The Hypertensive Phase

- Jeffrey Freedman MB.BCh. PhD, FRCSE., FCS(SA).
- Professor (HS) Emeritus Dept.

  Ophthalmology, SUNY, Brooklyn, New York.

Conflict of Interest Disclosure

- I have the following potential conflict of interest to report:

- Travel Support By Katena Products Inc.

Hypertensive Phase

- What is **“the hypertensive phase”** and how did it come about?

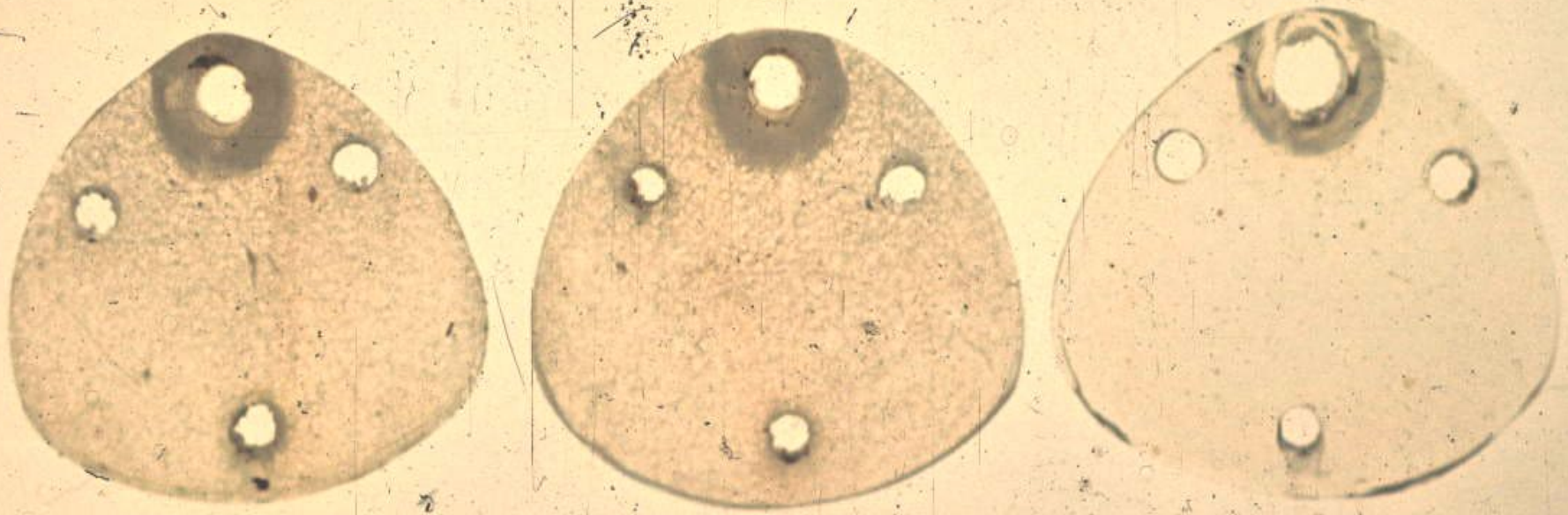
History of term "Hypertensive Phase"

- Dr. Epstein 1959 reported that fine polypropylene tubes (prototype XEN) placed from the sub-conjunctival space to the AC resulted in the development of a fibrous cap over the tube ends after a few months.
- Reason he surmised, was the presence of a substance in the aqueous that was fibrosing in nature called "The Epstein Factor"

History of the term "Hypertensive Phase"

- Epstein suggested to the then resident, Dr Molteno, who was looking for a research project, to develop a "bleb spreading device" to dilute the effects of the so called **"Epstein factor"**

- Thus the birth of the original juxta-limbal bleb-spreading device by Molteno.



Molteno Implants and hypertensive phase.

- The development of the long tube implant, 1966-1975, allowed Dr. Molteno to describe the pathophysiology of bleb development over the plate, allowing the discovery of the "Hypertensive phase.

Bleb physiology after aqueous reaches the plate surface

- **Hypotensive** phase as bleb is forming lasting 7-10 days, related to effect of plate on conjunctiva, called the **"plate effect"**

- **Hypertensive phase** 4-5 weeks **after aqueous** reaches plate surface, called **"the cytokine effect"**

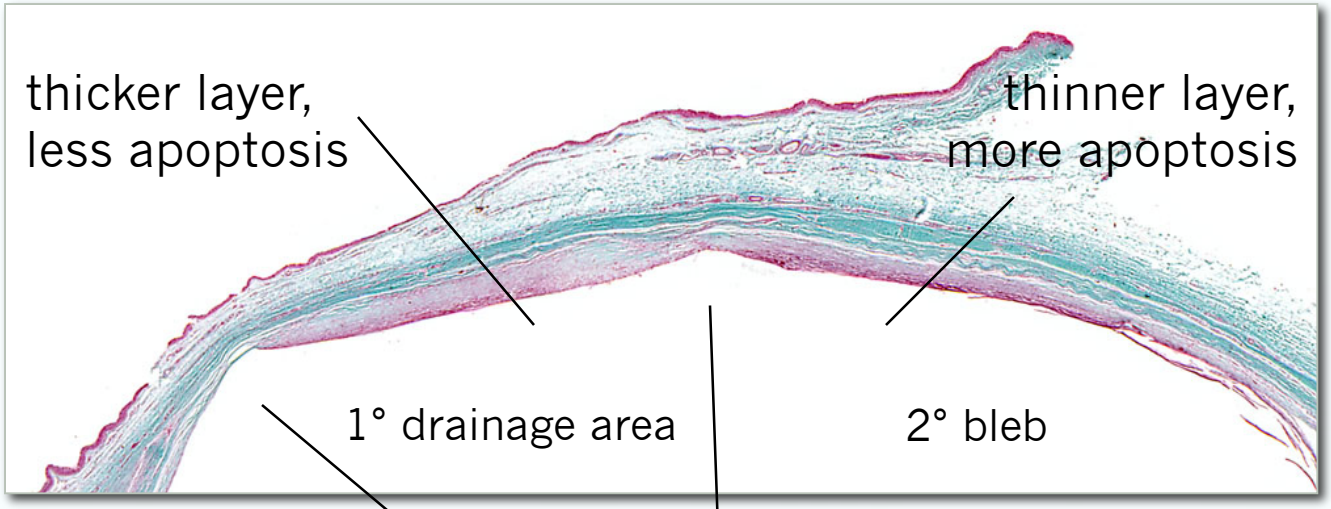
- Stable stage. The thickness of the capsule depends on the intensity of hypertensive phase.

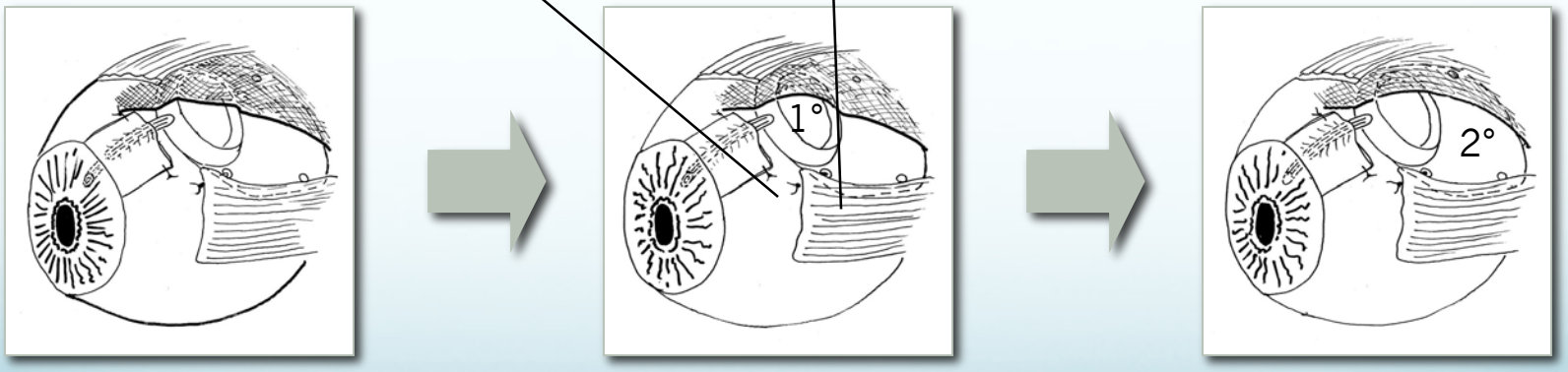
Role of cytokines in capsule development.

- Allowing (“ glaucomatous” ⇧ IOP) aqueous to reach plate surface intra-operatively, causes an initial combined reaction of aqueous and plate effect.

- Result is a thicker and less functional capsule in final bleb.

Bleb capsule at 8 weeks courtesy Dr. Molteno





completed op

1° bleb

2° bleb

Incidence of the Hypertensive Phase.

- Most importantly the hypertensive phase **does not occur** in every patient receiving a Tube shunt.
- Frequency:
- Valve implants 40-80%.
- Non-valve implants 20-30%

56% of Valved implants (no stent) have an hypertensive phase. Nour-Mahdavi, Caprioli 2003

Reason: Immediate Exposure to **"Glaucomatous" cytokine containing aqueous.**

Cytokines & Glaucomatous aqueous

- **Transforming Growth Factor beta (TGFβ)found in glaucomatous aqueous (Jampel1990).(Tripathi 1994).**

- **TGFβ and Prostaglandin E_2 found in glaucomatous aqueous (Freedman, Goddard1997)**

Aqueous cytokines.

- Search for the presence of other possible pro-inflammatory cytokines in glaucomatous aqueous: 21 of 23 cytokines tested for were found.

- **TGFβ& MCP- 1, MCP-2. (monocytic chemotactic protein) CCL2 MOST PROLIFIC**

- IL1a,1b,4,5,6,8,10,13,15,17. IP-10, 1-309, RANTES, TNF (Freedman. Iserovich 2012)

Controlling factors for the hypertensive phases.

- **Aqueous** and thereby **cytokine** content.
- **IOP** Both **before** and **after** bleb formation.
- The **idiosyncratic tissue response** of patient to the inflammatory potential, of the aqueous cytokine levels.

Cytokines and IOP

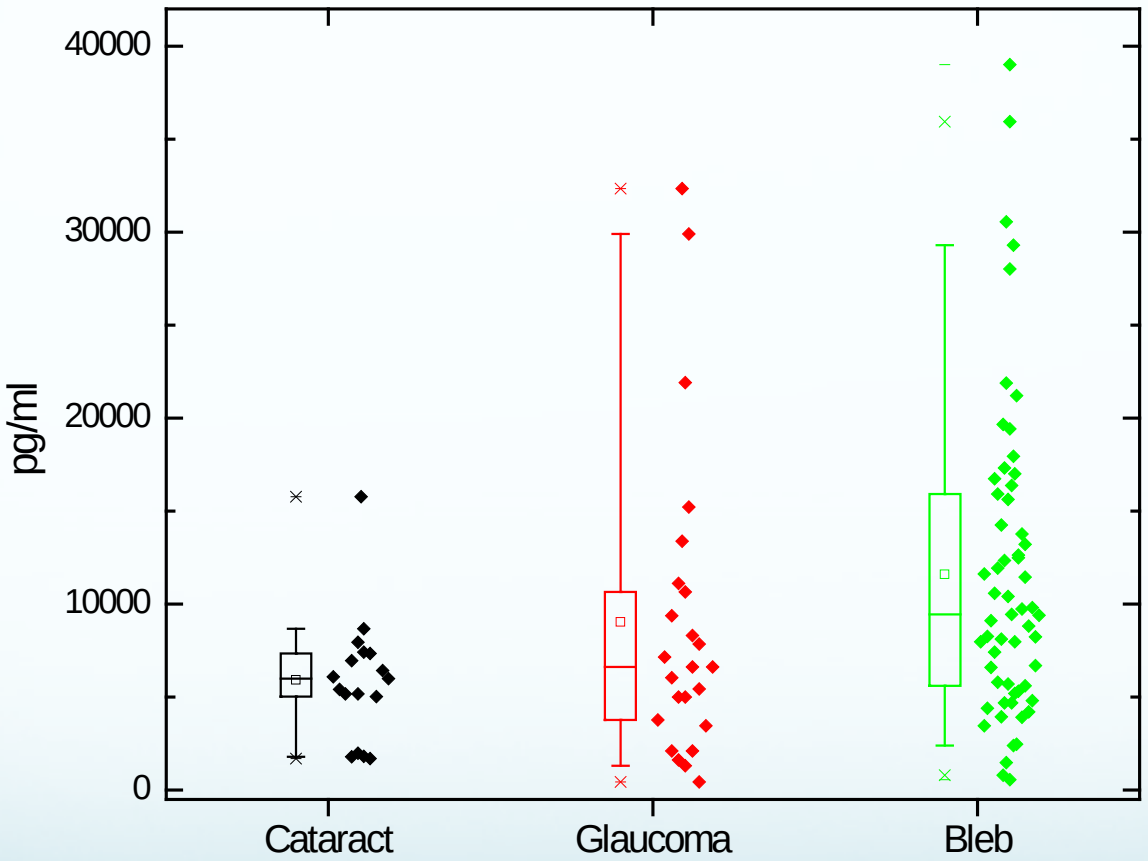
- **Raised IOP** causes breakdown of blood aqueous barrier.

- **Aqueous cytokine levels increase** with breakdown of blood aqueous barrier.(BAB)

Pro-inflammatory Cytokines. IOVS July 2013.

- Cytokine levels are **directly related to IOP.**
- The **higher** the **IOP** the **higher** the levels of **cytokines.**

TGF-β2 (activated)



★ Significant difference with control

Cytokines

.

- **TGFβ has ability to promote unrestrained proliferation of cells which have a benign phenotype. eg fibroblasts, macrophages.**

- **Results in fibrosis of bleb capsule.**

Hypertensive phase

- Is there a clinical significance of the hypertensive phase and its long term effect on the function of the final bleb. ?

The Role Of IOP and Implant Blebs

- Molteno:
- "The prevailing level of IOP has a long term effect on bleb permeability.
- If the IOP is maintained within physiological limits then there will be a long-term tendency for the bleb to become more permeable.
- if the pressure is allowed to rise to as little as 25-30 mmHg then this long-term improvement will not occur."

Hypertensive Phase.

- More successful bleb if **IOP** is lowered during the **hypertensive phase.**
- Reason: **High IOP** acts as shearing force on inner bleb wall resulting in **cytokine production.**
- Result is increased inflammation, bleb fibrosis and persistence of high IOP.

- **Indirect control of bleb fibrosis can be achieved by maintaining normal IOP levels from time of surgery to 10-12 weeks post operatively.**

- **This technique reduces bleb capsule thickness, and increases permeability of the stable-stage bleb.**

- **Reason: Low IOP = low cytokine effect.**

Treatment of Hypertensive phase

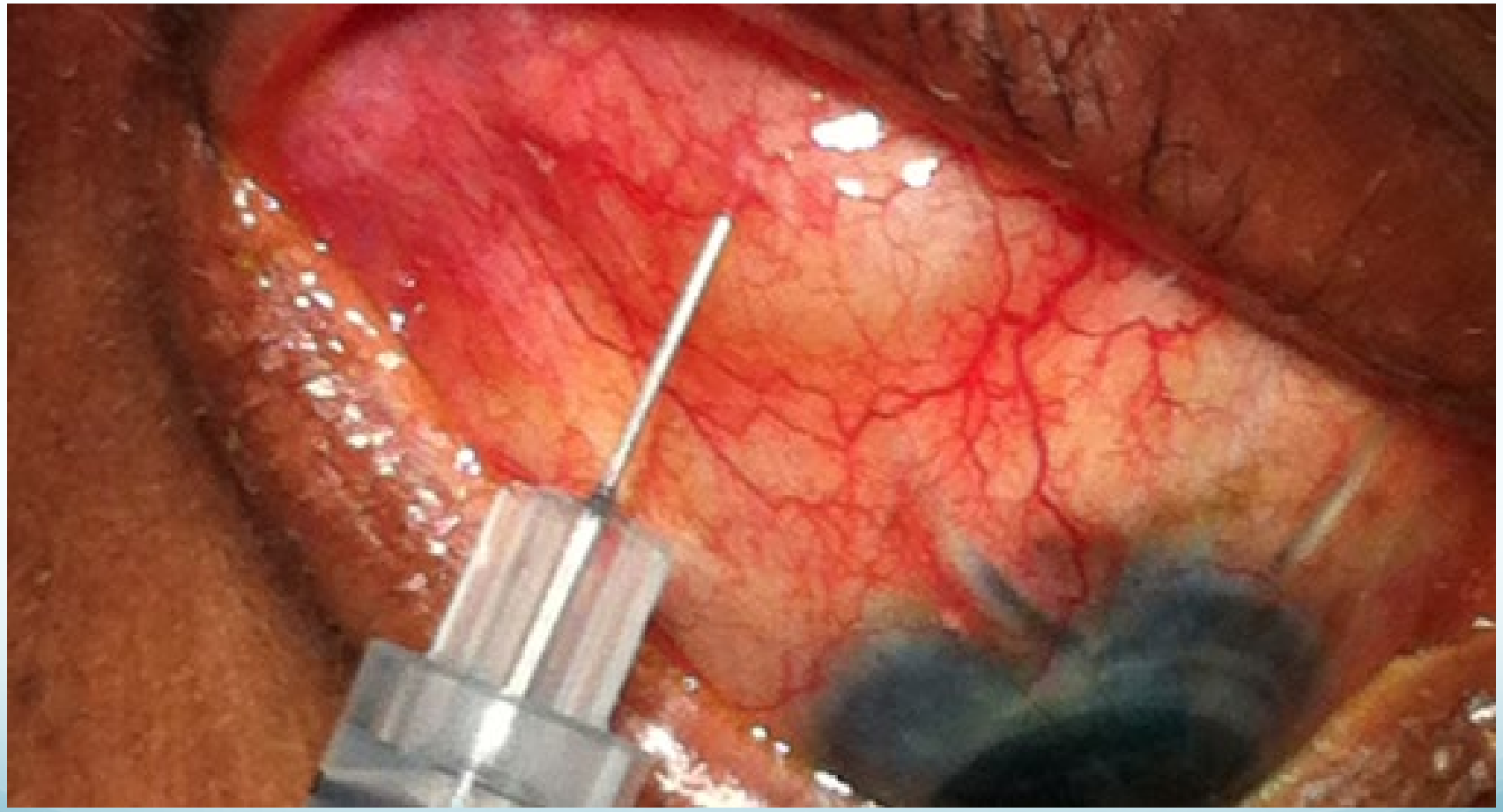
- Suggested treatment is both topical and systemic
- **Topical:** pressure lowering drops. Treats **IOP.**
- **Systemic: prevent fibrosis.** Results improve with use of Molteno anti-fibrosis medication. prednisone; NSA: Colchicine.

Alternative Treatment of hypertensive phase.

- **Removal of aqueous from bleb by needle aspiration. (Molteno implant treatment for refractory glaucoma in Black patients. Freedman 1991)**

- **Reason: Removal of aqueous from bleb results in rapid lowering of IOP, hopefully preventing bleb lining from forming cytokines.**

Aqueous removal from implant bleb.



Results of aqueous removal from hypertensive blebs

- Aqueous was removed from hypertensive blebs of 15 patients. Done if IOP 25mmHg or higher.
- Patient seen at weekly intervals.
- Procedure repeated if IOP increased above 25mmHg, stopping when IOP was stable or bleb failed.

Cytokines in aqueous removed from hypertensive blebs

- Results: Success in 7 patients.

  Failure in 8 patients.

Levels of TGFβ: Success 5760 ± 1349 pg/ml.

Failure 17008 ± 3293 pg/ml

- **Pattern seen in successful blebs.**
- **No patient required more than 2 taps.**
- **Persistent lowering of IOP and low cytokine (TGFβ) level following first tap.**
- **Cytokine(TGFβ) levels were below 10000pg. In all patients..**

Effect of aqueous removal from implant blebs

- **Pattern seen in failed blebs.**
- **Repeat taps did not show any change in original trend of high IOP and cytokine (TGFβ) levels, all remaining above 10000 pg.**
- **Suggests that bleb may have become a permanent ‘factory’’ for producing cytokines.**

Do Blebs form Cytokines?

- **Clinical observation**: Placement of second implant into eye with failed implant is **often** not very effective.

- Possible reason: Original implant, is **supplying cytokines** to aqueous resulting in bleb fibrosis in **second implant.**

Effect of failed implant on second implant.

- Two patients seen with failed implants. **Cytokine levels high in both eyes. IOP very high in both eyes >30mm.**

- Original Implants removed at time of second implant insertion, at request of patients.

Second implant resulted in successful IOP control in long term follow up of both patients.

Possible reason: **First implant is making cytokines**, which are passing back into the eye causing inflammation and fibrosis of second implant.

- The bleb remains active throughout its existence.
- **IOP** fluctuates. When elevated it will allow **bleb wall to produce cytokines.**
- Inner wall of bleb will undergo periods of increased inflammation and fibrosis, followed by decreased inflammation and thinning..

Effect of Increased IOP in implant bleb.

- **Bleb makes cytokines.** Analogous to **"Selye rat pouch."**

- Injection of air subcutaneously in rat results in production of **cytokines as pressure rises in pouch.**

Prevention of effect of failed tube on new tube.

- Exteriorize first tube, cinch with 7-0 prolene suture to occlude, and replace into anterior chamber.

- Bleb will collapse and not feed cytokines into AC

Effect of tying off tube in failed bleb on new implant

- 4 patients had failed tube tied off
- Pre-Op IOP Ave 36mm Hg. TGFβ 22,733pg/ml.
- Post-op IOP Ave. 18mm Hg. TGFβ 10,238 pg/ml
- Second implant inserted successful in all cases.

Cytokine Effect on Established Bleb

- **Prevailing IOP** and thereby **cytokine levels** control the dynamic activity present at all times in bleb

- **IOP fluctuates**. When elevated it will allow bleb wall to produce cytokines.(Selye Rat Pouch)

- Controlling the **IOP (cytokines)** throughout the life of the bleb Is more likely to ensure its longevity

- Successful blebs require a persistence of **LOW** IOP **before**, **during** and **after** the bleb has formed.
- Methods for achieving this goal :-
- **Before:** Lower IOP prior to surgery especially in valved implants.
- **During:** Treat hypertensive phase.
- **After:** Do not allow IOP to rise.

Conclusion.

- **High IOP, and thereby cytokines, occurring at any time during or after bleb formation, will ultimately be toxic to the bleb and destroy it.**

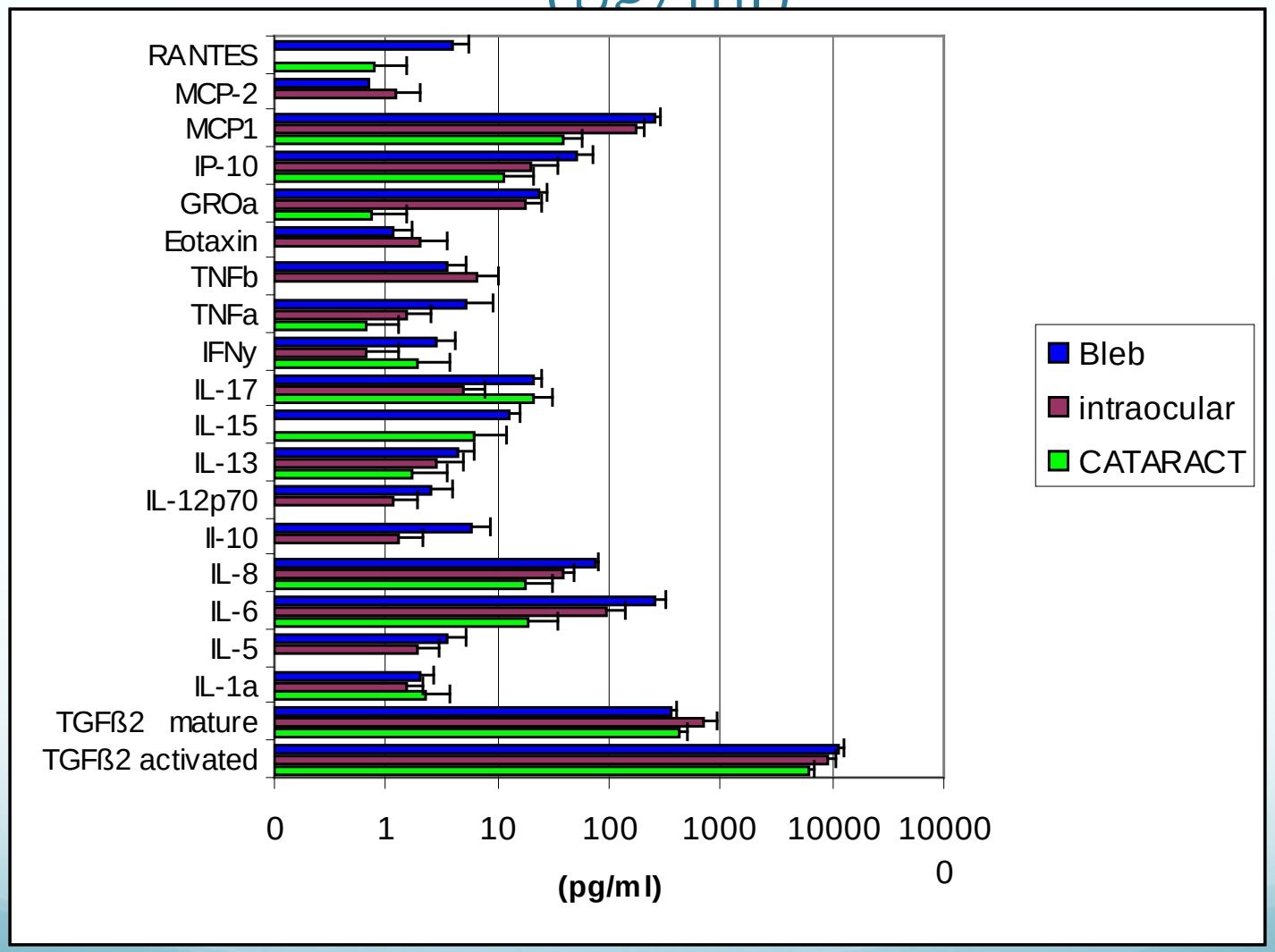
Pathophysiology of blebs,conclusions.

- The shunt itself plays only a small role in determining the effectivity of the bleb.
- The patient's inflammatory reaction, the nature of the tissue, and the aqueous contents(cytokines) are more important.
- The bleb is a viable & changing structure.
- This is the reason that different results are obtained in different patients using the same device often by the same surgeon.

Conclusion.

- Treat Hypertensive phase by removing aqueous (cytokines) from bleb.
- Maintain IOP below 25mm Hg to preserve the life of the bleb.
- Occlude tube of failed implant when inserting second implant in same eye.(prevents cytokines from failed implant effecting new implant adversely.)

Cytokines and chemokines concentrations (pg/ml)



Conclusion.

- Treat Hypertensive phase by removing aqueous (cytokines) from bleb.
- Maintain IOP below 25mm Hg to preserve the life of the bleb.
- Occlude tube of failed implant when inserting second implant in same eye.(prevents cytokines from failed implant effecting new implant adversely.)

The “Living” Bleb

- Pressure in implant blebs is not static but may become elevated long after the hypertensive phase has ended.
- Factors associated with increased IOP are medications including steroids, cataract extraction, prolonged periods of uncontrolled IOP, laser therapy, young age and uveitis.
- All these factors result in elevation of cytokines.

The “Living” Bleb

- Increased cytokines in aqueous will result in inflammation in bleb wall decreasing the permeability.
- Result is increased pressure in bleb resulting in cytokine production by bleb wall lining.
- Failure to decrease pressure perpetuates bleb wall thickness, as result of excessive cytokine production.

The Role Of IOP and Implant Blebs

- **Molteno:**
- **“The prevailing level of IOP has a long term effect on bleb permeability. If the IOP is maintained within physiological limits then there will be a long-term tendency for the bleb to become more permeable. Conversely if the pressure is allowed to rise to as little as 25-30 mmHg then this long-term improvement will not occur.**

The Role of IOP and Implant Blebs.

- Persistent high IOP destroys implant blebs.
- High IOP stimulates bleb to produce cytokines.
- Cytokines induce inflammation in bleb wall.
- Bleb wall thickens, IOP rises and a vicious circle has been initiated as more cytokines are produced.
- **Raised IOP induces cytokine presence.**

The Role of IOP and Bleb Implants

- Successful blebs require a persistence of LOW IOP before, during and after the bleb has formed.
- Before: Lower IOP prior to surgery if possible.
- During: Treat the hypertensive phase.
- After: Don't allow IOP to increase.

Practical Points Regarding Glaucoma implants.

- Implant material…Does it matter?
- Bigger is better…..True or false?
- Selecting patients for implant surgery. Primary or secondary?
- Will microsurgical devices effect glaucoma implant use?
- Glaucoma implants effect the cornea. True or False?

Evaluation of Ahmed valve. Nour –Mahdavi, Caprioli 2003.

- **Valved implants have severe hypertensive phase, resulting in decreased efficiency of blebs.**
- **Reason: Glaucomatous aqueous with higher level of cytokines reaching plate surface causing inflammation and fibrosis.**
- **Subsequently the final blebs were shown to be less effective due to increased wall fibrosis.**

The “Living” Bleb

- High levels of cytokine (TGFb) results in eventual bleb failure. (Recent research).
- The bleb has become an “apoptotic” bleb, due to its own production of cytokines.
- Persistence of high IOP, results in self destruction of implant blebs.

- The bleb remains active throughout its existence thus the hypertensive phase becomes **“hypertensive phases”.**

- **IOP fluctuates. When elevated it will allow bleb wall to produce cytokines.(Selye Rat Pouch)**

- **? delete**

Cytokine Effect on Established Bleb

- The bleb remains active throughout its existence. (Molteno).

- IOP fluctuates. When elevated will allow bleb wall to produce cytokines.

? delete

- Inner wall of bleb will undergo periods of increased inflammation and fibrosis, followed by decreased inflammation and thinning..

What to learn from hypertensive phase?

- Bleb outcome depends on ability to control **IOP** between insertion of implant and onset of drainage.
- **High IOP** increases inflammation (cytokine effect) resulting in a thickened bleb wall.
- **Low IOP** causes minimal bleb inflammation at onset of drainage resulting in a thin-walled bleb.

Cytokines and Capsule Development

- Jeffrey Freedman MB.BCh., PhD, FRCSE., FCS(SA).
- Dept. Ophthalmology, SUNY, Brooklyn, New York.

Cytokines and Capsule development.

- The nature of the capsule will be determined by the interplay of aqueous, tissue & inflammatory response of patient.
- The major components in the aqueous are the **cytokines,** the levels of which are influenced by the **IOP.**
- The major tissue component is Tenon capsule which contains the mRNA for the **cytokine TGFβ**
- The whole concert is conducted by the inherent inflammatory response of the patient.

Components in bleb formation.

- Aqueous. (Cytokines)
- Tissue above plate surface. (Cytokines)
- **IOP acting as the main facilitator**. (Elevated IOP= Cytokines)
- *Implant acting only as a conduit for aqueous*.

Bleb capsule formation

- Without aqueous flow, the episcleral plate of the glaucoma implant stimulates encapsulation by a thin avascular collagen layer.(Plate effect)
- With aqueous flow an immediate inflammatory reaction develops in the episcleral tissue consisting of collagenous and vascular components.(Aqueous effect)
- **This reaction will be modified by the cytokine content in the aqueous.**

Aqueous & cytokines in bleb capsule formation.

- Result of ↑ IOP on blood aqueous barrier.
- Blood aqueous barrier is broken down resulting in the accumulation of cytokines, producing ‘‘glaucomatous aqueous’’.
- Glaucomatous aqueous contains pro-inflammatory cytokines, **TGFβ,** MCP1(CCL2),IL 6&8,as well as others.
- **The higher the IOP the greater the concentration and level of the cytokines**.

Bleb capsule formation.

- Placement of implant disturbs the subconjunctival space, thereby tissue repair begins.
- Early tissue repair is dominated by inflammatory cells, viz. macrophages, lymphocytes, platelets and fibroblasts.
- Cytokines are produced by these cells, especially by fibroblasts. .
- Main cytokine is **TGFβ**.The mRNA of this cytokine is also expressed in Tenon fibroblasts, enhancing tissue repair.

Bleb capsule formation.

- Placement of implant disturbs the subconjunctival space, thereby tissue repair begins.
- Early tissue repair is dominated by inflammatory cells, viz. macrophages, lymphocytes, platelets and fibroblasts.
- Cytokines are produced by these cells, especially by fibroblasts. .
- Main cytokine is TGFβ.The mRNA of this cytokine is also expressed in Tenon fibroblasts, enhancing tissue repair.

Bleb capsule formation.

- Bleb requires mechanism whereby excessive tissue healing around the bleb is retarded, but allows normal tissue repair to occur.

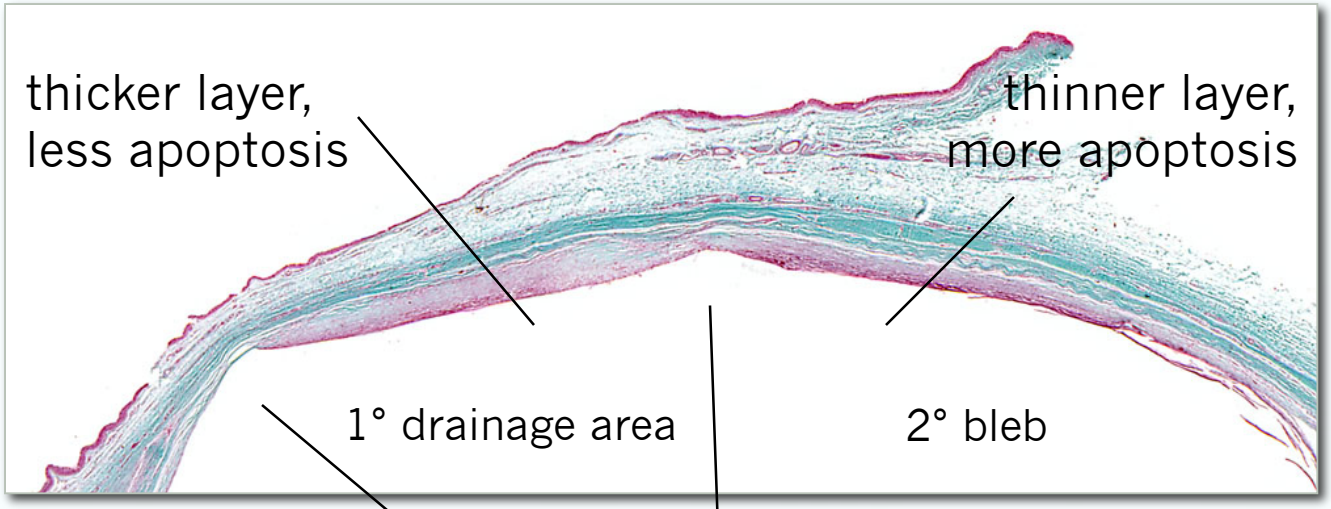
- **This results in the functional and anatomical integrity of the bleb, discouraging infection and bleb leakage.**

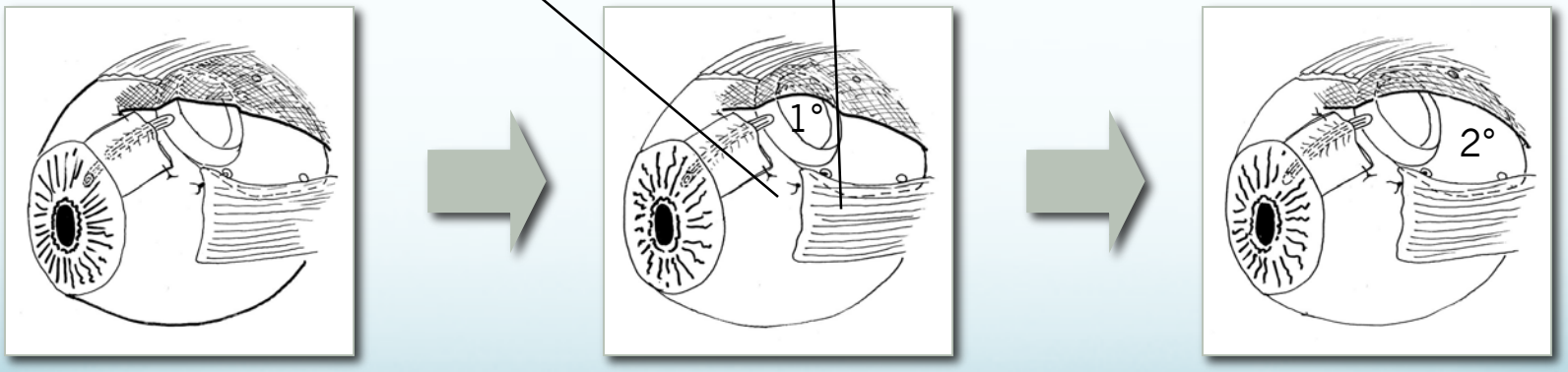
Role of cytokines in capsule development.

- Allowing ‘‘glaucomatous’’(↑IOP) aqueous to reach plate surface intra-operatively, causes an initial combined reaction of aqueous and plate effect, resulting in thicker capsule formation initially.

- Result is a thicker and less functional capsule in final bleb.

Bleb capsule at 8 weeks courtesy Dr. Molteno





completed op

1° bleb

2° bleb

Role of cytokines in capsule development.

- "Glaucomatous aqueous" due to high IOP has high pro-inflammatory cytokine content.

- **Lowering IOP prior to allowing aqueous onto plate surface, results in decreased inflammation (cytokines), and thinner bleb wall**

Stages of capsule development

- Following the hypertensive phase, a fibro-degenerative process develops in the deeper layers of the capsule.
- This is maintained by activation, migration, apoptosis and production of death messengers by mesodermal cells.
- The fibro- degenerative process may depend on a moderate increase of IOP, for aqueous to displace interstitial fluid from the deeper layers of the capsule.

Aqueous flow, initiates stages of bleb development.

- Hypotensive phase with edema and vascular congestion lasts7-10 days.
- Pressure rises, edema decreases and bleb forms.
- About 3-6 weeks after aqueous reaches the plate surface, the hypertensive phase(HP) occurs.
- HP Lasts 2-4 weeks, bleb becomes less congested, pressure falls until stabilized, about 3-6 months after implant insertion.

Hypertensive Phase.

- More successful bleb if IOP is lowered during the hypertensive phase.
- Reason: High IOP acts as shearing force on inner bleb wall resulting in cytokine production.
- Result is increased inflammation, bleb fibrosis and persistence of high IOP.

Hypertensive Phase.

- **Common Treatment:**
  - **Medical therapy (drops and systemic medications)**
- **Suggested treatment:**
  - **Remove aqueous from bleb, utilizing a 30 gauge needle, at regular intervals until IOP lowering is stabilized.**
- **Reason: Removal of pro-inflammatory cytokines, and eliminating the stimulus for their production, the elevated IOP.**

Stable Phase

- Stable bleb that occurs with normalization of IOP, shows loss of fibroblasts, with degeneration, fragmentation and disappearance of collagen fibres.
- This occurs mainly in inner half of bleb wall.
- The aqueous is removed by a small network of vessels in the inner bleb wall.
- These changes require normal levels of TGFβ for venous dilation.

Cytokine Effect on Established Bleb

- **IOP and thereby cytokine levels control this dynamic activity present at all times in bleb**
- **Recent research strongly suggests that the bleb wall is a source for cytokine production.**
- **Controlling IOP controls integrity of bleb.**

Molteno Stated……

- The prevailing level of IOP has a long-term effect on bleb permeability.
- In established blebs, maintaining IOP within normal limits, results in a tendency for the blebs to become more permeable with time.
- Allowing IOP to rise to as little as 25-30mmHg, will decrease long term improvement, and may result in long term deterioration of bleb.

The anatomy of a successful bleb.

- Control IOP prior to allowing aqueous access to plate.
- Control the hypertensive phase consistently, until IOP normalized.
- Prolonged normalization of IOP in postoperative period, will enhance the success of the bleb.

Template for managing bleb fibrosis.

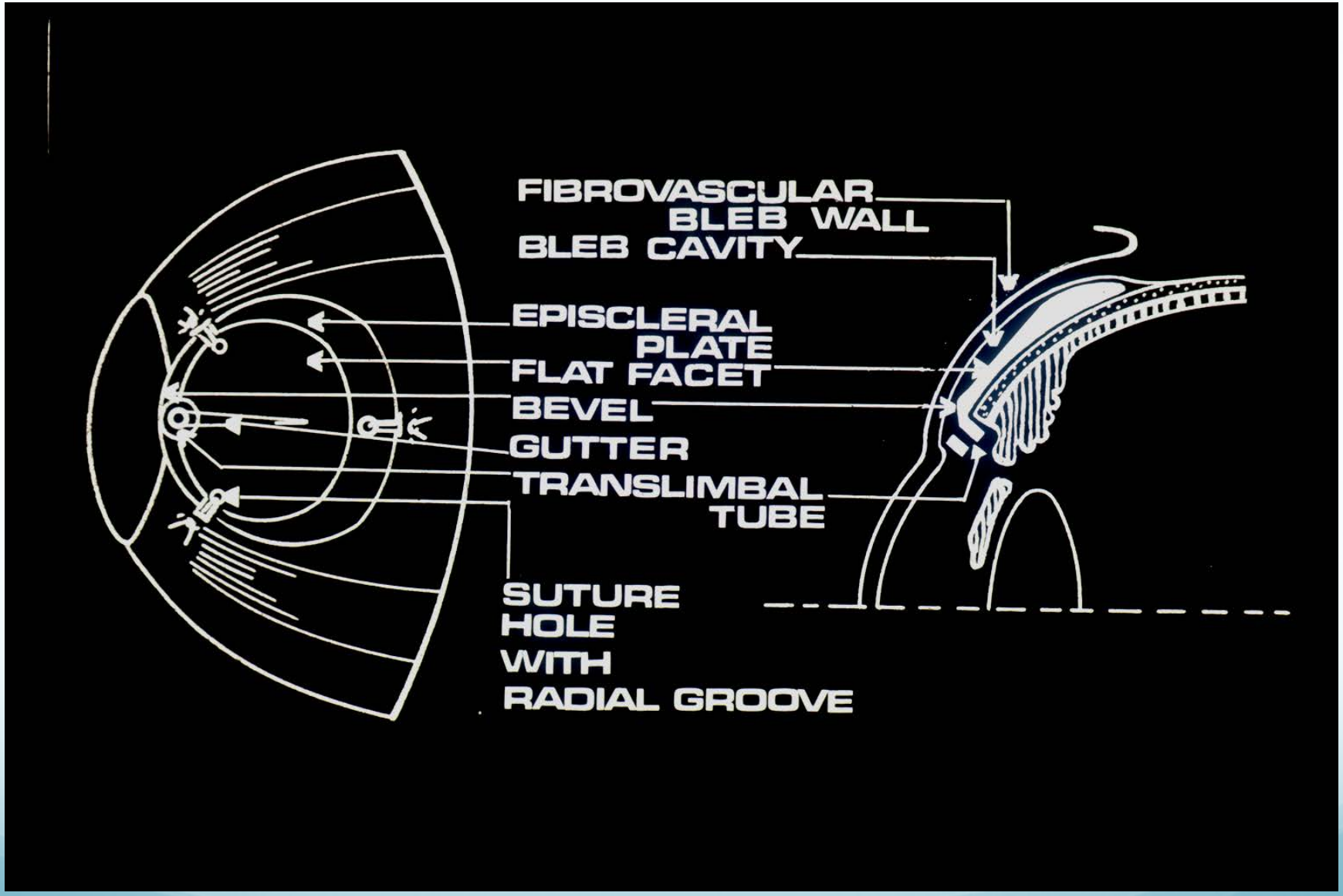
- **Raised IOP causes cytokine production, & thereby fibrosis.**
- **Prevent aqueous from reaching plate until IOP has been lowered. Occlude tube, and insert a slit to control IOP.**
- **If immediate lowering of IOP cannot be done, use systemic anti-inflammatory regime as soon as aqueous reaches plate surface.**
- **Steroids treat and prevent a "cytokine storm."**

Conclusion.

- To improve results in IOP lowering, research should be directed into better understanding of the mechanisms involved in bleb formation, & methods that might be employed to improve bleb filtration.
- Recent research has indicated that IOP influences cytokine production, and that cytokines play a significant role in bleb pathophysiology.

Key to successful blebs.

- “Control of intraocular pressure requires control of intraocular pressure.”


FIBROVASCULAR
BLEB WALL
BLEB CAVITY
EPISCLERAL
PLATE
FLAT FACET
BEVEL
GUTTER
TRANSLIMBAL
TUBE
SUTURE
HOLE
WITH
RADIAL GROOVE