p16.1-p13 (1% non-PR)
- HPS6 gene: chromosome 9p21 (1% non-PR)
- Immunodeficiency, congenital neutropenia

Network (eyeGENETM)

- Male: female 3:2
- Bilateral 75%

With no family history of glaucoma, affected parent has 5% chance of having an affected child

National Ophthalmic Disease Genotyping Network (eyeGENETM)

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- Interoperability with clinical and pathogenic data
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- Genetic disease
- Gene/phenotype database
- Enhanced ability to recruit patients

http://www.nei.nih.gov/genet/types/glaucoma.htm
Ophthalmic Genetic Testing

- National Eye Disease Genotyping Network (eyeGENETM)
- John and Marcia Carver Nonprofit Genetic Testing Laboratory (http://carverlab.org/index.shtml)
- Project 3000: Chicago Cubs star Derrek Lee and Boston Celtics CEO and co-owner Wyc Grousbeck plan to find every individual affected with LCA in the US (~3000 people), and offer free gene testing. (http://carverlab.org/project3000/index.shtml)
- GeneDx (http://www.genedx.com/) and Signature Genomic Laboratories (http://www.signaturegenomics.com/)

References

- GeneTests (genetests.org)
- Thompson & Thompson, Genetics in Medicine, Nussbaum, McInnes, and Willard
- http://www.hgvs.org/mutnomen

Pediatricians, Ophthalmologists, Optometrists are often in the front line
- Knowledge of clinical and molecular features is paramount to good patient care
- Developmental age of disease onset
- Heritable probability
- DNA testing parameters
- Treatment options

Thank You

The Duke University Eye Center and Albert Eye Research Institute

Family trees reveal many interesting facts
I. Types of Genetic Testing

A. Fee for Service Testing is carried out by CLIA approved laboratories. These laboratories must meet strict standards and comply with regulations guaranteeing a high quality of service and reproducibility.
   1. Not all patients will have a genetic diagnosis discovered, but all patients will receive a result, either positive or negative.
   2. A negative result does not rule out a diagnosis.
   3. A positive result is often definitive, confirming a clinical diagnosis and offering the possibility for accurate genetic and family counseling, and accurate prognosis.

B. Research-based testing is carried out in research laboratories which may or may not be CLIA approved
   1. Patients must sign an IRB (Institutional Review Board) approved consent in order to have research-based testing performed.
   2. They may or may not receive a result depending on the research protocol and the progress of the research.
   3. Results that are obtained may or may not be reported to them depending on the project.

C. The John and Marcia Carver Nonprofit Genetic Testing Laboratory (CNGTL) model
   1. The CNGTL is a CLIA approved laboratory at the University of Iowa.
   2. [www.carverlab.org](http://www.carverlab.org)
   3. The non-profit structure makes the laboratory sustainable and scalable.
   4. Philanthropic funding paves the way for start-up and special projects.
   5. Pre-certification of testing with insurance carriers, Medicaid, and Medicare insures that most testing is covered by third party payers and reinforces the concept that these tests are now standard of care.
   6. Coverage by third party payers, and co-pays by patients when applicable, reinforces the concept that this testing is a valuable service.
   7. Philanthropic support offsets costs incurred by patients who cannot pay for some disorders, e.g. Project 3000 (see www.project3000.org).
   8. Non-profit testing by [www.retinoblastomasolutions.org](http://www.retinoblastomasolutions.org) for Retinoblastoma gene mutations has been successful with a similar model; the CNGTL does not duplicate this already excellent service.

II. The Goals of Non-Profit Testing
A. Our goal is to offer “clinically useful tests” for every nonfatal inherited eye disease that 1) one or more genes have already been discovered to cause, 2) is likely to be seen at least once per year in a tertiary care center. Our definition of a “clinically useful test” is one that has a 50% chance of a positive result in the hands of a knowledgeable clinician, an easily interpretable written report, a turnaround time of less than 8 weeks, and a sustainable total cost to the patient of less than $500. We are still working toward achieving all of these goals.

B. The keys to achieving the above are excellent clinical diagnoses which improve the yield of the genetic testing, developing mutation detection probability distributions (MDPD) [Stone, Am J Ophthalmol. 2007 Dec;144(6):791-811], which allow us to search in the most likely mutation locations first, and the Estimate of Pathogenic Probability (EPP), [Stone E, et al.Trans Am Ophthalmol Soc. 2003;101:437-84] which allows the clinician to rapidly and accurately interpret a genetic test result.

C. The EPP uses an easy to understand scoring system of 0 to 3 to grade each DNA change found. It has been found to be accurate and has been verified by expression studies of some mutations. A score of 0 or 1 means the change is a polymorphism; a score of 2 means it is very likely disease causing, but may be rare. A score of 3 means it is known to be disease-causing. Using this system, clinicians can confidently discuss results with their patients.

D. Project 3000 is a nationwide initiative to genotype every Leber Congenital Amaurosis patient in the U.S. Based on the gene frequency in the population, we estimate this to be about 3000 individuals. This project is important from the standpoint of genotype-phenotype correlation, as well as being able to move ahead with gene therapy clinical trials.

Recent gene therapy clinical trials in both dogs and humans have shown improved vision in LCA patients with mutations of RPE65. This suggests that gene therapy may have promise for many retinal dystrophies. But in order to replace a defective gene, one must know which gene is malfunctioning in each patient. Thus accurate genetic testing is an important first step for gene-based therapy.

III. Tests currently available on a fee for service basis

A. Go to www.genetests.org to access all tests offered at all laboratories nationally and internationally. Follow instructions given for each laboratory to send a sample.

B. For tests currently available at the University of Iowa Carver Non-profit Genetic Testing Laboratory (CNGTL) see table 1.

IV. How to Send a Sample
A. Go to www.genetests.org and follow instructions given for each individual lab
B. To send a sample to the Carver Lab, instructions can be found on our website www.carverlab.org.
   a. Follow these steps to request a genetic test from the Carver Laboratory:

   1. An individual or family is diagnosed with an inherited disorder.
   2. A physician recommends a genetic test that is offered by the Carver Laboratory for molecular diagnosis and draws a blood sample to send in for testing.
      o The physician or physician’s assistant must register online. There is a onetime registration for the physician’s office, then information for each new patient may be entered when ordering.
         1. Go to www.carverlab.org, click on Physician Login, then Physician Registration. Either the physician themselves or one of their staff can register. There are fields for information for a contact person in the office, e.g. a nurse or technician, and for physician and hospital. There is a request for a physician UPIN or other ID number but N/A can be placed in this spot if no number is known.
         2. After the initial registration, go to the site and Log in. Click on “Test requisition.” Fill out information for the patient and for which test is requested. Click finish and “submit.”
         3. A PDF link will pop up; click this link and 3 copies of a form will be generated to print out. The form has the patient’s bar code and ID number on top. One copy should be mailed with the sample, one given to the patient, one for the chart. Instructions for mailing will also print out.
         4. The patient and/or physician can use the ID number to log in to the site and track progress of their test at any time.
      o Get pre-certification for the test from patient's insurance; a letter to send to insurers to explain the test is available for printing on the website
      o Send the patient with the forms to the nearest outpatient hospital laboratory, if possible. Any phlebotomist can draw and send the sample, however hospital laboratories usually are familiar with “send out” labs and will often send the sample under the hospital’s account and then
bill insurance to repay the hospital, as long as the precertification has been done.

- Special instructions and the form for Project 3000 participants can be found online at the website.

3. Have the lab that drew the blood mail the blood sample along with completed forms and payment (if applicable) to the **John and Marcia Carver Nonprofit Genetic Testing Laboratory** at the University of Iowa.

   - Sample requirement: Lavender (EDTA) top tubes (2 tubes for adults)
   - Minimum Sample Volume: 3 mls per tube (Child), 6 mls per tube (adult)
   - Ship to: John and Marcia Carver Nonprofit Genetic Testing Laboratory, University of Iowa, 375 Newton Rd. 4111 MERF, Iowa City, IA 52242
   - Shipping Requirements: Room temp. *(DO NOT FREEZE)*
   - Delivery: Monday-Friday *Sample may be stored at refrigerator temperature if shipment must be delayed.

4. The DNA will be processed immediately after the sample is received.

5. Genetic testing will take place on the extracted DNA.

6. Screening for genetic variations can take anywhere from four to twenty four weeks depending on the test requested (see specified turn around time on Table 1)

7. A written report will be sent to the referring physician after testing is complete. You should not expect any communication until this time.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Mode of Inheritance</th>
<th>Gene(s)</th>
<th>Cost and Turnaround</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardet-Biedl Syndrome</td>
<td>Autosomal Recessive</td>
<td>BBS1 (Met390Arg mutation)</td>
<td>$35  4-6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BBS10 (Leu90 ins1T mutation)</td>
<td></td>
</tr>
<tr>
<td>Best Disease</td>
<td>Autosomal Dominant</td>
<td>BEST1 (Exons 2-8)</td>
<td>$167  8-10 weeks</td>
</tr>
<tr>
<td>Choroideremia</td>
<td>X-Linked</td>
<td>CHM</td>
<td>$335  10-12 weeks</td>
</tr>
<tr>
<td>Cone-Rod Dystrophy</td>
<td>Autosomal Dominant &amp; Autosomal Recessive</td>
<td>CRX (full coding region)</td>
<td>$125  8-10 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GUCA1A (Leu151Phe mutation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GUCY2D (Exon 13)</td>
<td></td>
</tr>
<tr>
<td>Corneal Dystrophy-Stromal</td>
<td>Autosomal Dominant</td>
<td>TGFBI (Exons 4 &amp; 11-14)</td>
<td>$125  8-10 weeks</td>
</tr>
<tr>
<td>Enhanced S-Cone Syndrome</td>
<td>Autosomal Recessive</td>
<td>NR2E3 (Exons 2-8)</td>
<td>$188  10-12 weeks</td>
</tr>
<tr>
<td>Juvenile Open Angle Glaucoma</td>
<td>Autosomal Dominant</td>
<td>MYOC (full coding region)</td>
<td>$125  8-10 weeks</td>
</tr>
<tr>
<td>Juvenile X-Linked Retinoschisis</td>
<td>X-Linked</td>
<td>RS1 (full coding region)</td>
<td>$146  6-8 weeks</td>
</tr>
<tr>
<td>Leber Congenital Amaurosis</td>
<td>Autosomal Recessive</td>
<td>AIPL1</td>
<td>$713  Phase 1 (Project 3000) approximately 4 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEP290 (IVS26 mutation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CRB1</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>CRX</td>
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<tr>
<td></td>
<td></td>
<td>GUCY2D</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>RDH12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPE65 (full coding region)</td>
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<tr>
<td></td>
<td></td>
<td>RPGrp1</td>
<td></td>
</tr>
<tr>
<td>Leber Hereditary Optic Neuropathy</td>
<td>Mitochondrial</td>
<td>3460</td>
<td>$35  4-6 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11778</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>14484</td>
<td></td>
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<tr>
<td>Malattia Leventinese</td>
<td>Autosomal Dominant</td>
<td>EFEMP1 (Arg345Trp mutation)</td>
<td>$35  4-6 weeks</td>
</tr>
<tr>
<td>Norrie Disease</td>
<td>X-Linked</td>
<td>NDP (full coding region)</td>
<td>$62  4-8 weeks</td>
</tr>
<tr>
<td>Pattern Dystrophy</td>
<td>Autosomal Dominant</td>
<td>RDS (full coding region)</td>
<td>$63  6-8 weeks</td>
</tr>
<tr>
<td>Condition</td>
<td>Inheritance</td>
<td>Panels/Genes</td>
<td>Cost</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------</td>
<td>---------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Primary Open Angle Glaucoma</td>
<td>Autosomal Dominant</td>
<td>MYOC (full coding region)</td>
<td>$125</td>
</tr>
<tr>
<td>Retinitis Pigmentosa</td>
<td>Autosomal Dominant</td>
<td>RHO &amp; RDS (full coding regions)</td>
<td>$96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RP1 (Arg677Stop mutation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C1QTNF5 (Ser163Arg mutation)</td>
<td></td>
</tr>
<tr>
<td>Sorsby Dystrophy</td>
<td>Autosomal Dominant</td>
<td>TIMP3 (Exon 5)</td>
<td>$41</td>
</tr>
<tr>
<td>Stargardt Disease</td>
<td>Autosomal Dominant</td>
<td>ELOVL4 (Leu263 del 5 CTTAA mutation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(done with ABCA4 for one price)</td>
<td></td>
</tr>
<tr>
<td>Stargardt Disease</td>
<td>Autosomal Recessive</td>
<td>$105 ABCA4</td>
<td>$105</td>
</tr>
</tbody>
</table>
Albinism and Other Pigmentary Disorders: Current Concepts

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Albinism = deficient ocular melanin

Ocular Albinism = normal skin
Oculocutaneous Albinism = skin and eyes affected

Melanocytes
Basal layer of skin
“pseudopods”
1:25 keratinocytes
pigment transfer

Melanosomes
Maturation stages
I premelanosome: no pigment
internal membrane vesicles
II elongated, no pigment
striated intraluminal matrix fibres
III black pigment deposited along fibres
IV mature, fully pigmented

Where is melanin in the eye?
RPE cells
Uveal melanocytes

Iris Pigmentation
pigmented posterior epithelium
melanocytes (anterior)
clump cells (mid stroma)
phagocytosis
not production

Iris Pigmentation
Due to number and size of melanosomes
(not number of melanocytes)
(not pigmented epithelium)

Melanin Embryology
RPE = neuroectoderm
Uveal melanocytes = neural crest
Albinism: Animal models
- Siamese cat
- mice
- chinchilla
- ferret
- whale
  [vs hypomelanotic]

Albinism Epidemiology
described in all populations

Albinism: Eyes
- iris transillumination
- nystagmus
- strabismus
- refractive errors
- macular hypoplasia
- retinal hypopigmentation
- grey optic nerves

Iris Transillumination
Albinism
- Albinism carriers
- Albinoidism
- Malformations/Secondary
- Normals?
- Neonsates?

Albinism (Partial Albinism)
cutaneous hypopigmentation
iris transillumination
normal vision/macula
no nystagmus
no photophobia

Albinism Syndromes
isolated dominant
punctate hypopigmentation
+ deafness
+ Apert
+ immune deficiency
+ Menke?

Albinism: Eyes
iris transillumination
nystagmus
strabismus
refractive errors
macular hypoplasia
retinal hypopigmentation
grey optic nerves

Albinism: Eyes
iris transillumination
nystagmus
strabismus
refractive errors
macular hypoplasia
retinal hypopigmentation
grey (?small) optic nerves
Ocular Development: RPE Melanin

regulation of retinal maturation

RPE Melanin Deficiency...

decreased cell density all layers

ganglion & rod cells

= early and late

only cones spared

Albinism: Visual Pathways

abul decussations (3 lead VEP)
decreased stereo
increased strabismus
7role in nystagmus

Albinism Decussations

why?

the secret of life is….

…timing

Abnormal 3-lead VEP

albinism (not all)
unilateral anophthalmia
anblyopia
7uni cataract with bilateral nystagmus

Albinism: Reduced Visual Acuity

?nystagmus
?macula hypoplasia
?amblyopia
?light scatter
?ONH

Albinism: Skin/Hair

Hypopigmentation

failure to tan: burn
increased skin cancer
7/ freckles

Snowflake

Barcelona Zoo
Captured 1986, Guinea
A 41 y/o (live to 25 in wild)
Dying of skin cancer
http://www.zoobarcelona.com

Eumelanin

Phaeomelanin

Browns / Blacks

Tanning

Reds Poor Tanning
**Albinism: Old Nosology**

- tyrosinase negative OCA
- tyrosinase positive OCA

**Ocular albinism**

**Albinism: Hair Bulb Test**

- incubate with tyrosine
- look for pigmentation
- not correlated with genotype tyrosinase mutation can be +

**Melanin metabolic pathway**

- bottleneck step: tyrosinase

If subnormal tyrosinase (but not 0)

- then preferential shunting to pheomelanins

**Pigment genes**

- >50 in mice!!!

**Albinism: Changing Nosology**

- OCA Type 1: tyrosinase related
- OCA Type 2: p gene related
- OCA unclassified

- TYRP1, TYRP2, other genes, HPS, CHS, syndrome
- OA1: X linked
- OA unclassified
- OA “recessive”

**Type 1 OCA**

- 1/16,000 - 20,000

**Tyrosinase Gene (TYR): 11q14-2**

- AR OCA
- 5 exons, 65Kb
- exon 1 = >50% code
- >50 mutations
- 1st: Tomita (Japan)
- promoter known
TYR Mutations

- most common: P81L, T373K
- Amish: P406L
- most others unique
- heterozygotes always normal

TYR Mutations

- missense, nonsense, frameshift, splice site
- no large deletions

TYR Mutations

- compound heterozygotes
- 25% 1 allele not detected

Type I OCA: TYR

- I A
- I B
- I MP
- I TS

Type I A OCA

- “tyrosinase negative” (t -)
- no melanin
- severe

Type I B OCA

- “yellow mutant” (ty or y/t -)
- white at birth
- white-tipped hair
- moderate pigment later (pheomelanin)
- V275F, R403S, P406L (Amish homozygote)
- 7% ty activity
- dark eyed albino mouse

Type I MP OCA

- “minimal pigment”
- white skin + nevi
- white then yellow hair
- variable iris
- low ty activity

Type I TS OCA

- “temperature sensitive” (ts/t -)
- white at birth
- dark hair arms & legs
- white axilla and scalp
- decreased ty activity >35°C

Tyrosine “positive” OCA

- blacks: p gene, other OCA, AR OA
- Caucasians: p, other OCA, XL OA, AR OA
Type II OCA

"tyrosinase positive"  
= tyrosinase unrelated  
multiple phenotypes  
classification changing

Type II OCA: Incidence

1/10,000 ROCA in Ibo’s, Nigeria  
1/15,000 to 36,000 USA  
1/14,000 Tanzania  
1/100 Prader Willi/Angelman

p gene

15q11.2-11.3  
25 exons (1st non coding)  
multiple mutations known  
cluster 3’ = mouse homology  
between PWS and AS  
1992 linkage (Ramsay)  
1993 1st mutation (Rinchik)

p gene mutations

usually compound heterozygotes  
some common mutations  
Val443Ile: blacks or Caucasians  
18bp deletion: Afro Americans  
deletion in exon 7: Tanzania  
more severe OCA

Type II OCA: p gene

human homologue of  
mouse pink-eyed dilute gene (p )

p gene product

838 amino acids  
12 melanosome transmembrane domains  
probable transporter protein  
tyrosine into melanosome  
regulation of melanosome pH/structure  
increases postnatal  
TYP, TRP’s

Type II OCA: p gene

skin white to fair  
hair yellow to red to brown to black  
Va usually better than I A OCA  
less nystagmus  
can mimic I B

OCA: p gene mutations

very variable phenotypes  
Type II OCA  
Brown albinism (ROCA)  
OCA with ephelides

OCA + Ephelides

intra p gene duplication  
(pink eyed unstable)  
S. Africa  
ephelides = reverted duplication  
no increased cancer risk
Brown OCA (BOCA)

p gene
S. African
AD or AR

Type III OCA: TRP 1 (Brown gene)

Brown albinism (BOCA): Nigeria, USA
- tan
- light brown hair
- blue/brown eyes

TYRP 1

9p23
- 8 exons (#1 untranslated)
- all mutations null so far
- transmembrane melanosomal glycoprotein
- mouse: brown (b) locus

OCA3 = TYRP1

BOCA - 1 case
ROCA
S166X AND 368delA = 95%

Red (Rufous) Albinism (Xanthous)

Southern Africa, Papua New Guinea
- “brick red” skin
- ginger red hair
- hazel/brown eyes
- fair/red hair
- +/- nevi & freckles
- no increased cancer risk

Rufous Albinism (ROCA)

Black populations
- Africa (S. Africa 1/8500)
- Papua New Guinea

OCA 4

MATP gene
- membrane associated transport protein
- proton transport re melanosomal function
- Turkey (1 case) and Japan (24% of OCA1)
- mouse underwhite (uw)
- “ty negative” phenotype

Red (Rufous) Albinism: Eyes

Va normal - 20/200
- colour vision usually normal
- less nystagmus
- “red retinas”
- mild transillumination
- normal VEP
- is it albinism?
Tyrosine Related Protein 2 (TRP 2)

1p31-32

Tyrosine Related Pseudogene (TYRL)

11p11.2

Pigment genes

>50 in mice!!!

"digenic"

(...the influence of > 1 gene)

Red Haired OCA 2

p gene mutation +
MC1R (melanocortin 1 receptor)

intermediate albinism phenotype
red hair at birth

Digenic Inheritance

Waardenburg WS2 MITF heterozygote
(microphthalmia associated transcription factor)
+ tyrosinase heterozygote
= OA + deafness

Digenic

Tyrosinase hetero + CYP1B1
= worsened ant seg dysgenesis (mice)
than CYP1B1 or FOXC1 GL alone
Rx: L-DOPA [di-OH-phenylalanine, tyr product] reverses severity
?Applicability in human glaucoma

Hermansky-Pudlak Syndrome

very variable phenotype intra/inter family
ocular albinism
“ty positive”
“ty negative”
macromelanosomes
common in Swiss, PR

Macromelanosomes

?autophagolysosomes of melanosomes
Hermansky-Pudlak Syndrome

- 50% ceroid/lipofuscin deposition
- Increase with age
- Interstitial lung disease
- Granulomatous colitis
- Cardiomyopathy
- Bleeding disorder

CAUSES OF DEATH

- Renal failure
- Cardiomyopathy
- Granulomatous colitis

HPS: Bleeding Diathesis

- Storage pool-deficient platelets
- Absent dense bodies
- Ca, ATP, ADP & serotonin
- Decrease membrane thioredoxin reductase
- Decrease tyrosinase in melanosomes

Hermansky-Pudlak OCA

- HPS gene
- 10q23.1-23.3
- PR, Swiss, and Japanese
- Frameshifts
- Unlinked families exist
- Region of CHS homology

Hermansky-Pudlak Syndrome

- Multiple mouse models
- 10q = pale ear, ruby eye (19)
- Role in organelle membranes
  - E.g., melanosomes

Hermansky-Pudlak Syndrome

- HPS1*
- 10q23 HPS1
- HPS2 5p14.3-q14.3 ADT3BA
- HPS3* 3q24 HPS3
- HPS4 *
- 22q11.2-12.2 HPS4
- HPS5 11p13-15 ru2
- HPS6* 10q24.32 ru
- HPS7 6p22.3 DTNPB1
- HPS8 19p13 BLOC1S3

* = Colitis, ϰ = Pulmonary fibrosis
All have a role in vesicle sorting

Hermansky-Pudlak: Diagnosis

- Bleeding time
- Ceroid deposition on biopsy
- Platelet morphology
- Platelet aggregation

Chediak-Higashi

- “Tyrosinase positive” OCA
- Metallic gray sheen to hair
- Slate gray patches on skin
- ON edema (acceleration phase)
- Macromelanosomes

Chediak-Higashi OCA

- Giant peroxidase lysosome granules
- Decrease neutrophil chemotaxis
- Decrease bactericidal capacity
- Gram + infections
- Lymphoreticular malignancy
- Peripheral neuropathy
Chediak-Higashi OCA
- death in childhood
- accelerated phase
- papilledema
- organ infiltration
- lymphocytes
- histiocytes
- pancytopenia
- coagulopathy

Chediak-Higashi OCA
- CHS gene
- 1q43
- homology to mouse beige
- BEACH domain
- Protein
  - role in membrane identification
  - role in vesicular sorting

Griscelli Syndrome
- Similar to CHS
- cellular immune deficiency
- also similar to PAID

Griscelli Syndrome
- CHS gene
- 1q43
- homology to mouse beige
- BEACH domain
- Protein
  - role in membrane identification
  - role in vesicular sorting

Griscelli Syndrome
- AR
- albinotic skin + silvery grey hair
- pigment clumps in hair shafts
- hemophagocytic syndrome
- acceleration phase
- uncontrolled activity of T's & macro's
- bone marrow Tx or fatal
- secondary CNS effects (type 2)

Griscelli Syndrome
- GRS1
- 15q21 MYO5A
- targeting & fusion of transport vesicles

Griscelli Syndrome
- GRS2
- 4p13 RAB27A (GTPase)
- targeting & fusion of transport vesicles

Elejalde Syndrome
- Griscelli Syndrome
- aka
- neurocutaneous melanocytic disease
- AR
- albinotic skin + silvery grey hair
- abnormal irregular melanin granules in hair shafts
- primary severe CNS

Elejalde Syndrome
- 15q21 MYO5A
- same gene as Griscelli type 1
- OMIM says same disease

OCA Syndromes
- albinism: microphthalmia - digital (203340)
- Cross (257980)
- aniridia
- MK + albinism/CNS
- Prog. nystagmus + hypopigmentation (257980)
- patau, lentis, anemia
- Nijmegen breakage (257900)
- Short stature
- Axenfeld/Reiger Anomaly +/- glaucoma
- PAID
- ......and more

OA Syndromes: OA 1 +
- OA 8: dystrophia congenita (Xq28)
- DM, HgF, (?macromelanosomes)
- OA 10: dysmorphism, delay
- OA 11: hearing, delay, renal
**Albinism + Deafness**
cDNA 10-20% sharing cilia melanocytes

**Dominant OCA**
very rare variable expressivity complete penetrance

**Ocular Albinism**
X linked Recessive Autosomal Recessive

**OA 1 (Nettleship Falls)**
10% of all OA + OCA

**OA 1 Protein**
G protein-coupled receptor (GPR143)
1st ever localized to intracellular membrane = melanosome
signal transduction ligand unknown

**Recessive OA**
p gene
TYR
Arg402Gln + t -
(= polymorphism +)
50% neither

**OA 1 Contiguous Gene Deletions**
Tel-SS-CDPX-MRX-XL(STS)-KAL-OA1-cen

**OA 1**
Xp22.3-22.2 (Ballabio et al, 1995)
Protein = GPR143
424 aa, expressed in RPE controls melanosome number and size [explains macromelanosomes]

**OA 1**
Xp22.3-22.2 (Ballabio et al, 1995)
Protein = GPR143
424 aa, expressed in RPE controls melanosome number and size [explains macromelanosomes]
OA1: Carrier Females

- RPE abnormal (80-90%)
- Iris transillumination (75%)
- Macromelanosomes (85%)
- Hypopigmented macules
- Nystagmus

OA2 (Forsius-Eriksson, Aland Island eye Disease)

- Incomplete CSNB
- Iris transillumination
- High myopia
- Atrophic retina
- Xp21.3-21.2 vs Xp11.23-11.4

Melanosome Disorders

Piebaldism

- (1st autosomal dominant described)
- Ventral spotting (100%) [leukoderma]
- White forelock (90%)
- Poliosis (80-90%)
- No melanocytes in spots
- W mutant mouse (dominant spotting)

Piebaldism: c-kit gene

- 4q12-13
- Tyrosine kinase receptor
- 21 exons, 75 Kb
- Melanocyte proliferation

Piebaldism: kit gene function

- Induces cell proliferation
- E.g. melanocytes
- Ligand = steel factor (mast/cell stem growth)

Piebaldism: kit gene mutations

- 3\': mod-severe
- 5\': extracellular ligand binding
- No mutation detected
- Patch mouse = upstream mutation
Homozygous kit mutation (n=1)
- OCA
- retina nl
- iris transillum
- deaf
- Died in infancy without w/u

Hypomelanosis of Ito
- swirling hypopigmentation
- ?p gene, ?mosaicism
del 7q34-ter
del 15pter-q13
del 15q11

Albinism Diagnosis
- Clinical
  - especially transillumination
- Pedigree
- Other Tests
  - skin biopsy
  - coagulation studies etc.
- Molecular

Albinism Prenatal Diagnosis
- Fetoscopy
- Scalp Biopsy
- Tyrosinase
  - Moroccan homozygote (Spritz et al)
  - Japan homozygote (only 2 t -)
- OA1 – prenatal vs sex selection

Albinism Management
- Glasses
  - Correct lenses
- Low vision aids
  - Near DR as kids
- Telescopes
- Strabismus (rops)
- Nystagmus
- Surgery

Albinism Management: UV protection
- Decr melanin= increased UV sensitivity
  - blacks: squamous cell
  - Caucasian: basal cell
- Head and neck
- Start in infancy
  - 42 sun block/covering

Albinism History
- Noah
- Rev. Dr. Spooner

Albinism Psychosocial: History
- 1666 Yossins - Africa
- Reversed
drivers
- S. African “death myth”
- Skin
  - infanticide
  - deformed
  - contagions
- 1960’s social work study...

Albinism Psychosocial
- Appearance
  - culture dependent
- Eye appearance
- Low vision
- Lifestyle
  - photophobia
  - avoid UV
"The youngest of the mercenaries turned away. Ivarr saw fear in his face. Fear the need to hide, people avoided looking at him at all, with the glint of horror in his eyes, and there was always fear. Ivarr Ragnarsson was white as a bone, malformed at one shoulder, his eyes were strange (and not good in bright sunlight) - and men were riddled with fear of the unknown, of spirits, of angry, unassuaged gods.

The Last Light of the Sun
Guy Gavriel Kay

QUIZ!

National Organization for Albinism and Hypopigmentation
NOAH

Alex V. Levin
Hospital for Sick Children
University of Toronto
AAPOS, April 2007
Managing a Child with an External Ocular Disease

Inez BY Wong FRCSEd(Ophth); Ken K Nischal FRCOphth

National University Hospital, Singapore; Great Ormond Street Hospital for Children, United Kingdom

**Course outline**

There are some common external eye diseases that affect children commonly. This interactive workshop presents an anatomical and physiological understanding for the basis of treatment of external eye diseases that result in ocular surface disruption.

Four areas are specifically covered using case scenarios and evidence based detail:

**Chronic conjunctivitis** -
1. Blepharokeratoconjunctivitis - management strategies for recurrent chalazia and corneal involvement together with simple clinical clues for diagnosing lid margin disease
2. Allergic conjunctivitis - rationale for systemic and topical treatment and indications for surgical intervention
3. Infection related conjunctivitis - case scenarios to show how infection related cases were missed and treated for other conditions

**Persistent epithelial defect** - Therapeutic modalities are discussed including autologous serum, botulinum-induced ptosis, lateral tarsorrhaphy, and if the cornea is thinning, amniotic membrane graft. The role of different tissue glues is discussed.

**Persistent epithelial erosions** - may occur for a variety of reasons. It is important to differentiate exposure keratopathy from inflammatory, toxic or mechanical traumatic causes because treatment varies. The workshop will demonstrate signs that help differentiate these various causes.

**Lubricants for children** - In the past 12 months, there has been an explosion of different topical lubricants that have been marketed for 'dry eyes'. We explain the rationale for using different lubricants in the different conditions described above and when to combine different lubricants for greatest efficacy and perhaps most importantly, when to consider alternative strategy.
Chronic Conjunctivitis

I. Blepharoconjunctivitis (BKC)

BKC is a common but under-recognized problem in children. The condition is similar to that seen in adults, including an association with acne rosacea in some children, but there are also important differences.

BKC is divided into anterior and posterior disease but these often co-exist. It is primarily an eyelid disease with secondary conjunctival and corneal involvement.

<table>
<thead>
<tr>
<th>Anterior blepharitis</th>
<th>Posterior blepharitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(anterior lid margin, hair follicles/ oil glands)</td>
<td>(meibomian gland dysfunction)</td>
</tr>
<tr>
<td>Inflamed eyelids</td>
<td>Meibomian gland pouting, capping, hypertrophy or inflammation</td>
</tr>
<tr>
<td>Lid margin telangiectasia</td>
<td>Posterior lid margin telangiectasia</td>
</tr>
<tr>
<td>Scales and collarettes base of lashes</td>
<td></td>
</tr>
<tr>
<td>Madarosis</td>
<td></td>
</tr>
<tr>
<td>Trichiasis</td>
<td></td>
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<tr>
<td>Lid notching</td>
<td></td>
</tr>
<tr>
<td>Meibomian gland pouting, capping, hypertrophy or inflammation</td>
<td></td>
</tr>
<tr>
<td>Posterior lid margin telangiectasia</td>
<td></td>
</tr>
</tbody>
</table>

Important features in children:

- Age of presentation is around 6-7 years, although there is usually a delay of 1 to 2 years between the onset of symptoms and diagnosis.

- Presenting symptoms:
  - Red eye
  - Photophobia
  - Epiphora
  - Recurrent chalazia
    - history of recurrent chalazia necessitates the exclusion of eyelid/corneal disease

- Cornea involvement is common (up to 81%). This includes punctate epithelial erosions (PEEs), subepithelial infiltrates, phylctenules, marginal keratitis and ulceration, or even total cornea opacity. Cornea scarring and vascularization may develop.

- Location of cornea involvement tends to be central or paracentral rather than the classical peripheral or marginal inflammation seen in adults.

- Visual may therefore be significant in BKC. Superimposed amblyopia due to prolonged corneal opacification and/or refractive changes (in particular astigmatism due to cornea scarring) is frequently present. Delayed treatment may result in decreased final vision.

- Adequate management requires both topical and systemic treatment. Frequent courses of topical steroids may be required for recurrent exacerbations.
Treatment strategies:

1. **Lid hygiene/ warm compresses** – using cotton wool tipped swab sticks and warm water, diluted baby shampoo or special products like Blephagel or Lid Care. Modified lid hygiene using a clean fingertip or warm damp flannel to rub the eyelids at the base of lashes during showering may be more easily implemented in small children.

2. **Topical antibiotics** - A variety of topical antibiotics have been used including chloramphenicol 0.5%, ciprofloxacin, gentamicin, fusidic acid. *Staphylococcus aureus* or *Staphylococcus epidermis* are the most common organisms cultured form conjunctival or lid swabs taken.

3. **Topical steroids** – prednisolone acetate 1%, prednisolone 0.5%, or fluoromethaolone (FML) 0.1% depending on severity. Patients should be converted to FML once the disease comes under control as it is less likely to induce secondary glaucoma.

4. **Lubricants** – important due to the functional drying that follows. See later.

5. **Systemic antibiotics** – Oral tetracycline is contraindicated in children under the age of 8 years because of its effect on dental enamel. Oral erythrymycin is usually recommended - dosage ranges from 25% to 80% of the recommended dose in children (50mg/kg per day in divided doses). Treatment is usually required in the longterm but should be reduced quickly to the minimum dose required to control lid margin disease.

6. **Flaxseed oil (α-linolenic acid)** – can be considered for children who unable to tolerate or reluctant to use longterm systemic antibiotics. It is a source of omega-3 essential fatty acids which have been found to have anti-inflammatory effects and improve dry eye syndrome. In addition, they appear to have a thinning effect on meibomian secretions. The dosage recommended is 2.5ml od reducing to alternate days for up to 6 months.

7. **Treatment of chalazia** – Medical treatment such as lid hygiene, warm compress, topical and systemic antibiotics can result in improvement or resolution within 1-3 months. Surgical treatment is considered for non-resolving lesions particularly if large and multiple. Incision and curettage can be augmented by intralesional triamcinolone injections in selected cases.

8. Last but not least, **Refraction and Amblyopia therapy**
II. Allergic conjunctivitis

Clinical entities:

- Acute allergic conjunctivitis (AAC)
- Seasonal allergic conjunctivitis (SAC)
- Perennial allergic conjunctivitis (PAC)
- Vernal keratoconjunctivitis (VKC)
- Atopic keratoconjunctivitis (AKC)
- Giant Papillary Conjunctivitis (GPC)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age group</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAC</td>
<td>Any (especially in children)</td>
<td>• A large amount of allergen inoculated into the eye&lt;br&gt;• Swelling of conjunctiva and lids&lt;br&gt;• Intense itching</td>
</tr>
<tr>
<td>SAC</td>
<td>10 - 40 years</td>
<td>• Caused by seasonal allergens such as pollen&lt;br&gt;• Itchy, burny, watery eyes&lt;br&gt;• Conjunctival redness and oedema +/− papillary reaction</td>
</tr>
<tr>
<td>PAC</td>
<td>Similar to SAC</td>
<td>• Caused by perennial allergens e.g. house dust mite&lt;br&gt;• Similar to SAC but symptoms present for at least 1 year</td>
</tr>
<tr>
<td>VKC</td>
<td>Onset &lt;10 years</td>
<td>• Boys &gt; girls&lt;br&gt;• Prevalent in warm dry climates e.g. Mediterranean, India&lt;br&gt;• Majority has family history or personal history of atopy&lt;br&gt;• Self-limiting, lasting 2 to 10 years&lt;br&gt;• May be unilateral or asymmetrical&lt;br&gt;• Conjunctival injection with thick ropy discharge&lt;br&gt;• Giant papillae on superior palpebral conjunctiva - “cobblestone” appearance&lt;br&gt;• Limbitis&lt;br&gt;• Horner-Trantas dots may be present at limbus&lt;br&gt;• Punctate epithelial erosions&lt;br&gt;• Maceroesions&lt;br&gt;• Shield ulcers&lt;br&gt;• Keratoconus in 15% (6% develop hydrops)</td>
</tr>
<tr>
<td>AKC</td>
<td>Young adults 20 – 60 years</td>
<td>• Males &gt; females&lt;br&gt;• Associated with atopic dermatitis&lt;br&gt;• Chronic and more severe&lt;br&gt;• Usually bilateral&lt;br&gt;• Scaly and crusty eyelids&lt;br&gt;• Papillae upper and lower palpebrae conjunctiva&lt;br&gt;• ConjunctIVAL scarring including symblepharon&lt;br&gt;• Puntate epithelial erosions&lt;br&gt;• Corneal scarring and vascularisation&lt;br&gt;• Anterior subcapsular cataracts (5%)</td>
</tr>
<tr>
<td>GPC</td>
<td>Any age (contact lens wear)</td>
<td>• Giant papillae on superior conjunctival tarsus&lt;br&gt;• Cornea usually spared</td>
</tr>
</tbody>
</table>
Pathophysiology

The pathophysiology of an allergic response is type 1 hypersensitivity reaction, in which the allergen binds to the sensitized IgE antibody on the mast cell, causing the mast cell degranulation and release of mediators such as histamine, prostaglandins, and leukotrienes. This early phase response is immediate but a late phase response involving eosinophils and T cells occurs 4-6 hours later.

- Only AAC & SAC are pure Type I hypersensitivity reactions
- VKC & AKC more chronic and severe
- Type I and Type IV hypersensitivity reactions involved
- Conjunctival biopsies show massive infiltration of eosinophils and T cells
- VKC thought to be a TH2 driven disease

TH2 cells play a crucial role in conjunctival infiltration of eosinophils
**Therapeutic strategies**

1. **Preventive Measures**
   - Allergen avoidance
   - Cold compress
   - Lubrication

2. **Pharmacotherapy**

   i. **Topical Antihistamines**
   First generation non-specific antihistamine is available over the counter combined with vasoconstrictors. Longterm use is not advised because of rebound hyperaemia and inflammation.
   - Opcon-A (B&L) (combination of naphazoline and pheniramine)
   - Levocabastine HCL suspension 0.05% (Livostin) qds
   - Emedastine difumarate solution 0.05% (Emadine) qds

   ii. **Systemic Antihistamines**
   - Loratidine (Claritin) 10mg od (6 years or above)
   - Fexofenadine (Allergra) 60mg bd (30mg bd 6-11 years)

   iii. **Mast Cell Stabilizers**
   They do not relieve existing symptoms and need to be used on a prophylactic basis, or combination with other drugs.
   - Sodium cromoglycate 4% (Cromolyn Sodium) qds
   - Lodoxamide tromethamine 0.1% (Alomide) qds
   - Pemirolast potassium ophthalmic solution 0.1% (Alamast) qds

   iv. **H1 Antagonist and Mast Cell Stabilizer (Dual-acting Agents)**
   - Olopatadine HCL solution 0.1% (Patanol) bd, or 0.2% (Pataday) od
   - Nedocromil sodium 2% (Alocril) bd
   - Ketotifen fumarate solution 0.025% (Zaditor) tds
   - Azelastine HCL solution 0.05% (Optivar) bd

   v. **NSAIDS**
   - Ketorolac tromethamine 0.5% (Acular) qds

   vi. **Steroids**
   Topical corticosteroids are extremely effective, but may be associated with complications, including increased intraocular pressure, cataract formation and viral or fungal infections. Short pulses are therefore recommended for acute flare-ups:
   - Prednisolone acetate ophthalmic suspension 1% (Pred forte) or 0.12% (Pred mild)
   - Dexamethasone suspension 0.1% (Maxidex)
   - Fluorometholone ophthalmic suspension 0.1% (FML) – less likely to increase IOP

   Two modified steroids which are derivatives of prednisolone are rapidly inactivated once they enter the anterior chamber thus reducing the risk of raised intraocular pressure.
   - Loteprednol etabonate ophthalmic suspension 0.2% (Alrex) or 0.5% (Lotemax)
   - Rimexolone ophthalmic suspension 1% (Vexol)
vii. Immunomodulators

Topical cyclosporine A has been shown to be effective in treatment of AKC and VKC. The 2% formulation has the longest track record but lower concentrations (1%, 0.5%, 0.05%) have been tried and shown to be efficacious. Low dose systemic tacrolimus has been reported to be effective in severe AKC, and the ointment is licensed for use in atopic dermatitis.

- Cyclosporine A 0.05% (Restasis) to 2%
- Tacrolimus (FK-506)

Future therapy

- Immunotherapy
- Anti-IgE
- Anti-leukotrienes
- Adhesion molecule inhibitors
- Anti-cytokine

3. Surgical Treatment

**Supratarsal steroid injection**
Particularly useful in patients non-compliant to topical therapy. Effect typically lasts 3 to 5 months.
Under general anaesthesia, the upper eyelid is everted, and a mixture of triamcinolone 20mg/0.5ml & betnesol 2 mg/0.5ml is injected into the subconjunctiva 1mm above the superior tarsal border with a 27-gauge needle.

**Excision/ cryotherapy of giant papillae**
Help in resolution of epitheliopathy or ulcer.
Papillae may recur.

**Debridement of shield ulcer**
Promotes re-epithelialization of vernal ulcer resistant to medical therapy.

**Amniotic membrane transplantation**
Can be considered for persistent epithelial defects or vernal plaques.
III. Infection-related conjunctivitis

What is the diagnosis?

Case 1: 8 month old boy with hazy cornea. Is this congenital glaucoma?

Case 2: 10 year old boy with bilateral conjunctivitis. Are these PEEs?

Case 3: 12 year old boy with unilateral follicular conjunctivitis.
**Persistent Epithelial Defect**

Persistent epithelial defects may occur due to a variety of reasons but in order to treat these efficiently one must look at the micro-environment of the ocular surface to improve them.

**Causes:**

1. Lashes- trichiasis or entropion
2. Lid congruity - lagophthalmos

**Tear film/ TBUT**

3. Lipid - Meibomian gland dysfunction
4. Aqueous – Dry eyes is rare in children, and may indicate underlying pathology
5. Mucin – Goblet cell destruction as in Stevens Johnson syndrome

6. Corneal anaesthesia
   - Herpes simplex keratitis
   - Trigeminal nerve damage
   - Congenital – rare, either confined to the cornea only, or associated with anaesthesia in V1 and V2.

7. Limbal stem cell deficiency - aniridia

8. Raised intraocular pressure
Treatment options:

1. **Lubrication** see later

2. **Other topical treatments**
   - Autologous serum
   - Albuminate
   - Healon
   - Hyaluronic acid drops

3. **Punctal plugs**
   - Dissolvable collagen plugs (lasting 7 to 10 days)
   - Semipermanent silicon plugs
   - Permanent punctual occlusion using thermocautery or radiofrequency needle

4. **Amniotic membrane transplant**
   - use as patch graft to fill in defect
   - use as bandage contact lens
   - for treatment for tarsal conjunctival scarring

5. **Tarsorrhaphy**
   - Central
   - Lateral

6. **Botulinum toxin – induced ptosis**

7. **Treat any lid problem**
   - Tarsal eversion for trichiasis
   - Anterior lamellar repositioning for trichiasis

8. **Limbal stem cell transplant**
   - Living related
   - Cadaveric

---

**Tissue glue**

Cyanoacrylate-based glues have traditionally been the most widely used. They have been specially useful for treating corneal perforations and have had significantly improved long-term outcomes. More recently, fibrin-based glues have gained a major role as a suture substitute for attaching biologic tissues and as surface sealants e.g in AMTs
**Persistent Epithelial Erosions**

**Causes:**

The most common causes of corneal erosions are trauma and epithelial basement membrane dystrophy in adults. Dry eye is another common cause but is rare in children, but may be secondary to other problems such as BKC.

In children, the following causes should be considered:

- Trauma – following epithelial abrasions
- Dry eyes
  - primary (very rare in children)
  - secondary e.g. BKC
- Exposure keratitis - lagophthalmos, proptosis
- Neurotrophic keratitis
- Viral keratitis – esp molluscum contagiosum
- Herpetic keratitis
- VKC
- Trichiasis
  - Epiblepharon is the commonest cause of persist keratopathy in East Asian children, and in contrast to Western population, a larger majority require surgical correction for symptomatic relief
  - Circatricular entropion secondary to infection or immune disease
- Cornea dystrophies (anterior stromal dystrophies can present with recurrent corneal erosions in childhood)
  - Reis-Buckler
  - Meesman
  - lattice dystrophies
- Epidermolysis bullosa (junctional type)
- Cystinosis
Lubricants

- In the form of drops, gels or ointment
- Hydrogels are polymers added to enhance viscosity and retention time
  - HPMC
  - CMC
  - PVA
  - Propylene glycol
  - Carbopol
  - Dextran
  - Hyalouronic acid
  - Carbomer 940
- Despite this, the effect may be shortlived. To provide longer term relief, various strategies have been used to increase retention time.
  1. Increased viscosity, but blurring occurs after instillation.
     - Celluvisc (1% CMC) - 24 mins
     - Refresh Liquigel (1% CMC but blended with lower viscosity CMC) - 13 mins
  2. Systane uses HP-Guar which forms a soft gel once exposed to the eye, with increased viscosity and bioadhesive properties

<table>
<thead>
<tr>
<th></th>
<th>Viscosity</th>
<th>Retention time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celluvisc</td>
<td>350</td>
<td>++++++</td>
</tr>
<tr>
<td>Liquigel</td>
<td>70</td>
<td>+++</td>
</tr>
<tr>
<td>Systane</td>
<td>10</td>
<td>+++</td>
</tr>
<tr>
<td>Refresh Tears</td>
<td>3</td>
<td>+</td>
</tr>
</tbody>
</table>

- Preservatives
  - Benzalkonium chloride (BAC) can increase irritation and disease
  - Newer preservatives such as GenAqua (sodium perborate) and Polyquad (Polyquaternium-1) preferred.
  - Preservative-free solutions are the best choice, but expensive
  - Non-toxic “disappearing” preservatives e.g. Refresh Tears (purite)
Which ones should you use?

- Consider preservative-free formulations to avoid surface epithelial toxicity, especially if given more than 4 times a day
  - Refresh Plus
  - Tears Naturale Free

- Prolong contact time on the cornea
  - Celluvisc
  - Refresh Liquigel
  - Systane

- Oil containing eyedrops will replenish the lipid layer and prevent tear evaporation. This may be useful in meibomian gland dysfunction
  - Soothe
  - Refresh Endura

- Petroleum-mineral oil-based ointments are usually reserved for night time use, or for treatment of lagophthalmos or blink paralysis as they cause blurring and feel sticky
  - Genteal Gel
  - Refresh PM ointment
  - Tears Naturale PM ointment
  - Lacrilube ointment
  - Advanced Eye Relief

- Tear osmolarity increases in dry eyes, and moderately hypotonic artificial tears have been show to promote ocular surface healing in dry eyes.
  - Hypotears

- Different eyedrops may be used in combination to achieve the desired effect in individual patients

In severe dry eyes, consider

- Punctal plugs

- Anti-inflammatory therapies
  - Cyclosporin 0.05% bd (Restasis, Allergan) – may take several weeks for effect and up to 6 months for maximal improvement
  - Topical corticosteroids – short-term pulse therapy
  - Autologous serum

- Omega-3 essential fatty acids supplement
Abusive Head Trauma

Homicide is the leading cause of injury and death in infancy, and half of infant homicides occur during the first four months of life (1,2). The majority of these deaths are caused by abusive head trauma, which results from violent, non-accidental shaking, blunt impact to the head, or both. Historically, the injuries resulting from repetitive unrestrained head and neck movements from shaking were termed the “whiplash shaken infant syndrome” which was commonly referred to as the “Shaken Baby syndrome”(3)and more recently Abusive Head Trauma,. Those perpetrators who have confessed support the prominence of repetitive violent shaking as the key element in generation of Abusive Head Trauma. Clinical findings in affected infants include subdural hemorrhage, hypoxic-ischemic brain injury, retinal hemorrhages, skeletal injuries, and cutaneous or other injuries.

Acute Ophthalmic Findings in Abusive Head Trauma

Autopsy and in-vivo studies of the acute ocular findings in infants and toddlers less than 3 years with non-accidental head injury from Abusive Head Trauma have described a consistent clinical picture. These characteristic ophthalmic findings include intraocular hemorrhage with a reported frequency of 50-100% with most papers reporting approximately 80% (4-12). Retinal hemorrhage occurs at all levels of the retina, including blot, flame-shaped and pre-retinal hemorrhage as well as vitreous hemorrhage. Retinal hemorrhages can be few in number, exclusively intraretinal, and confined to the posterior pole though often they are too numerous to count, present at all layers, and extend to the ora serrata. The frequency of RH is highest in autopsy cases and lowest in intact survivors and typically the hemorrhages are present in both eyes, although asymmetry and unilaterality are well recognized. Papilledema occurs in less than 10% of cases (13). Retinoschisis may occur, most often in the macular area. These lesions, seen both histopathologically and clinically, have also been called “hemorrhagic macula cysts” and “perimacular circular folds”(14-17).

Late Ophthalmic Findings in Abusive Head Trauma

Late changes associated with Abusive Head Trauma are neither consistent nor specific to Abusive Head Trauma. Permanent visual impairment is frequent and central visual impairment related to the hypoxic ischemic brain injury from the Abusive Head Trauma and optic atrophy, is the most common cause of long-term reduced vision. Amblyopia caused by visual deprivation due to prolonged vitreous hemorrhage may occur (18). Optic disc pallor, optic atrophy non-specific vitreous hemorrhage, macular hole, vitreous opacities, retinal thinning, and high myopia may also be seen in survivors(18-20).

The age of intraocular hemorrhage is very difficult to assess clinically. It is assumed that the hemorrhages occur immediately at the time of injury. Some evolution, including darkening of the retinal hemorrhages, organization of vitreous hemorrhages, and
disappearance of the retinal hemorrhages occurs gradually over 2-4 weeks following the acute injury.

**Differential Diagnosis of Retinal Hemorrhages in Infancy**

Idiopathic retinal hemorrhages of newborns, related to obstetrical and perinatal hemodynamic changes, are frequent. Retinal hemorrhages secondary to normal birth has been extensively studied both retrospectively and prospectively. From this data it can be concluded that superficial retinal hemorrhages resolve by 1 week postpartum and deeper retinal hemorrhages resolve by 6 weeks.

Retinal hemorrhages also have been reported in association with severe accidental injury. Multiple clinical and post-mortem studies of eyes in patients with severe head injury suggest that the rate of retinal hemorrhage is less than 3% of instances (21-23). When retinal hemorrhages do occur they are confined to the posterior pole, few in number, and rarely subretinal. The types of accidental trauma that result in retinal hemorrhages are usually severe life threatening injuries as even with severe head injury and severe brain injury sufficient for hospitalization; retinal hemorrhage is quite uncommon (21-24).

Many infants with severe abusive head injury have cardiopulmonary resuscitation (CPR). From case reports and prospective studies it can be concluded that retinal hemorrhages only rarely occur from CPR and when they do, they are few in number and confined to the posterior pole.

Purtscher’s retinopathy may occur following acute compression injuries to the thorax or head with characteristic manifestations including cotton wool spots, retinal hemorrhages and retinal edema most commonly surrounding the optic disk.

Terson syndrome, retinal hemorrhages associated with subarachnoid hemorrhage, is well recognized in adults though it appears to be uncommon in children. The lack of correlation between the side of involvement of the subarachnoid hemorrhage and ocular hemorrhage suggests that this is not a sufficient explanation for the retinal hemorrhages seen in Abusive Head Trauma.

There is no evidence to support a link between immunizations and retinal hemorrhages in children (25).

Coagulopathies and other bleeding disorders, including thrombocytopenia, anemia, leukemia, factor deficiencies, vitamin K deficiency, as well as metabolic diseases such as glutaric acidemia must be considered in the differential diagnosis of intraocular hemorrhage in infants. In general, retinal hemorrhages related to hematologic abnormalities are less numerous and less extensive and do not extend peripherally in the retina.

**Pathophysiology of Retinal Hemorrhages in Abusive Head Trauma**
Many theories as to the cause of retinal hemorrhages in Abusive Head Trauma continue to be debated in the literature. Venous obstruction in the retina occurring from increased intracranial pressure due to cerebral edema and subdural hemorrhage has long been proposed as the source of retinal hemorrhages. Sudden increases in chest or head pressure may be contributing factors as well. Another theory postulates that traction of the vitreous on the retina during the acceleration and deceleration of shaking and impact causes circular retinal folds and hemorrhagic retinoschisis cavities, as well as smaller hemorrhages. Subdural hemorrhages in Abusive Head Trauma are thought to be caused by the shearing of small vessels from inertial injury, most likely due to rapid acceleration/deceleration movements. The body of literature suggests that it is the shaking itself, with resultant shearing injury that is the primary factor in the generation of retinal hemorrhages seen in Abusive Head Trauma. The optic atrophy often seen in survivors is best explained by direct optic nerve injury within the orbit.

References:


Reading, Dyslexia, & Vision Therapy

Sheryl Handler, M.D.
Megan Rees, M.D.

Early Speech and Language Milestones

- Smile 1-2 months
- Initiate speech sounds 4-6 months
- Monosyllabic babbling 6-8 months
- Polysyllabic babbling 5-9 months
- Comprehends individual words 6-12 months
- Mama / Dada correct use 7-12 months
- First word (other than above) 9-14 months
- Two word combination 16-22 months
- Vocabulary 50(+) words 16-24 months

Oral language is pre-programmed into human development.

Oral Language

- Phonemes - sounds signaling differences of meaning
  - Consonant - break letters into phonemes
  - “Pet” & “Bet” are distinguished by the sounds of their initial consonants
- Semantics - meaning of words, combining words into phrases and sentences
- Syntax - use of language to communicate needs, get information - grammatical structure
- Pragmatics - use of language for functional communication - connected sentences

Written Language

- Writing is the use of abstract symbols to represent language
- Written language must be actively learned
- Writing Systems
  - Alphabetic - symbol represents an abstract building block of that language’s phonemes
  - Ideographic - symbol represents an idea
  - Logographic - symbol represents an object

Reading

- Reading is not pre-programmed into human development and must be learned
- There is no single neural infrastructure designed for reading
- The oral language neural areas are “moonlighting” for reading

How We Read - Language

- Orthographic Perception
  - This is nearly the same shape turned in different directions
  - Creating 5 unique letters & 2 numbers
- New Concept -
  - Partial Object Constancy
- Attention

Oral language is pre-programmed into human development.
How We Read - Language

Decoding - Lower Order Linguistic Function
- Phonetic awareness
- Automatic phonemic decoding
- Phonological decoding
- Rapid automatic naming (RAN)
- Phonological - verbal memory
- Word recognition - instant identification
- Sight reading
- Fluency

Fluency
- Ability to read connected text with expression rapidly, smoothly, effortlessly, and automatically with little conscious attention to the mechanics of reading such as decoding
- Automatic phonemic decoding
- Word recognition
- Memory
- Attention
- Comprehension

How We Read - Language

Fluency
- Forms the bridge between decoding and comprehension
- Reading must be accurate and fluent to gain comprehension
- Requires between 4 - 14 exposures to automatize the recognition of a new word

How We Read - Language

Comprehension - Higher Order Linguistic Function
- General Intelligence
- Reasoning
- Vocabulary
- Syntax - grammar
Comprehension - Other Factors
- Attention
- Knowledge
- Memory
- Cultural influences

Learning Disabilities

Definition
- A group of disorders in the psychological processes involved in understanding or using spoken or written language that may manifest themselves in an imperfect ability to listen, speak, read, spell, write, reason, or do mathematical calculations.
- 15 - 20 % of the population has a learning disability

Dyslexia

Derived from Greek
- "Dys" - Poor or inadequate
- "Lexis" - Words or language
- 80 - 85 % of learning disabilities
- 5 - 17 % of the general population

Dyslexia - A Definition

International Dyslexia Association

Dyslexia is a specific learning disability that is neurological in origin. It is characterized by difficulties in accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction.

Dyslexia - Secondary Forms

Dyslexia is a primary reading disorder and should be separated from other secondary forms of reading difficulties.
- Secondary causes include:
  - Mental retardation
  - Environmental deprivation
  - Educational deprivation
  - Physical (Organic) disease

Dyslexia - Secondary Forms

*Environmental deprivation*
- Exposure to words over 1 year
  - Children in Professional Families
    - 11 million words
  - Children in Working Class Families
    - 6 million words
  - Children in Welfare Families
    - 3 million words
**Dyslexia - Common Signs**
- Significance of signs are age dependent
- Difficulty remembering the names of the letters
- Difficulty remembering the sounds of the letters
- Reversing letters and words
- Scrambling letters in reading or writing
- Reading words incorrectly - guessing
- Adding, dropping, changing words, & skipping lines
- Slow reading in adolescents & adults
- Difficulty writing

**Dyslexia - Magnocellular Deficit Theory**
- Magnocellular deficits produces a visual trace of abnormal longevity that creates a masking effect and causes visual trace
- Magnocellular system - Responds to high frequency & movement
- Parvocellular system - Responds to low frequency & fine spatial details
- In reading:
  - The Parvocellular system is active during fixations
  - Magnocellular system suppresses the parvocellular input during saccades
- Data is inconsistent
  - Contrast sensitivity studies
  - Subtle support
  - Abnormalities also found in "normals"
  - Positive results not repeatable by others
- Negative results
  - Functional MRI studies
  - Deficit in responding to moving stimuli
- Conclusion by experts in Learning Disabilities:
  - Not a significant cause of dyslexia

**Dyslexia - Shaywitz**
- Epidemiology
  - Reading ability and reading disability occur along a continuum
  - Reading disability represents the lower tail of a normal distribution of reading ability
  - Boys minimally more than Girls; but schools identify four times as many boys
  - Dyslexia is a persistent, chronic deficit it does not represent a transient "developmental lag"
  - Dyslexia occurs at all levels of intelligence

**Neuropathology by functional MRI scans:**
- Underactivation of the faster Left Posterior Superior Temporal Gyrus (Wernicke’s Area) and the Angular Gyrus
- Overactivation of the Right Superior Temporal Gyrus
- Overactivation of the slower Inferior Frontal Gyrus - (Broca’s Area)

**Early Detection of Learning Disabilities**
- Family History of Learning Disabilities:
  - ➥ 40 % affected parent
  - ➥ 25 - 40 % affected sibling
Early Detection of Learning Disabilities

History of:
- Speech delay
- Difficulty with rhymes
- Confusing words that sound alike
- Delay in learning letters
- Delay in learning phonics
- Difficulty with spelling
- Reading delay and difficulties

Since remediation is more effective during the early years, prompt diagnosis is essential. Early identification procedures are sensitive but not specific so tend to over-identify children with dyslexia. Evaluation for learning disabilities should be considered in all children presenting with school difficulties.

The Effects of Weaknesses in Oral Language on Reading Growth (Hirsch, 1996)

<table>
<thead>
<tr>
<th>Reading Age</th>
<th>Chronological Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2 years difference</td>
<td></td>
</tr>
</tbody>
</table>

Role of Education

- Elementary teachers and families are usually the first to suspect a learning disability.
- Assessing phonemic awareness skills in K & 1st grade can predict most of those who will have difficulty learning to read.
- Dyslexic children who receive effective phonological training in K & 1st grade will have fewer problems in learning to read than do children not identified until 3rd grade.

- 2 approaches can be utilized in the young underachieving child:
  - Response To Intervention (RTI) method: Allows earlier identification of LDs than the "wait to fail" approach.
  - Child is directly placed in an educational intervention program when difficulties arise.
  - Only children who do not show significant improvement with both the group intervention & second tier targeted intensive individual intervention will undergo a full educational assessment.

- Persistently poor academic achievement prior to referral & assessment.

Skilled educators, educational psychologists, or neuropsychologists use standardized evaluations to diagnose learning disabilities. Educational therapists use their professional expertise to design and monitor individualized remedial programs. Educational therapists recommend a variety of methods for a multisensory structured individualized language program.

Multidisciplinary Approach

- Comprehensive Medical & Psychological Evaluation & Treatment Team:
  - Primary Care Physician
  - Developmental Pediatrician
  - Pediatric Ophthalmologist
  - Pediatric Otolaryngologist
  - Pediatric Psychiatrist
  - Pediatric Neurologist
  - Pediatric Psychologist
  - Educational Psychologist
  - Neuropsychologist

Formal Assessment for Learning Disabilities:
- Cognitive ability
- Information processing
- Psycho-linguistic processing
- Academic skills
- Social-emotional development
- Adaptive components

Neuropsychologists can determine if any co-morbid conditions exist:
- ADD/ADHD
- Obsessive compulsive disorder
- Oppositional defiance disorder
- Anxiety
- Depression
Multidisciplinary Approach
Special Services Team & more
- Educational Therapy
- Speech Therapy
- Occupational Therapy
- Physical Therapy
- Educational Legal Advocate
- Schools specializing in Learning Disabilities

Overcoming Dyslexia
- The Individuals with Disabilities Education Act (IDEA) section 504 of the Rehabilitation Act of 1973 and the Americans with Disabilities Act (ADA) define the rights of students with dyslexia and other learning disabilities
- Individualized Educational Plan - I.E.P.

Overcoming Dyslexia - Treatment
- Advocate for the student
- Overcoming Dyslexia
- Life span perspective
- Remediations
  - Based on the specific needs of the child
  - Finding remediations is a dynamic process
  - Finding successful interventions become easier as the child's abilities and learning approach becomes clearer
  - Utilized in elementary school
- Accommodations & Modifications
  - Utilized in elementary school
  - Most important in secondary school & college

Overcoming Dyslexia - Treatment
- Requires early diagnosis and effective treatment of sufficient duration
- Individual or small group instruction
- Individualized multi-sensory (visual, auditory, tactile) reading and language program by an educational therapist or high quality instructor using a direct structural approach which sequentially teaches language skills

Overcoming Dyslexia - Treatment
- Phonics
  - Learning about and using different sound and letter combinations to decode words
  - The word provides clues to its identity
  - Letter-sound relationship
  - Vowel sounds
  - Complex letter-sound patterns (ex. shr, -ng, -dge, -ight)
  - Rules (ex. silent e rule)
  - Spelling

Overcoming Dyslexia - Treatment
- Fluency
  - Fluency is built on accuracy
  - Practice on materials that the student can already decode
  - Speeded word training
  - Guided repeated oral reading
  - 20 minutes of oral reading daily

Overcoming Dyslexia - Treatment
- Comprehension
  - Active reading
    - Prior to reading
    - Purpose for reading
    - Predictions
    - During reading
    - Who, what, where, when, and why
    - Visualization and predictions
    - After reading
    - Recall the sequence of events
    - Summarization and drawing conclusions

Other activities to improve language development
**The National Reading Panel**
- Promotion of evidence-based programs supporting phonics instruction since current research supports reading disorders as language disorders.
- Teaching phonics beginning in Kindergarten or 1st grade produces the best results.
- Rekindled the debate between phonics instruction, whole word, whole language, and a balance of all three.
- Need for extra time, quiet surroundings, repetition, and other mechanisms to help dyslexics decode the written word.

**Overcoming Dyslexia - Treatment**
- Accommodations & Modifications can include:
  - Extra time
  - Separate quiet room
  - Shortened assignments
  - Testing alternatives - oral instead of written tests
  - Computers
  - Spell checkers
  - Recorded books
  - Lecture notes
  - Tape recorders

**Resources For Parents**
- Education and Information on Learning Disabilities
  - International Dyslexia Association
    - [www.interdys.org](http://www.interdys.org)
  - Learning Disabilities On-Line
    - [www.ldonline.com](http://www.ldonline.com)
  - National Center for Learning Disabilities
    - [www.ncld.org](http://www.ncld.org)
  - Schwab
    - [www.schwablearning.org](http://www.schwablearning.org)
  - CHADD
    - [www.chadd.org](http://www.chadd.org)
  - "Overcoming Dyslexia" – Sally Shaywitz, M.D.

**How We Read - Visual Functions**
- Visual acuity
- Accommodation
- Convergence
- Saccades
- Fixations

**How We Read - Visual Acuity**
- Visual acuity: Clarity and resolution
- Refractive problems:
  - 10% of children aged 1-12 years old need correction of refraction error
  - Low Hyperopia is normal
  - Average refraction of children +1.50 - does not require treatment
  - Normally accommodation is used to "correct" farsightedness

**How We Read - Acuity Problems**
- Bilateral refractive disorders
  - Hyperopia (farsighted)
    - Correct if moderate (≥ +3.00 D) and near complaints
    - Correct if moderately-severe (≥ +4.50 D)
  - Astigmatism (blurring)
    - Correct if moderate (≥ +1.50 D)
  - Myopia (nearsighted)
    - Correct if ≥ -1.00 D
  - Anisometropia (asymmetric refractive error)
    - Correct if ≥ 1.00 D

**How We Read - Accommodation**
- A blurred image triggers adjustment of lens thickness to clear the image.
- The ability to alter and maintain the focal length of the eye to see things clearly at different distances.
- Greater accommodation is needed at near.
- Normally accommodation is used to "correct" hyperopia (farsightedness).

**How We Read - Vergence**
- The ability to keep the eyes aligned on a visual target to maintain fusion (binocular interaction).
- Convergence:
  - Turning the eyes inward.
  - Is needed for near reading.

**How We Read - Fixations**
- The ability to keep the eyes aligned on a visual target to maintain fusion (binocular interaction).
**How We Read - Vergence Problems**

- **Convergence Insufficiency**
  - Unable to fully and properly converge eyes at near
  - 2 - 8 %
  - Less common in children
  - May be more common in ADHD
  - Possibly secondary to medications

- **Treatment**
  - Make reading more comfortable but does not improve decoding or comprehension directly
  - Treatment can include:
    - Near point exercises taught in office and performed at home
    - Prism reading glasses
    - Minus-lens glasses

**How We Read - Saccades**

- **Saccades**
  - Small jumping eye movements
    - Forward saccades: 85% of saccades
      - Adult saccade average distance is 2 degrees (eight letters)
      - Saccade length is dependent on the ability to recognize letters, the difficulty of the text and the length of the word prior to the saccade
    - Backwards saccades: 15% of saccades
      - Half the distance of forward saccades
      - Increase with difficulty of the text
      - Used for verification & comprehension
      - Used to jump to the next line

**How We Read - Fixation**

- **Fixation**
  - Visual information is perceived during foveal fixation
  - Short words are read with 1 fixation, longer words with 2 fixations
  - 90% of our reading time are fixations
  - Duration of fixation 45-450 milliseconds
  - (average 180 milliseconds)

**How We Read - Saccades & Fixation**

- Child or early reader
  - Saccades: 1/2 length
  - More backwards saccades
  - Fixates: 2 times as long and twice as often
  - Dyslexic readers show saccadic eye movements and fixations similar to the beginning reader

**How We Read**

- **NOT involved in reading**
  - (under normal circumstances)
    - Vestibular System
    - Optokinetic System
    - Smooth Pursuit (tracking)

**How We Read**

- Children with dyslexia often skip words or lines when reading
- Some people call this word and line skipping an “eye tracking problem”
- Fluent reading is not “eye tracking”
- This type of “reading tracking” has nothing to do with either ocular smooth pursuit or horizontal saccades
- It has to do with comprehension
Believe it or not, you can read this...

I cdnuolt blviee taht I cluod aulaclty uesdnatnrd wht I was rdgnieg. The phaonmneal pweor of the hmuan mid. Aoccdrnig to rscheearch at Cmabrigde Uinervtisy, it deosn't mttaer in waht oredr the ltteers in a wrod are, teh olny  iprmoatnt tihng is that the frist and lsat ltteer be in the rghit pclae. Yeh and I awlyas thought slpeling was ipmorantt!

The following disorders have not been found to occur with greater frequency in patients with dyslexia compared to age-matched controls:
- Strabismus: including esotropia and exotropia
- Saccadic eye movements
- Pursuit eye movements
- Vergence amplitudes
- Vestibular ocular functions
- Dyskinetic nystagmus
- Relationship of ocular dominance to handedness
- Visual acuity
- Refractive error
- Color vision deficiency

No greater incidence of eye problems than their non-dyslexic peers
No specific eye-related defect causes dyslexia
While it is important to have effective eyesight and ocular motility in order to read with the greatest efficiency, these eye-related factors, even if defective, do not cause decoding difficulties.

If deficiencies in motor and visual-motor development or defects in eye movements caused perceptual impairment reading problems one would be at a loss to explain why:
- So many children with cerebral palsy, strabismus, amblyopia, nystagmus become good readers
- So many children with dyslexia play video games

PCP’s do not diagnose learning disabilities
Determine if medical, neurological, or behavioral problems exist that would affect the child’s ability to learn
Complete medical history and physical examination

Help parents decide if further evaluation is needed
Referral to appropriate educational evaluation, medical, psychological, and other services
Coordinate care between the family and other health care services
Distribute information on learning disabilities
Dispel myths surrounding learning disabilities
Encourage family to become the child’s advocate

Detection & treatment of vision problems
Children with diagnosed or presumed learning disabilities should undergo a comprehensive pediatric medical eye examination
As some of these children may also have a treatable visual problem along with their primary reading or learning dysfunction.

The ophthalmologist does not diagnose learning disabilities
Distribute information on learning disabilities
Discuss the lack of efficacy of vision therapy and other alternative treatments
Assist with referral to appropriate educational evaluation, medical, psychological, and other services
Pediatric Eye Evaluation

- Complete eye examination
  - Visual acuity: distance, near
  - Ocular alignment: distance, near
  - Convergence: Near point, amplitude
  - Accommodation: near point, amplitude, facility
  - Saccades & Smooth pursuit
  - Stereopsis (depth perception)
  - Visual field by confrontation
  - Color vision
  - Head position
  - External Ocular Examination
  - Dilated Retinal Examination
  - Cycloplegic Refraction

Important Ophthalmic Findings

- Refractive errors
- Amblyopia
- Strabismus
- Convergence insufficiency
- Accommodative insufficiency
- Nystagmus
- Abnormal head positions
- Down gaze problems
- Scotopic Sensitivity Syndrome
  - Scotopic Sensitivity Syndrome = SSS = Irlen Syndrome = Mears-Irlen Syndrome
  - Possibly due to Magnocellular Dysfunction
  - Supporters relate that the SSS affects 12-15% of general population and 45% with L.D.
  - Reading problems
  - Writing problems
  - General symptoms - headaches, nausea, fatigue, burning eyes, & tearing

Ophthalmic Treatment

- Significant refractive errors - glasses
- Strabismus - glasses and/or surgery
- Amblyopia - glasses, patching and / or penalization
- Accommodative insufficiency - glasses
- Convergence insufficiency (symptomatic) at home exercises and / or prism glasses
- Dry eyes - tear drops
- Ocular allergies - drops

Controversial Treatments - Silver

- The treatment is proposed to the public prior to research or before preliminary research has been replicated
- The treatment proposed goes beyond what research data supports
- The treatment is used in an isolated way when a multimodal assessment & approach is needed
- The treatment is commercially pushed before the research shows any support
- The treatment is advertised commercially when there is clear research evidence that it does not work

Irlen Lenses

- Helen Irlen proposed using colored lenses in certain types of dyslexics (1983)
- Tinted lenses are used because of presumed perceptual dysfunction causing visual distortion & sensitivity to particular wavelengths of light
- Lenses are now being used to treat a variety of non-ocular conditions: headaches, trauma, language deficits, autoimmune disease, & depression
- Irlen 1983 used term "scotopic sensitivity syndrome"
Tinted Lenses / Filters

- Color selection methods are highly variable
- Yellow, blue, precision tint method
- Woerz’s study - poor test-retest reliability
- Stone’s study - 25% needed their color changed within a year

Robinson - Literature Review - 1993
Problems with Tinted Lens Studies
- Poor planning of study
- Inadequate numbers
- Inadequate control group
- Anecdotal information
- Heightened expectations of the investigator
- Placebo effect

Robinson - Literature Review - 1993
Problems with Tinted Lens Studies
- Positive findings may have been confounded with other remedial interventions given at the same time
- Positive findings have not been sustained on retesting within same study
- Positive findings have not been reproducible in subsequent studies
- Variable positive findings
- Many studies showed no significant improvement

Wilkins - 1994
Double-blind placebo controlled study
- Placebo & tint groups - ( greater in tint group) SSS symptoms decreased
- Reading rate, accuracy & comprehension were not affected in either placebo or tint group

Robinson & Foreman - 1999
Placebo controlled study
- Control and 3 experimental groups placebo filter, blue tint & precision tint
- All 3 experimental groups showed improvement in SSS symptoms
- All 3 experimental groups showed improvement in reading accuracy & comprehension

Behavioral/Developmental Optometry

- Nearpoint stress model
- Binocular anomalies & refractive errors are not primary conditions
- Nearpoint stress causes under-accommodation & over-convergence
- Esophoria usually develops
- Sometimes exophoria or myopia develops
- Best treated “preventatively”
21-point examination compares to OEP “expected” values
OEP “expects” 6 exophoria @ near
Clinical value shows 1 exophoria
“Relative esophoria” is diagnosed
Presumed secondary to nearpoint stress
Treated with low-plus “Training/Developmental Lenses” “which help the visual system develop and mature normally”
Treated with behavioral vision therapy

Optometric Use of Training Glasses

Studies
- Greenspan - improvement in pencil & paper visual tasks & posture
- Keller & AMS - reviewed Greenspan’s data - Effect is insignificant
- Barry & Cochran - plano vs +.50 No significant difference in visual performance
- Wildsoet & Foo - plano vs +.50 - +1.00 No significant difference in reading comprehension

Beauchamp - Review 1986
- Overprescription of spectacles
- The justification and benefit for routine integration of costly spectacles into the program is unsupported

Jennings - Review 2000
- No convincing experimental evidence of any benefits from low-plus prescriptions

Olitsky - Review 2003
- No proof that there is a difference in focusing ability between normal and abnormal readers or that there is a correlation between reading performance and a need for glasses
- The very low power of the reading glasses or bifocals that are often prescribed throws further doubt on their usefulness in a child who will often show large amplitudes of accommodative ability

American Academy of Optometry
American Optometric Association
Policy Statement 1997
- “Vision therapy does not directly treat learning disabilities or dyslexia”
- “Vision therapy is a treatment to improve visual efficiency and visual processing, thereby allowing the person to be more responsive to educational instruction.”

Optometric Use of Training Glasses

Orthoptic techniques are used to change specific visual functions
- Convergence
- Accommodation
- Ocular motility
- Binocular fusion capability
Behavioral vision therapy is used to improve visual efficiency
- Improves scanning
- Improves locating

Behavioral VT treats visual processing deficiencies
- Visual spatial orientation skills
- Visual discrimination
- Visual memory & visualization
- Visual-motor integration
- Visual-verbal integration

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Behavioral optometrists spot and remedy subtle but serious vision problems before they can limit your child’s learning.”
Behavioral optometrists test for and prevent visual problems, and develop visual abilities using lenses and optometric visual training."
“Because most learning problems are visually related, correction of visual problems allows learning to occur more effectively. Use of lenses for near and optometric visual training is highly successful.”

Vision Therapy (Vision Training = VT)

Vision Therapy (Vision Training = VT)
Many students' visual abilities just aren’t up to the level of demands of learning situations in the classroom. Nearpoint visual stress is the result of sustained visual activities done at less than arm’s length. They adapt by becoming nearsighted, or by suppressing the vision of one eye.

Through visual training people are able to develop more efficient visual performance. Visual training also has proven to be a remarkably effective tool in helping people with learning-related visual problems. Dozens of experimental programs involving thousands of children and adults indicate that when visual skills are enhanced through visual training, learning is easier, reading levels rise, and in some cases, IQ scores have increased.

One visual skill builds on another, step-by-step as we grow. But many people miss a step, or do not complete a step, or must begin to perform school or other visual demanding tasks before an acceptable foundation of basic visual skill is in place. Even 1 or 2 deficient visual skills can produce enough strain and frustration to create a nonachiever. Many problems in learning to read and write are made worse by poorly developed visual skills. Vision problems do not “cause” learning disabilities. However, poor visual performance in the learning process, can impede remedial efforts.

Visual training appears ineffective since visual-perceptual problems do not underlie dyslexia then approaches designed to improve visual perception by training are misdirected. Visual perceptual training appears ineffective and that controlled evidence for treatment efficacy has been found to be contradictory, conceptually flawed, and scant.

Optometric Vision Therapy Studies
Sheryl Handler

2. UCLA Professor of Special Education
3. The necessary and sufficient components of vision training are unspecified thus untested
4. Little definitive evidence for its effectiveness
5. Paradoxical that VT is being recommended and used for a broad range of problems including preventative treatment

Optometric Vision Therapy Studies
Beauchamp & Kosmosky – Review 1987
- Eye movements are secondary to a brain processing dysfunction and are not the controlling factor in dyslexia or learning disabilities
- Since visual perceptual problems do not underlie dyslexia then approaches designed to improve visual perception by training are misdirected
- Visual perceptual training appears ineffective

Optometric Vision Therapy Studies
The Institute for Clinical Systems Improvement Technology Assessment Report on VT – 2003
- 2 Ophthalmologists & 2 Optometrists performed a thorough literature search and review on VT studies. Their conclusions include:
  1. No consistent scientific evidence supports behavioral vision therapy, orthoptic vision therapy, or colored overlays and lenses as effective treatments for learning disabilities
  2. Subsequent studies have been inconsistent and have failed to reproduce many of these findings

Optometric Vision Therapy Studies
- Childhood included in the studies have been diagnosed with learning disabilities using different criteria, may have been misdiagnosed, or may have additional conditions that may confound the findings
- During a course of VT, children are simultaneously receiving continued and even enhanced instruction in a standard or remedial educational setting, as well as undergoing natural maturational changes

Signs of Vision Problems
- Holding books very close
- Tilting head, moving head
- Blinking, rubbing, or burning
- Poor posture
- Poor attention
- Too much time
- Leaning on desk, skipping words
- Writing up or down hill, irregular letter or word spacing
- Reversing letters or words
- Driving small items
- Falls to recognize word in next sentence
- Poor comprehension
- Blurring or double vision
- Poor attention
- Poor posture
- Squinting
- Covering one eye
- Tilting head, moving head
- Holding books very close
Trials should include clearly defined patient populations, control groups, clearly defined treatment programs, relevant outcome measures, and adequate patient follow-up to determine whether any observed benefits are maintained.

Encouraged blinded, randomized, controlled trials of VT.

Small controlled trials and many case reports support the use of eye exercises in the treatment of convergence insufficiency. No clear scientific evidence published in the mainstream literature supporting the use of eye exercises in the remainder of the areas reviewed including learning disabilities and dyslexia.

Therefore the use of VT remains controversial.

Vision therapy / orthoptics was more effective than pencil push-ups or placebo vision therapy in reducing symptoms and improving signs of convergence insufficiency in children 9 - 18 years old. 8/15 = 53% “cured” with office-based VT.

Orthoptic therapy 
Taught in the office 
Carried out by the patient at home 
Reevaluated in the office on a monthly basis.

Near point convergence exercises
Push-up exercises using an accommodative target of letters, numbers, or pictures
Push-up exercises with additional base-out prisms
Jump to near convergence exercises
Stereogram convergence exercises
Recession from a target

Intensive office based vergence / accommodative and home reinforcement therapy 75%
Home pencil push-ups 43%
Home computer vergence therapy 33%
Placebo vision therapy 35%
In reducing symptoms and improving signs of convergence insufficiency.

Both intensive office-based VT and home-based orthoptic treatments are effective.

Both intensive office-based VT and home-based orthoptic treatments are effective.
Optometric Vision Therapy Studies

UK College of Optometrists - AJ Jennings - Review of VT Studies - 2000
- Evaluation of the theory and practice of behavioral optometry
  - Found methodological & statistical weaknesses
  - Questioned whether improvement on the training task transfer to routine activities

Conclusions:
- The merits of VT are extremely difficult to assess
- There is a lack of controlled studies to support behavioral management strategies

UK College of Optometrists - BT Barrett - Review of VT Studies - 2009
- Positive evidence exists for:
  - Convergence insufficiency
  - Vision rehabilitation after brain disease / injury

Conclusions:
- Continued paucity of controlled trials to support behavioral optometric approaches
- A large majority of behavioral management approaches are not evidence-based and cannot be advocated
- Most behavioral optometry techniques are to be considered unproven until more rigorous trials are undertaken

Problems with Vision Therapy Studies
- Poor planning of study
- Inadequate numbers
- Inadequate control group
- Anecdotal information
- Failure to "mask" the investigator
- Investigator with a vested interest in the result
- Old studies
- Many of the findings have not been reproducible in subsequent studies

Behavioral Optometric - Examples
- "Visual Information Processing Evaluation"
- Dr. X, BSc., OD, FAAO

Behavioral Optometric Testing
- Two broad visual skill categories
  - 1. Tests of visual efficiency skills
  - 2. Tests of visual information processing skills
  - 3. Other tests - reading
- DDT - Dev Dyslexia Test

Behavioral Optometric Testing
- 1. Tests of visual efficiency skills
  - Eye health
  - Visual acuity
  - Refractive status
  - Eye structure
**Behavioral Optometric Testing**

1. Tests of visual efficiency skills
   - Ocular motility - eye movement
     - Saccades & Pursuits
     - Vectograph
     - Developmental Eye Movement (DEM)
     - King-Devick (K-D) Test

2. Tests of visual information processing skills
   - Tests for deficits in visual analysis
     - Visual Discrimination / Visual Form Perception
     - Visual Figure Ground
     - Visual Closure
     - Gardner Test of Visual-Perceptual Skills (TVPS-II)
     - Visual Memory / Visual Intake
     - TPMT (visual memory) subtest and visual sequential memory subtest
     - Getman Memory Test

**Visagraph**

**Accommodation**

- Amplitudes
  - Monocular vs binocular
  - +/- 2 flippers

**Behavioral Optometric Testing**

1. Tests of visual efficiency skills
   - Binocular integration - eye teaming
     - Worth 4-Dot
     - Cover testing
     - Vergences - NPC
     - Accommodation - focusing ability

2. Tests of visual information processing skills
   - Tests for deficits in visual spatial orientation
     - Bilateral Integration
     - Chalkboard Circles
     - Directional concepts
     - Gardner Reversals Test
     - Piaget Left - Right Test

**Behavioral Optometric Testing**

2. Tests of visual information processing skills
   - Tests for Visual Motor Performance
     - Visual Motor Integration
     - Beery Developmental Test
     - Word Sentence Copy Test
     - Fine Motor Skills
     - Grooved Pegboard Test

**Bilateral Integration**

- Chalkboard Circles
What is Vision Therapy?

Is it new?
- Orthoptics
  - Said to be the origin of Vision Therapy
  - Javal (French Ophthalmologist 1890's)
- Behavioral Optometry
  - Sherffington (American Optometrist 1920's)
  - Optometric Extension Program - OEP
  - College of Optometrists in Vision Development - COVD

Conditions Targeted
- blurred vision at distance and at near
- poor concentration
- difficulty with reading
- diplopia
- ocular discomfort
- frontal headaches
- nausea
- eye strain
- loss of concentration
- heavy lid sensation
- general fatigue
- “pulling” sensation of the eyes

Vision Therapy
How are we involved?
- First or Second opinions
- Advice based on knowledge of the process

Learning Disabilities
- AOA disclaimer
  - vision training doesn’t treat learning disabilities BUT improves visual efficiency
  - so improves responsiveness to educational instruction
1. Visual efficiency skills training

- Ocular motility - eye movements
- Binocular Integration
- Vergences
- Accommodation

Ocular Motility - Eye Movement Training

- Improve monocular saccades first
- Steps
  - Corner saccades
  - Hart chart saccades

Training Techniques - Ocular Motility

- Space Fixator and Rotating Pegboard
- Marsden Ball
- Walking Rotator
- Marsden Ball and VMC stick
- Saccadic Fixator

Binocular Integration - Vergences

- Pencil Push-up
- Brock String Training
- Vectographic and Tranaglyphic Targets
- Aperture Rule Trainer

Cl Treatment

- Computerized Vergence System
- Brock String and Vectograms

Accommodation Treatments

- Near-Far Rock
- Mental Minus
- Lens flipper Rock
- Aperture Rule

2. Visual Information Processing Training

- Divided into 3 components
  - Visual Spatial
    - Bimanual Integration
    - Laterality
    - Directionality
  - Visual Analysis Skills
    - Visual Discrimination
    - Visual Figure Ground
    - Visual Closure
    - Visual Memory and Visualization
  - Visual Motor Skills
**Pediatric Ophthalmology**

**Sheryl Handler**

**Bilateral Integration Treatments**
- Jumping jacks + metronome
- Windshield wipers
- Angels in the snow
- Chalkboard circles
- Snap-lap
- Bean bag toss

**Laterality and Directionality Treatment**
- Simon Says
- Floor map
- Directional arrows
- Directionality for Numbers and Letters
- Chalkboard circles

**Visual Perception and Visualization Treatment**
- Parquetry Blocks
- Tachistoscopic Activities (Numbers, Letters, Words)
- Hidden image Games (Figures, Numbers, Letters, Words)
- Computer/PC Perceptual Games
- Golf Visualization
- Flip Forms
- Visual Coding Games

**Visual Motor Integration Treatments**
- Geoboard

**Vision Therapy Summary**
- Overlap in different areas
  - Occupational Therapy
  - Educational Therapy & Special Education
  - Education psychology
- Not evidence based treatment
- CI exception

**Dyslexia**
- No scientific controlled study has proven the efficacy of any of these treatments for dyslexia
  - Tinted spectacle lenses/tinted filters
  - Eye movement exercises
  - Anti-vestibular medications
  - Perceptual motor training
  - General motor development exercises
  - Biofeedback
  - Special diets
  - Mega-vitamins
  - Chiropractic manipulation

**Dyslexia - Summary**
- Avoid remedies that have inadequate scientific proof of efficacy involving
  - Eye exercises
  - Tinted filters or lenses

**Dyslexia - Joint Policy Statement 1998**
- American Academy of Pediatrics
- American Academy of Ophthalmology
- American Association of Pediatric Ophthalmology & Strabismus

*"The AAP, the AAO, and the AAPOS strongly support the need for early diagnosis and educational remediation. There is no known eye or visual cause for these learning disabilities and no known strong evidence for multidisciplinary evaluation and management must be based on evidence of proven effectiveness demonstrated by objective scientific methodology. It is important that any therapy for learning disabilities be scientifically established to be valid before it can be recommended for treatment."*
An Evidence-based Update on Myopia, and Interventions to Retard Myopic Progression

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3Duke-National University of Singapore Graduate Medical School, Singapore

A. Epidemiology
   1. Prevalence rates world-wide
   2. Recent birth cohort data

B. Classification
   1. Axial
   2. Refractive

C. Complications
   1. Direct economic and social burdens
   2. Ocular complications
      a. retinal detachment
      b. myopic macular degeneration/ choroidal neovascularization
      c. premature cataract
      d. glaucoma
      e. strabismus fixus

D. Risk Factors
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E. Hereditary Basis of Human Myopia
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   4. Identified genes
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F. Interventions
   1. Medication
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      b. Pirenzipine
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      b. Orthokeratology
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      d. Pin-hole spectacles
      e. Bates technique
   3. Other Techniques
      a. Under-correction
      b. Progressive addition lenses
      c. Part-time lens wear
   4. Myopic Strabismus Fixus- Esotropia and Hypotropia
      a. Surgical management
OMIC Workshop: Dissatisfied Patients Resources

NONCOMPLIANCE

AMBYLOPIA

TREATING EMPLOYEES
• Menke AM. Employees: Providing Medical Care, Services, or Products. http://www.omic.com/resources/risk_man/recommend.cfm#providing

VIOLENCE/HOSTILITY
• ECRI Physician Office Safety Guidelines (posted on AAPOS website)
• Sample policy for hostile/disruptive patients (see next page)
  o Provided courtesy of Ophthalmic Consultants of Boston
Policy: Disruptive or Dangerous Patients

OMIC thanks Ellen Adams, Compliance Officer of Ophthalmic Consultants of Boston (OCB), for developing and allowing OMIC to use and distribute the OCB policy and procedure on handling disruptive or dangerous patients.

This sample policy and procedure assumes there is a practice compliance officer and compliance committee. However, in some offices the manager or the physician will be the de facto “compliance officer”. Therefore, it is assumed that duties and responsibilities in the sample policy will be assigned to meet the needs of the practice.

Policy Name: Disruptive or Dangerous Patients

Purpose: To educate and protect staff members from patients who behave in a disruptive or threatening manner.

Staff Affected: All Doctors and Employees

Introduction: Our practice has a mission of providing high quality eye care in a caring setting. In order to achieve our mission, the managers of our practice strive to maintain a caring and safe clinical environment. Management cannot completely control patient behavior. This policy addresses those rare instances when patients behave in an inappropriate way that disrupts a positive clinical setting.

Procedures:

For All Situations:
1. A quiet area needs to be used to speak to a disruptive person. Ideally a conference room or other common area can be used; if not, a counseling room, lane or administrative office may be used. Managers should plan in advance what room can be used for this purpose.
2. The manager involved should always consider his/her safety, and either leave the door open or have a second person (HR, manager, director or Compliance Committee member) present during interviews.
3. The manager should never position him/herself so the angry patient can block the door from the room.
4. If there is no security personnel at the location, calling 911 in a dangerous situation is the correct response to protect yourself, other staff members, and other patients.

Disruptive Patients
1. If a patient is being disruptive by raising his/her voice or using profanity, the staff member will speak in a calm voice and attempt to determine the cause of the patient’s behavior.
   a. If a patient is on the telephone and behaving inappropriately, the staff member should attempt to determine the cause of the anger. The staff
member can advise the patient that the call will be terminated if the patient continues to use inappropriate language. After warning the patient, the call should be terminated if the inappropriate patient behavior persists.

b. If the patient is in the clinic, the staff member should call a manager to assist as soon as possible. The manager should escort the patient to a quiet area to discuss the problem, as long as the patient is not behaving in a threatening manner (see #4, below).
   i. If the patient does not become calm, the manager should ask the patient to leave the clinic for the day, and politely suggest they resolve the issues then next business day.

c. If a patient mails a letter of complaint to the practice, it should be forwarded to the Compliance Officer. The Compliance Officer will assume responsibility for follow up.

3. The manager will contact the patient the following day to attempt to resolve the issue. If on follow up call the patient is still behaving unreasonably, the manager will terminate the call after advising the patient that someone will contact him/her within the week. The manager will then contact the Compliance Officer. The Compliance Officer will pull the patient chart, interview all staff members involved in the incident, and assume control of the situation.
   a. If the patient has no history of unacceptable behavior and the incident was patient-induced (e.g. unprovoked patient insulting a staff member appearance, making unreasonable statements regarding staff members, etc) the Compliance Officer will send a letter to the patient by regular mail. The letter will request the patient refrain from using inappropriate language while in the clinic. (OMIC website may have sample letters.)
   b. If the patient behavior seems to have resulted from a practice policy, billing statement, or employee behavior, the Compliance Officer will call the patient and attempt to resolve the issue. If the patient is not immediately available by telephone, the Compliance Officer will send a letter to the patient with an apology and a proposed resolution, as appropriate.
   c. If the patient continues to behave unreasonably after the manager and Compliance Officer's attempts to resolve the underlying issue(s), the Compliance Office will discuss discharging the patient with all practice doctors involved in the patient’s care. (OMIC website may have sample letters.)

4. In the unlikely event that a patient uses verbal or actual threats of physical harm, or is behaving in a completely irrational or unreasonable manner, the staff member must be careful to not be hurt.
   a. DO NOT approach the patient. Keep a safe distance. If in a confined area (e.g. exam lane), leave the room as soon as possible and contact a manager.
   b. Speak in a calm voice. DO NOT argue with the patient. Do not threaten the patient, or make any sudden movements.
c. Signal to a coworker to call 911 immediately. If a coworker is not available, tell the patient that you are leaving to get a manager. Call 911 as soon as possible.

d. If any weapons are ever displayed, stay calm and be sure an observer calls 911 immediately. Do not make sudden moves.

5. A Variance Report for any incident involving disruptive patient behavior must be completed and forwarded to the Compliance Officer as soon as possible.
   a. The Compliance Officer will contact the practice malpractice insurance company for guidance when necessary.

**Conclusion/Outcome:** A safe environment for all staff members and all patients of our practice, where mutual respect is recognized and supported by management, staff and patients.

For Use by Compliance Committee Only:

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Physician Office Safety Guide
Editorial and Technical Staff

Publisher: ECRI

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Preface

Drs. Marcus Welby and Kildare have, alas, gone the way of the dinosaur. The traditional, independently operated, fee-for-service physician office is undergoing a radical transformation. While many independent physician practices still exist, they are rapidly being supplanted by complex legal entities; for example, integrated delivery systems owned by hospitals or healthcare systems. But having an effective safety program is just as important for the physician office owned by a major university-based medical center as it is for a private practice operated out of the home.

Safety management has not always enjoyed the prominence it deserves in today's physician offices. Herein lies the challenge: to implement or improve your safety management program at a time when healthcare technology, regulations, and the delivery of services is rapidly changing. To do any less is to do a disservice to your patients, your staff, and the medical profession. Promoting safety is a task in which everyone reaps the benefits, directly or indirectly.

The goal of this Special Report is to present critical office-safety-related information in a useful and practical manner. It can be a useful supplement to the parent organization's current safety management program, or it can serve as a comprehensive safety management resource for the independent office. It is designed to provide any physician office with the necessary practical tools to implement a broad-based safety management program, focusing on key safety issues regardless of who owns the premises and what type of legal relationship the physician(s) may have with other entities.

Each chapter is devoted to a specific area of physician office safety management. And, where useful, we have provided tools to facilitate the implementation of a safety program. These tools range from Self-Assessment Questionnaires designed to provide a quick, yet comprehensive, way to evaluate current practices to tips and checklists that give easy-to-follow advice that can readily be implemented. The Special Report also includes glossaries, sample policies and procedures, and multiple Resource Lists that contain organization names, addresses, phone numbers, and Web sites to contact for further guidance.

We hope that this Special Report will serve as the cornerstone of your office safety program. Its presence alone will act as a reminder of the importance of safety management. Just as physician offices' composition and area of focus will vary, so will the applicability of this Special Report. One size does not fit all, and there is a need to customize your safety management program to meet your office's unique needs. The fabric of this Special Report is designed to afford you that flexibility while maintaining a common thread of minimum criteria. To the extent that this is useful in promoting staff and patient safety, this Special Report will have achieved its goal.
Identifying Potentially Violent Patients

Office staff can protect themselves and their coworkers by identifying potentially violent patients before a dangerous situation erupts. There are at least five different types of cues as to which patients may become violent: historical, diagnostic, psychiatric, behavioral, and chemical dependency.

Historical Cues

The best predictor of violence is a past history of violence, and those patients’ records should be flagged in an obvious place. Patients exhibiting certain signs of instability upon entering the office are likely to become violent later. Signs include excessive restlessness and agitation; tension and anger (e.g., clenched fists and jaw); loud or profane speech; argumentative, defiant attitude; refusal to follow directions; threatening behavior; paranoia; and defensive behavior when someone approaches.

Diagnostic Cues

Diagnostic cues are most familiar to clinical staff, especially those with training in psychiatry. People with head injuries or central nervous system infection may exhibit severe behavioral changes as a result of brain swelling. Patients who experience a seizure may demonstrate an altered level of consciousness immediately after the seizure, including disorientation and combative behavior, before returning to a normal level of consciousness.

Some systemic disorders are associated with violent tendencies, such as electrolyte imbalance, anemia, and endocrine disorders involving the thyroid, adrenal dysfunction, diabetes, uremia, and hepatic encephalopathy. Toxic levels of some medications (e.g., anticholinergics, anticonvulsants, digitals, steroids) and chemicals (e.g., heavy metals) have also been linked to violent behavior. Certain types of neurologic conditions also may make a person more inclined to act violently; these include head trauma, central nervous system infections, epilepsy in its ictal and postictal psychotic forms, degenerative dementias, and cerebrovascular disease.

Psychiatric Cues

Many psychiatric conditions can make a person more prone to violent behavior. A previous history of assault, substance abuse, or organic brain syndrome is often an indicator of an assaultive personality. However, studies suggest that a small number of patients are responsible for a majority of assaults on staff. Factors noted to trigger violent outbursts include denial of services and limiting eating, drinking, or tobacco use.

The following types of patients may have a tendency toward violence (note that all mental disorders mentioned are clinical assessments that must be made by a qualified individual):

- Mentally disoriented patients, who are sometimes frightened and irritable.
- Psychiatric patients in the process of becoming “deinstitutionalized,” who may present a violence risk for home healthcare staff required to make visits to care for them.
- Antisocial/borderline personalities, who are often irritable, aggressive, and likely to destroy property.
• Narcissistic individuals, who often appear to be normal but may become violent when their beliefs are challenged.
• Paranoid people, who, although usually quiet, can become violent when things do not go as they would like or if they believe they are being discriminated against.

Behavioral Cues

Behavioral cues — changes in the observable behavior of a patient — are indicators of impending acting out by a patient and require immediate intervention. These cues are similar to those for office staff exhibiting violent tendencies (e.g., paranoia, obsession with violence, veiled threats — see list on pages 270-1). All too often, office staff ignore behavioral cues, thinking the patient is in a bad mood or just needs to “get it out of their system.” Signs of paranoia and threats toward other patients or staff are not likely to stop without intervention.

Dependency Cues

Angered or intoxicated patients may threaten staff. One-third of all perpetrators of violence are alcoholics.22 Crack cocaine use and (to a lesser extent) cocaine use account for the second major cause of drug-related violence.23 Heroin use is not usually associated with violent outbursts except in the withdrawal stage. Patients requesting specific medication, usually for pain, may be exhibiting drug-seeking behavior. If their requests for drugs are denied, such individuals may become belligerent. Even abusers of prescription drugs such as pain medications or minor tranquilizers have an increased potential for violence. Appendix 6A presents sample policies and procedures for dealing with alcohol- and drug-impaired patients.

Training

Training and education are good ways to help office staff defuse violent situations and reduce injuries. Some violence management training should be provided to all staff at orientation, even if the office has a low risk of violence. The box on page 274 can be used as a handout to office staff. This training should include the following:

• What to do in the event of a violent incident, including:
  — Event reporting procedures
  — How to respond to alarms
  — What assistance is available if an incident occurs
• What the causes are and how to recognize escalating violent behavior
• What to do if outsiders are seen in the “wrong” areas of the office
• What to do if a colleague’s behavior suddenly changes
• How to prevent or defuse volatile situations

• How to interact with hostile individuals or colleagues
• Why it is important to inform the appropriate party in the office of any problem with domestic parties
• How and where to get medical treatment and psychological counseling after a serious incident

Physician offices at higher risk of violent incidents may want to add the following to their general orientation training:

• Multicultural diversity (being sensitive to different cultures’ beliefs, traditions, and languages)
• Safe methods of restraint application
• Contingency plans for treating hostile patients
• Contingency plans for emergency evacuation in the event of a high-risk violent situation
• Common-sense reminders, such as:
  — Office staff informing others of their whereabouts when they plan to be alone in an area
  — Exercising extra care in elevators, stairwells, and unfamiliar residences, if applicable
  — Checking cars before entering
  — Parking close to the building at night
  — Carrying handbags under the arm and not across the chest or over the shoulder

All training should be provided during normal working hours and should be convenient for all employees. The needs of employees who cannot read or speak English or are illiterate must also be considered. Local police may be willing to conduct security training (e.g., self-defense) for staff. Records of training program contents and a list of attendees should be kept.

Violence De-escalation

Many facilities are also implementing management of assaultive behavior, professional assault response, or police department assault-avoidance training, hoping to defuse situations before they become violent. Again, this training should be conducted by qualified trainers. Some local police or insurance carriers will perform this training for free. (See box on page 274.)

Postviolence Support

The following eight steps should be taken after an event:
1. Care for the victim(s).
2. Clean the area. Do not allow people back into the area until it is safe.
3. Debrief employees involved in the event.

(continued on page 275)
Aggressiveness De-escalation Training Checklist

Identifying Potentially Violent Individuals

The following may be attributes of a violent person:

- Talks and complains loudly, uses profanity, or makes sexual comments
- Demands unnecessary services
- States that she or he is going to lose control
- Paces rapidly
- Appears tense and angry
- Challenges authority
- Appears intoxicated
- Has a history of violence
- Has had multiple stressors, such as divorce, death in the family, or financial problems
- Continually uses excuses and/or blames others
- Is exhibiting or doing any of the following:
  - Flushed face and/or sweating
  - Twitching face and/or lips
  - Shallow breathing
  - Keeping head down
  - Furrowed brows
  - Pacing

Dealing with Violent Individuals

- Do not argue with or provoke a hostile person. Some eye contact may be advisable, but avoid staring, which could be interpreted as confrontational.
- Keep out of the person's personal space. Maintain a relaxed, attentive posture. Keep at least two to three arms' lengths away, and do not get backed into a corner. Leave room for escape.
- Do not approach with hands on hips, arms crossed, or any other defiant posture.
- Acknowledge the individual's feelings, and show a desire to help, but do not accept blame.
- Do not reject the person's demands immediately, act impatient, or make him or her feel foolish.
- Do not treat the situation trivially.
- Clarify messages. Ask for specific responses from the person.
- Do not bargain or make promises you cannot keep.
- Establish ground rules, and describe the consequences for breaking the rules.
- Permit verbal venting when possible.
- Ignore challenge questions, and do not overreact.
- Do not make personal comments. Comment only on the person's behavior.
- Speak in a firm tone, using short, direct sentences. Move and speak slowly, quietly, and confidently.
- Do not act in a cold or condescending manner.
- Touch the person only when necessary and only after stating you are going to do so.
- Do not try heroic actions to subdue the person.
- Separate the person from other patients, if possible.
- Do not be rude to gang members; they may think being asked to sit down or to lower their voices is disrespectful.
- Develop an emergency code to trigger a rapid response (e.g., saying, "code green")

If Violence Does Erupt...

- Know how to protect yourself (e.g., block a punch, break a chokehold). Assume a self-defense stand (leaning 45° toward the person, feet apart at shoulder width, weight evenly distributed, knees slightly bent, arms at sides, hands open). Do not become the aggressor.
- Stay out of range of a violent person's hands and feet.
- Call the designated emergency code.
- Do not attempt to subdue the person yourself.
- Keep other patients away from the incident.
- Debrief staff on all violent episodes to better plan for the future and to calm employee apprehensions.

Sources


(continued from page 273)

4. Report the event.
5. Investigate the event.
6. Help fill out Workers' Compensation claim forms.
7. Provide emotional support.
8. Prepare for union involvement, if applicable.\(^{24}\)

Immediately following an event, and after the victim(s) have been cared for, the area should be assessed for any damage and to make sure it is secured. Staff and others who witnessed the event should be questioned. Once an initial investigation is complete, the event report must be completed, documenting who was involved; what happened; where, when, and how the event occurred; and contributing causes.

**Event Reporting**

Every security management plan must identify an individual responsible for filling out event reports, and employees should be taught the event reporting process during orientation. All events should be reported first to the affected employee's supervisor, who will determine what to do next. (Chapter 1 provides more detail on the event reporting process.)

If further action is necessary, legal counsel or the parent facility's risk manager (if applicable) may need to be involved.\(^{25}\) When an office employee is at fault, it is crucial that some sort of disciplinary action be taken, although immediate termination may not be necessary and in fact may conflict with procedures worked out by a union in a collective bargaining agreement.\(^{26}\)

The office must also report any incident resulting in a fatality or the hospitalization of three or more staff members to OSHA within eight hours. While all violent acts against office staff are recorded in an event report, not all staff injuries from violent acts are recorded on the OSHA Injury and Illness Log. For example, violence perpetrated by a family member is personal and is not usually recorded on the Injury and Illness Log unless the worker's employment contributed to the act.

If a staff member perceives a certain behavior as threatening, he or she should report it to a supervisor or other designated individual. Even with a goal of zero tolerance, sometimes it will be a judgment call as to whether a particular behavior is threatening (e.g., verbal intimidation, harassment). As a result, many violent acts go unreported. Employees may fear supervisors will blame them for, or minimize the seriousness of, the incident; they may also be reluctant to cause tension or may blame themselves. To reduce these fears, the office policy should state that discrimination against victims of workplace violence is not permitted and that all policies concerning violent incidents will be applied consistently to all victims.\(^{27}\)

Keeping accurate event reports enables offices to track trends that can be reviewed annually to identify areas in which most violent incidents are occurring and the types of perpetrators responsible for these incidents. This allows the office to revise its violence prevention program accordingly.

Violent incidents should be reported to the police, as appropriate, and the event report should document the content of communications with law enforcement. The police will make the initial determination on whether criminal prosecution is necessary. Victims should be reassured that there is no punishment for filing a report even if the assailant is their supervisor.

After the event has been reported, it should be investigated. Failure to thoroughly investigate an incident may be perceived by employees as the office taking a lax attitude toward employee safety.

**Workers' Compensation Claims**

Depending on the nature of the injuries, work time lost, and regulations in particular jurisdictions, employees injured during incidents may be eligible for Workers' Compensation. The office should inform injured employees of their right to be compensated and provide them with the proper forms. While employees will generally receive Workers' Compensation, other potential victims will not and may file a civil action against the office. (Office staff may also sometimes file such actions based on various other theories of law.) The better its records are, the better the office's ability is to protect itself in such a situation.

**Counseling**

Providing emotional support is important after a violent incident has occurred. The emotional impact may be more traumatic than any physical injuries.\(^{28}\) It is not uncommon for employees to fear returning to work after a violent incident or to feel incompetent because they were unable to prevent the incident. In extreme cases, employees may even experience posttraumatic stress disorder—a pervasive, chronic, emotionally painful, and life-altering ailment.\(^{29}\)

Certified employee assistance professionals, psychologists, psychiatrists, clinical nurse specialists, or social workers can provide this counseling, or the office can refer staff victims to an outside specialist. Peer counseling and employee support groups are also helpful.

As part of postviolence support, the office may want to consider giving victims the opportunity to transfer to another area, if possible. Legal advice regarding pressing charges, if appropriate, should be provided.
Mastering the Media: Are Reporters Friend or Foe?
The participant acknowledges that all ideas, concepts and models used in this manual are trade secrets of Spaeth Communications, Inc. and have been developed through the expenditure of substantial time, effort and creativity. The participant agrees that the system of ideas, concepts, and models will be held in confidence and will not be disclosed to anyone.

The participant acknowledges that the graphic and written materials used in this manual are also trade secrets of Spaeth Communications, Inc. that have been developed through the expenditure of substantial time, effort and creativity. The participant agrees that the graphic and written materials will be held in confidence and will not be disclosed to anyone.

The participant acknowledges that the graphic and written materials are copyrighted by Spaeth Communications. The participant agrees not to make copies of any of the copyrighted materials for any purpose whatsoever without the written consent of Spaeth Communications, Inc.
Firm Profile

Spaeth Communications, Inc. is recognized as a pioneering leader in the communication field. The firm was the first to create a business model for communication and to offer a definition of good communication. Spaeth has developed an approach that analyzes and details techniques for influencing what a target audience will remember.

The firm, with representatives around the country, is known for innovative training and strategic consulting. Founded in 1987, Spaeth has worked on a wide variety of engagements, ranging from improving the use of proactive communication to internal and external audiences to challenges and crises.

Spaeth has experience in handling a broad range of issues for clients including restructurings, plant and hospital closings, downsizings, labor negotiations, commercial disputes, acquisitions, mergers, product tamperings, industrial accidents, bankruptcies and key personnel changes. Their client base is equally diverse, covering service and manufacturing companies, technology and Internet companies, various trade associations, financial institutions and government agencies.

CEOs and top corporate officers from around the world seek the company's help to make communication a strategic tool. Spaeth's approach offers our clients a competitive edge because we show them how to improve investor relations, employee communication, contact with clients and customers, regulators and other key audiences.

The individuals at Spaeth are award-winning, creative thinkers with an exceptional success record on behalf of their clients. They take pride in their responsive, cost effective, dedicated relationships with clients. Spaeth professionals speak frequently to business and companies and at the nations top business schools.
Merrie Spaeth
Merrie Spaeth has a unique background in media, government, politics, business and the entertainment industry. She is a pioneer in communication theory and executive training, and acknowledged as one of the preeminent crisis management strategists in the country.

Merrie founded Dallas-based Spaeth Communications, Inc. in 1987. The Firm provides communication training and consulting for a wide range of companies and institutions.

Her government experience began as a White House Fellow assigned to FBI Director William Webster. From the FBI, she served two years at the Federal Trade Commission as Director of Public Affairs, and in 1984, President Ronald Reagan named her Director of Media Relations at the White House. During her tenure, Merrie introduced satellite communications to the White House, and launched the electronic White House News Service. One newspaper headline said she “Took the White House into the Space Age.”

She has worked in every area of print and electronic media. She’s been a radio and television talk show host, a producer for ABC’s “20/20”, and a reporter and writer for the Philadelphia Inquirer, the New York Daily News, Family Weekly, and many other magazines and papers. She currently writes a regular column for D CEO magazine. Most of her articles are available at www.spaethcom.com.

In the entertainment field, Merrie was honored as “Filmdom’s Famous Five” in the 1960s for her achievements as an actress in television and film. Her best known work is “The World of Henry Orient” with Peter Sellers and Angela Lansbury.

Merrie has received many honors. She is a cum laude graduate of Smith College and she holds a Masters degree from Columbia Business School. She teaches at the Cox Business School at Southern Methodist University. Merrie is on the Board of the Dallas Symphony Orchestra and the Children’s Eye Foundation. Merrie’s affiliation with the Children’s Eye Foundation comes naturally as she is the granddaughter of ophthalmology pioneer Dr. Edmund B. Spaeth, the daughter of ophthalmologist Dr. Philip G. Spaeth, and the niece Dr. George L. Spaeth, head of glaucoma research at Wills Eye Hospital.

Her firm commits between five and ten percent of its time each year to pro bono training for civic and charitable organizations.
Influence Model

**FORMAL NETWORKS**

**INFORMAL NETWORKS**

Target Audience
- customers
- prospects
- investors
- vendors
- regulators
- employees

**CONTROLLED VEHICLES**
- advertising
- brochures
- memos
- direct mail
- website

**MEDIA**
- local
- national
- international
- trade industry
- electronic

**GROUPS**
- geographic
- person to person
- profession
- employee
- special interest

message
You
Implications of the Spaeth Influence Model

The Influence Model developed by Spaeth depicts the routes of Communication. A brief description of the model follows:

The formal route is any information the target audience perceives that you control including marketing materials, advertising, collateral, internal publications, annual reports and so on.

The informal routes of communication are those the target audience perceives that you do not control. The two most powerful, credible informal routes for communicating your message are through the media and through the various groups in which the target audience congregates, including person-to-person communication.

Today, a sophisticated communication program should carefully identify the constituencies, examine the routes (formal and informal) available to reach them, and look at the vehicles currently being used and the frequency of their use. A proactive strategy using all routes will maximize the effectiveness of your communication. The idea of message alignment or consistency of communication along all three networks is crucial.

The model has vast implications for both your professional and private worlds. If you can execute and incorporate it into your communication plan on a daily basis, you will achieve a competitive edge that few executives and companies obtain.
Examples of How Communication is Changing

**New channels:** in 2007, a physician who teaches cardiology at Temple University Medical School realized that the two traditional methods of teaching students how to accurately diagnose heartbeats were out-of-date. (Traditionally, students followed a physician around a hospital with a stethoscope or went to the library and checked out 8-Track tapes. He loaded all the heartbeats onto an iPod – with dramatic results. The time required to master the heartbeats dropped from months to minutes and the correct diagnosis leaped from ten to twenty percent to eighty to ninety percent.

*Articles:*
- “iPods help docs improve stethoscope skills,” March 29, 2007, Temple University

**Twitter:** have you “tweeted” today? Invented in 2006, Twitter’s use has soared in 2008.

*Article:*

**Instant Connection:** “Real time communication tactics, such as Twitter, are providing technology-focused companies with a way to quickly address consumer concerns,” “Instant Connection,” *PR Week*, Nov. 3, 2008

**Blurring:** electronic and print are blurring. In June, *Time Magazine* revealed that they are routinely videotaping interviews and posting the video portions on their website. Reporters at many print publications are also being issued video cameras with the same instruction.

*Article:*

**Blurring:** internal and external communications have been completely separated, but, today are “blurred” more than ever, particularly for adverse news.

*Article:*

**Blogs:** a man in China waited three months for delivery of a Toyota and after three months got tired of waiting and posted a virulent anti-Japanese ranting on a blog. A Beijing-based firm regularly searches 500,000 online forums, spotting the complaint and brought it to Toyota’s attention.

*Article:*
- “Inside the War Against China’s Blogs,” *BusinessWeek*, June 23, 2008

**Video:** “Video” or “Person-to-person/Video enabled” communication has changed communication. You’ll be expected to be adept at using these channels and in managing them.

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Good / Bad Word Exercise

<table>
<thead>
<tr>
<th>GOOD</th>
<th>BAD</th>
<th>JARGON (AVOID)</th>
</tr>
</thead>
</table>

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Memory Tips

1. **Identify All Your Target Audiences**
   - Identify not only those who hear your remarks directly from you, but those who may hear your remarks from someone else. Consider what key words or short phrases that you would like to be remembered and repeated.

2. **The Key Word Exercise**
   - It’s useful to begin the thought process in preparing your remarks by creating a list of key words and phrases. Analyze those “good” or positive words that you want an audience to identify with your trade. But, also consider those “bad” or negative words that you do not want your audience to associate with you or repeat. Make sure that your “good” word list includes words or messages that counter those negatives. Every profession or trade has its own language, jargon and acronyms. Avoid jargon as you would negative words.

3. **Using Numbers Or Statistics**
   - Reporters love numbers. Numbers appear to be real information. Statistical information can help document or prove your point. But beware; make sure you put all numbers and statistics in context. Also, too many numbers are confusing.

4. **Making Predictions**
   - People are fascinated with predictions. As an expert, your opinion on trends, future conditions or actions are respected and valid.

5. **Use Verbal Cues**
   - Verbal “cues” highlight your comments and alert your listener to an important message. They help frame your response as a quote.
Structuring Your Remarks

Effective communication begins with the headline and moves upward.

**Headline:**
Rethink the way you organize your information. Begin by reducing the essence of your message into short, bold, simple “headlines” and incorporating your positive words. The headline prepares the listener for the information that is to follow. This follows the old journalism adage, “tell them what you’re going to tell them, tell them, tell them what you told them.”

**Proof:**
Every headline must be followed with evidence that makes the message credible and meaningful to a targeted audience. A proof includes:

- **Informational**
  - **Facts:** a real ‘fact’ or observation
  - **Statistics:** made relevant to the listener

- **Motivational**
  - **Examples:** identifies a target group
  - **Anecdotes:** story about a person, company or incident
  - **Quotes:** from any expert, individual, study, article, etc.
The Art of the Acknowledgment™

The role you assign yourself determines how you communicate. Many people listen to a question or comment and accept the framing or parameters and the topics raise.

You must “acknowledge” hearing the other person, but you need not accept the framing or parameter of the question.

NEVER ignore a question or comment.

Bad Example:

Q: “Are we going to have another round of layoffs?”
A: “We have to stay competitive.”

The “Acknowledgment”™ is your technique to meet the listener’s needs, meet your needs and put you in control of the communication.

You must “Acknowledge”™ that you heard every question or comment, but you can pick any acknowledgement phrase you wish.

An “Acknowledgment Phrase”™ is:
• Short
• Truthful
• Conveys that you heard the question

These acknowledgment phrases™ should handle most questions.

“Yes” “Sometimes”
“No” “Maybe not”
“Not necessarily” “I hope so”
“It depends” “I hope not”
“Yes and no” “We’re trying”
“On the contrary” “Let me put it in perspective”
“Of course” “It’s not quite that simple”
“We can’t predict” “Let me get back to that”
“I heard that” “I have not heard that”
“Before I tackle that…” “In part”
“Just a moment please, let me finish”
“Let me get back to that in a moment…”
“I’d like to go back to that earlier question for a moment…”

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Storytelling Basics

Tip 1: Focus on the Reader

The most memorable anecdotes/stories:

1- Are short...tell one story about one person/family/business/event

2- Are relevant to the reader

3- Makes the reader think “that could be me”

The ultimate goal is to have the reader identify with the story

Tip 2: Regular stories vs. Strategic stories

Regular stories have:
- Characters
- Plot (conflict?)
- Dialogue (who said what to whom?)
- Details (color, interest)
- A theme
- A point or moral
- Resolution?

Strategic stories:
- Have a name
- Are brief (can you repeat them?)
- Make you want to share them
- Are cost effective
- Frequently have humor
- Are placed on the right (Informal) side of the Influence Model

A good story will have elements of a regular story, but writers should review and include the elements that go into creating and making these stories strategic.

Tip 3: Stories create pictures

“A picture is worth a thousand words.”
Elements of Style

1. **Eye Contact**

Eye contact engages the speaker with the listener. Good eye contact establishes trust and determines likeability. If you don't establish eye contact, how will you know if they are listening and how can you gage their comprehension and response? Eye contact is not looking “out” at the group or across a room. Eye contact is your technique for turning group communication into person-to-person communication.

2. **Facial Expression**

Facial expressions convey your self-confidence, comfort, and enthusiasm.

3. **Voice**

A speaker’s voice should mimic its natural delivery with variety in range (sometimes called pitch or spectrum), pacing, and pausing.

4. **Posture and Body Movement**

Use your entire body in your presentation delivery with hand gestures and body movement to support your comments, not detract or distract.

5. **Gestures**

Hand gestures punctuate your language. Any problems with the pacing of your presentation will be eliminated by adding gestures for emphasis. Gestures are also an appropriate way to channel nervous energy, and they make your remarks more visual and interesting. Gestures convey energy and energy conveys conviction.

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