

Nonoxynol 9

Lessons In vitro

(Robin Shattock)

NONOXYNOL – 9



(Nonylphenoxypolyethoxyethanol)

Non-ionic surfactant

Active component of many spermicides (2-12%)

“Spermicidal action attributed to solubilization and disruption of the organization of plasma membrane”

(Toxicology letters 1986 31:65)

Dawning of a concept

0.05% N9 blocks infection of HIV pulsed cells (less than 60s).
(Hicks et al Lancet 1985 2:1422-23).

- All ready contained in spermicides used for nearly half a century.
- Already known to be active against a range of STDs (in vitro) including:
 - Herpes simplex.
 - N. gonorrhoea*.
 - T. pallidum*.

"When prevention is being considered a protective effect of N9 containing spermicides should be assessed".

The argument evolves.

0.05% directly inactivates HIV virions
(Malkovsky et al Lancet 1988. 1: 645).

"Sir, the incidence of sexual transmission of infectious agents has been greatly reduced in those who have used spermicides.....

....it is therefore likely that in vitro results can be extrapolated into the clinical setting and that preparations containing N9 can rapidly inactivate HIV in vivo".

First warning shots sound from in vivo studies

N9 may facilitate HIV transmission
(Kriss et al JAMA 1992).

But the band wagon rolls on.....

"Ideally, spermicidal agents will have virucidal and indeed, antimicrobial activity.....

.....0.025% N9 has in vitro activity against both HIV and HSV.

(Jennings J. Antimicrob Chemo 1993 32: 71-83).

The issue of selectivity is finally raised.

(Bourinbaïar & Lee-Huang, Contraception 1995)

*"Agents should have maximum efficacy and lowest possible toxicity
- ratio between effective and toxic dose".*

Can N9 be used at non toxic levels?

-the beauty of hindsight

IC₁₀₀: 0.05% CC₅₀: 1%

SI: 20 (Hicks et al 1985).

IC₁₀₀: 0.05% CC₅₀: 0.5%

SI: 20 (Malkovsky et al 1988).

IC₁₀₀: 0.01% CC₅₀: 0.01%

SI: 1 (Bourinbaiar 1995).

Are epithelial cells are more resistant?

IC₅₀: 0.005% CC₅₀: 0.0006%
(Hela cells)

SI: 0.12 (O'Connor et al 1995).

Or cervical explants?

IC₅₀: 0.005% CC₅₀: 0.0005%

SI: 0.1 (*Shattock et al unpublished*)

N9 only displays antiviral activity at doses that are cytotoxic".

(AIDS 1996 10:558).

Nonoxynol-9 increases vaginal permeability

- Diffusion studies using ex vivo vaginal tissue from rabbits demonstrates that ; 0.42% N9 shows a significant enhancement of vaginal permeability over 4 hours.
- On N9 treatment of ex vivo vaginal tissue from ovariectomized rabbits, linearity cannot be maintained

(Acatürk and Robinson, Pharm Res 1996, 13, 950-9520)

Final nails in the coffin ?

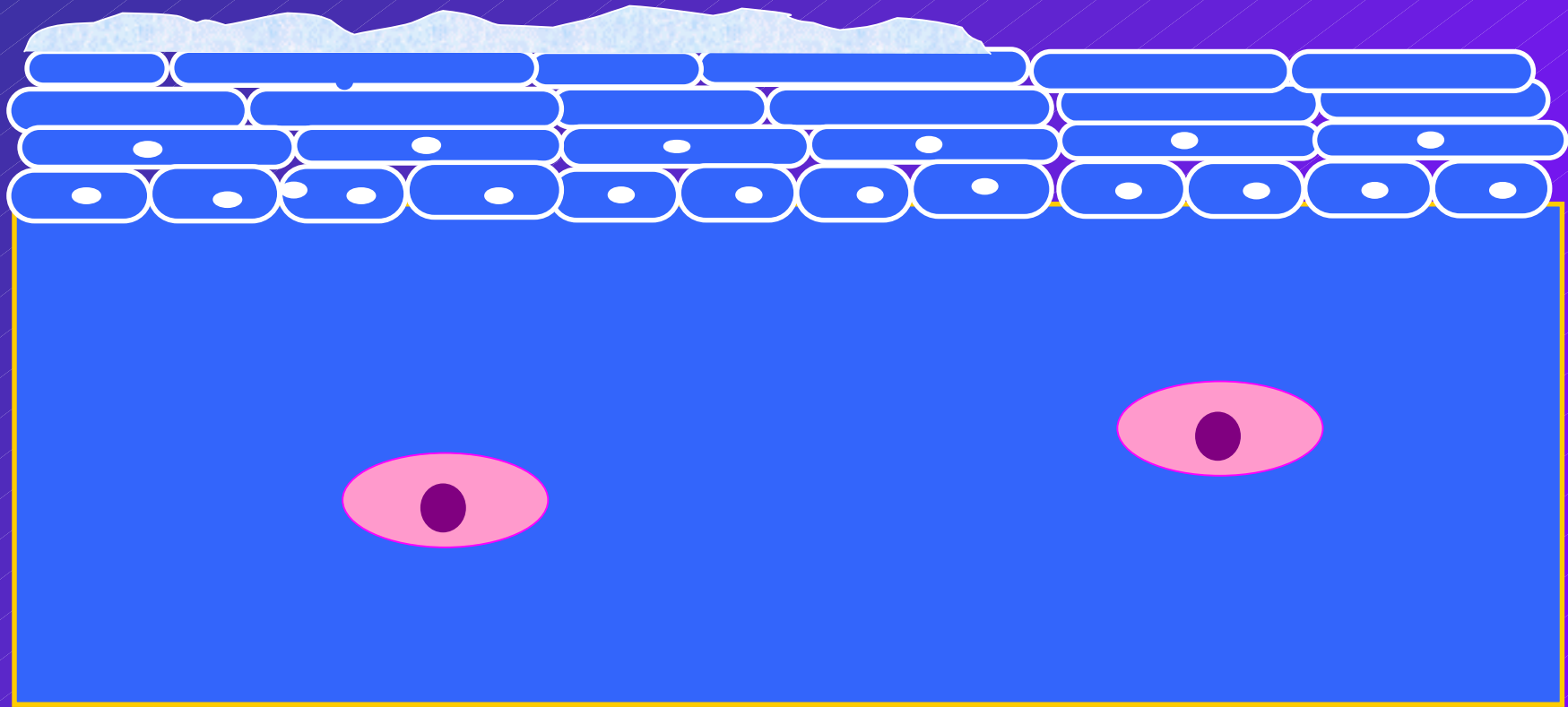
- in vitro informs in vivo -

- 0.00025% N9 kills primary vaginal epithelial cells in 48hrs.
- Time dependent cytotoxicity
 - correlation with duration of exposure
- Frequency dependent cytotoxicity
 - repeat exposure increases cytotoxicity.

Threshold effect for N9

- influenced by concentration, duration and repeat exposure
(Krebs et al, Antimicrob. Agents Chemother 2000 44: 1954-1960).
- Inverse correlation between cytotoxicity and IL-1 α release.
 - Lysis of epithelial cells causes release of IL-1 α , IL-1 β
and secondary release of IL-8
(Fichorova et al, JID 2001 184:418-428).

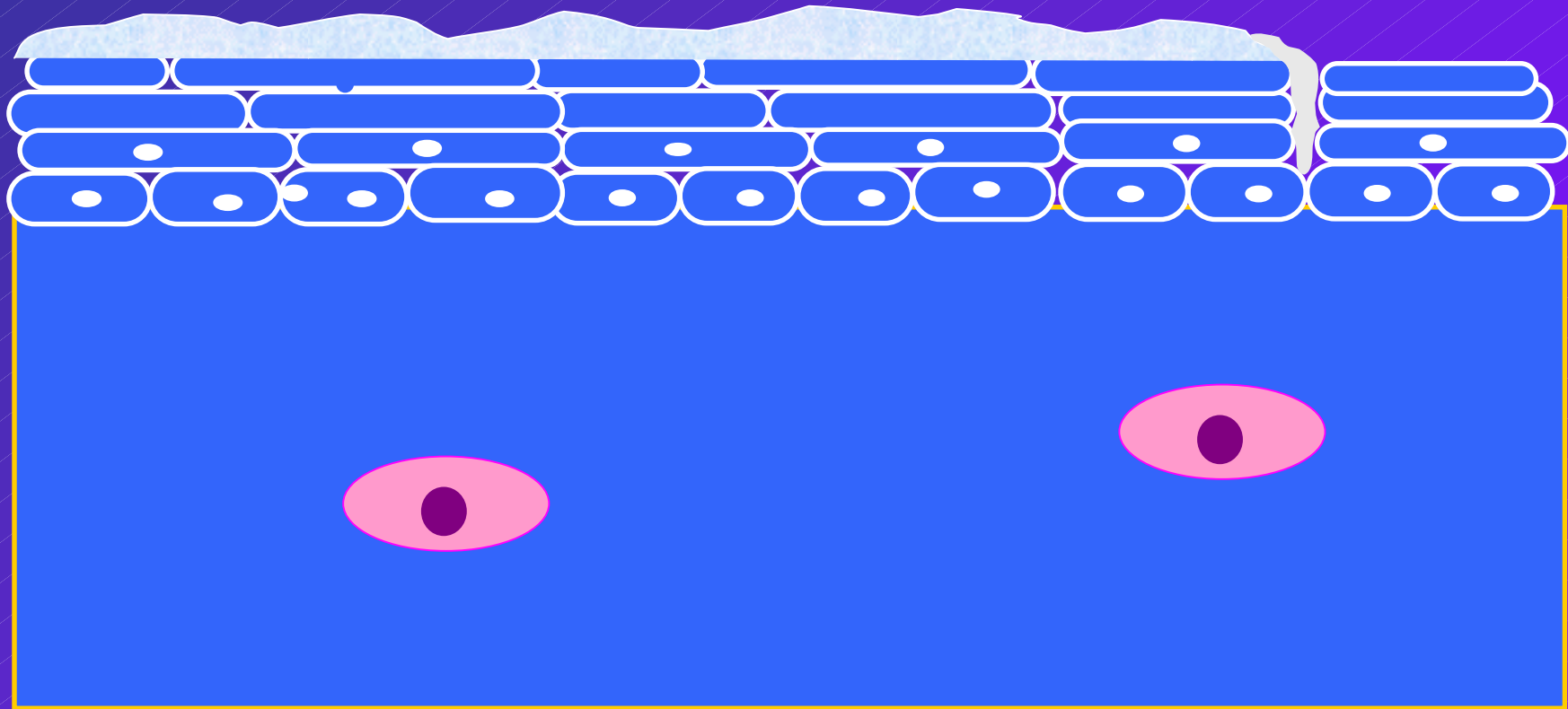
Predicted effects of Nonoxynol -9



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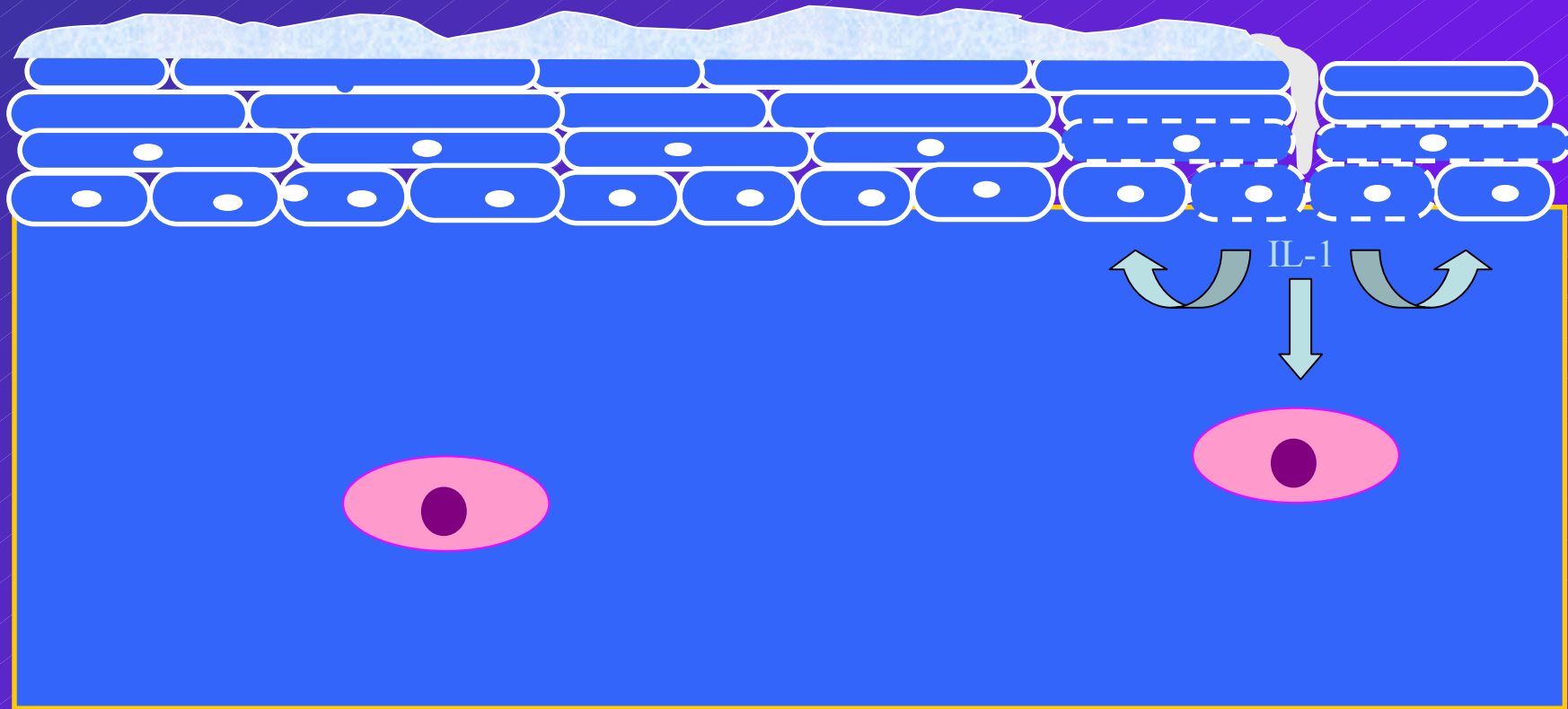
Modulation of
Epithelial permeability



Predicted effects of Nonoxynol -9

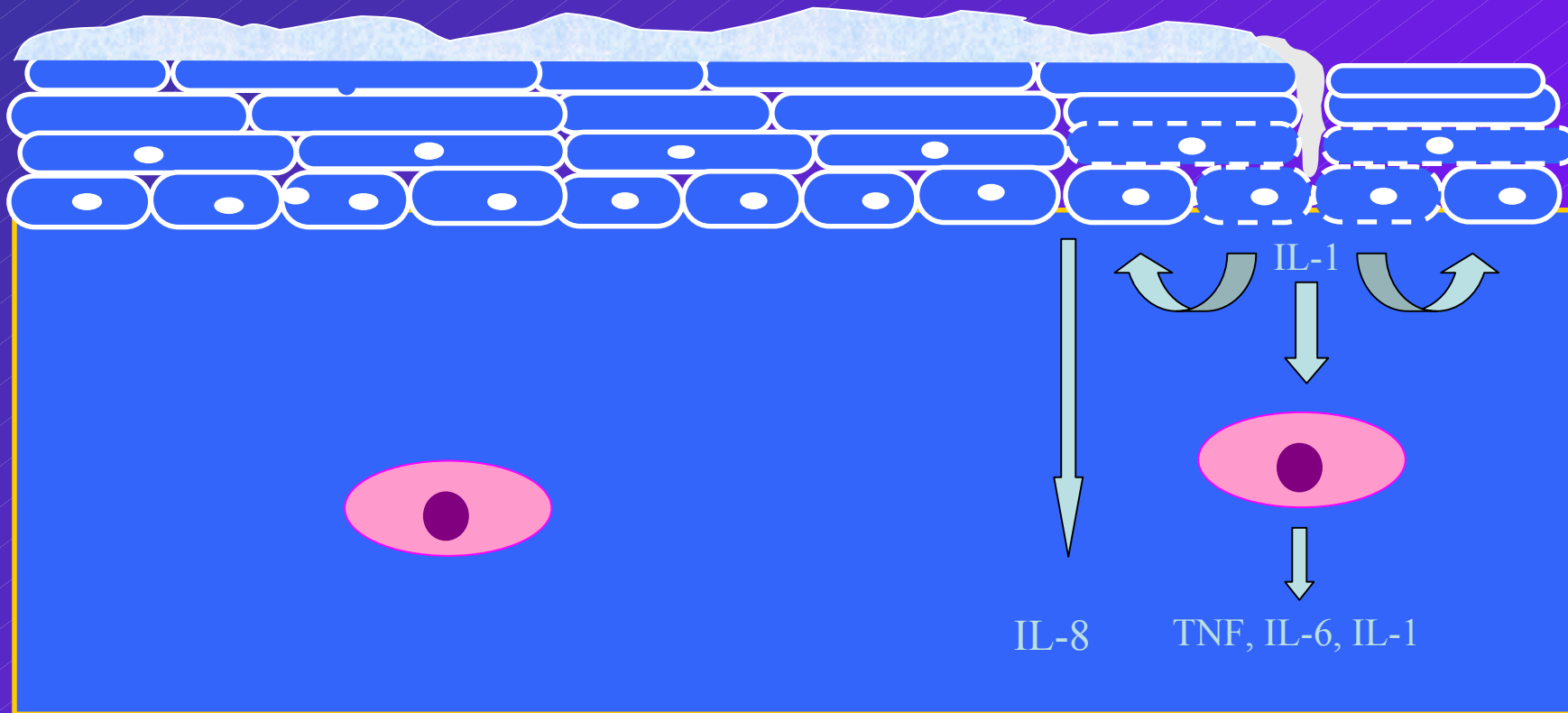

Viral disruption

Cell lysis,
IL-1 release



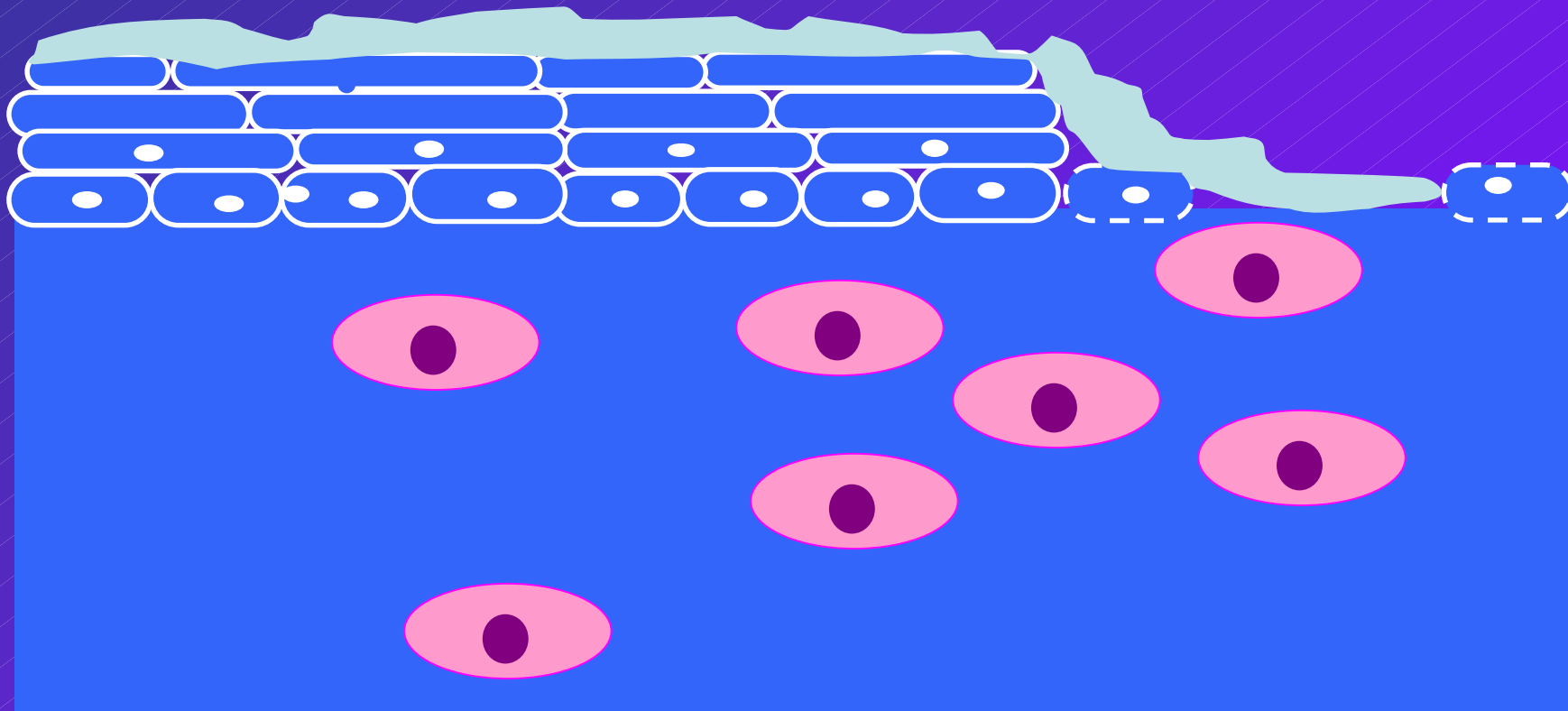
Predicted effects of Nonoxynol -9

Pro-inflammatory cascade



Predicted effects of Nonoxynol -9

Influx of PMNs
And susceptible target cells



Predicted effects of Nonoxynol -9

Absence of compound
Increased susceptibility

