

EPIDEMIC KAPOSI'S SARCOMA &
OPPORTUNISTIC INFECTIONS IN HOMOSEXUAL MEN:
Expression of an Acquired Immunoregulatory Disorder

REVISED SCHEDULE

Thursday, March 17, 1983

7:45 Registration & Continental Breakfast

8:30 Opening Remarks:
Irwin Freedberg

KAPOSI'S SARCOMA: Clinical Features and Treatment
Moderator: Frederick Siegel

8:40 Overview of classical and epidemic Kaposi's Sarcoma
Alvin E. Friedman-Kien

9:10 Kaposi's Sarcoma in equatorial Africa
Charles Olweny

9:30 Pathology of Kaposi's Sarcoma and its simulators
A. Bernard Ackerman/Geoffrey Gottlieb

9:50 Kaposi's Sarcoma in renal transplant patients
Andrew Harwood

10:10 Coffee Break

10:30 Treatment of classical and epidemic Kaposi's Sarcoma
Linda J. Laubenstein

10:50 Use of interferon and other immunomodulators
Bijan Safai

11:10 Discussion and Questions

11:45 Break for Lunch

EPIDEMIOLOGY

Moderator: David J. Sencer

1:00 Overview of the epidemiology of AIDS and Kaposi's Sarcoma
James E. Curran

1:30 Evaluation of patients with AIDS related to transfusion of blood
products
Joseph Bové

1:50 AIDS in a colony of macaque monkeys: A possible animal model
Norman Letvin

- 2:10 AIDS in children: Difficulties in distinguishing primary and
 secondary immunodeficiency
 Steven Schutzer
- 2:30 Coffee Break
- 2:45 The changing lifestyle of homosexual men in the last fifteen years
 Daniel William
- 3:00 Results of a case control epidemiologic study of Kaposi's Sarcoma
 in homosexual men
 Michael Marmor
- 3:15 Epidemiology of apparently healthy homosexual men
 James Goedert
- 3:30 Changing patterns of sexually transmitted diseases in the last
 fifteen years
 Marcus Conant
- 3:45 Discussion and Questions

Friday, March 18, 1983

- 8:00 Continental Breakfast
- IMMUNOLOGY
 Moderator: Pablo Rubinstein
- 8:30 Opening Remarks
- 8:40 The basic immunologic problem: Interrelationship between viruses,
 immunologic responses and tumorigenesis
 Arthur S. Levine
- 9:05 Spectrum of immunologic dysfunction in homosexual men
 Susan Zolla-Pazner
- 9:20 Immunologic spectrum in AIDS patients with opportunistic infections
 Anthony Fauci
- 9:40 Manifestations of AIDS in Haitians
 Sheldon Landesman
- 10:05 Coffee Break
- 10:25 Lymphocyte effector cell function in vitro in AIDS
 Susanna Cunningham-Rundles
- 10:35 Autoimmune disease and thrombocytopenia in homosexual men
 Simon Karparkin

(3)

10:50 Immunogenetic factors associated with Kaposi's Sarcoma and
opportunistic infections
Pablo Rubinstein

11:10 T cell defects in immunologic disorders: Experimental
approaches to restorations of immunocompetency
Stuart Schlossman

11:30 Questions and Discussion

12:00 Break for lunch

INFECTION

Moderator: Vittorio Defendi

1:00 Consideration on viral etiology: Causes and Effects
Joseph Pagano

1:25 The role of cytomegalovirus in Kaposi's Sarcoma
Eng S. Huang

1:45 Pneumocystis carinii in vitro and in vivo
Henry Masur

2:05 Mycobacterium avium and unusual opportunistic infections
Jeffrey Greene

2:30 Coffee Break

2:40 A search for retroviruses in patients with diseases associated with
acquired immunodeficiency
Edward Gelmann/Robert Gallo

3:10 Presence of interferon in patients with AIDS and autoimmune diseases
Jan Vilcek

3:30 Discussions and questions

4:00 KEYNOTE ADDRESS
Lewis Thomas

Saturday, March 19, 1983

8:30 PANEL ON EVALUATION OF CLINICAL PROBLEMS IN PATIENTS WITH AIDS

Moderator: Franco Muggia

- Prognostic factors in Kaposi's Sarcoma
Robert Krigel
- Generalized lymphadenopathy
Craig Metroka/Don Abrams
- Results of prospective ophthalmology study
Dorothy Friedberg
- Mucocutaneous infections in patients with AIDS
Virgil Hatcher
- Gastrointestinal manifestations of Kaposi's Sarcoma and AIDS
Lawrence Horowitz
- Neurologic complications in AIDS
Jerome Posner

10:30 Coffee Break

10:45 PANEL ON NEW THERAPEUTIC MODALITIES: Chemoimmunotherapy, interferon, interleukin II and other biologic response modifiers

Moderator: Ezra Greenspan

- Results of treatment with alpha2 recombinant interferon
Paul Volberding
- Interleukin II in patients with Kaposi's Sarcoma and AIDS
Richard Mertelsman
- Immunorestorative therapy for patients with Kaposi's Sarcoma and AIDS
Peter Mansell

11:45 PANEL ON SUPPORTIVE MEASURES, MONITORING AND PREVENTION

Moderator: Jeffrey Greene

- Alpha thymosin as a possible useful marker for screening patients with AIDS -
Allan Goldstein
- The next to the last word on AIDS
Roger Enlow
- Psychosocial impact of AIDS: Advice to patients at risk
Ronald Grossman

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ophthalmic in AIDS -

II cotton wool ocds disappear.

II Retinitis - 7/11 dead. Majority → blind

GI involvement

MENTIONS TRANSITIONAL ADENOCARCINOMAS, SQUAMOUS CA OF ANUS.

KS in GI tract.

36/86 had endoscopically demonstrated GI involvement.

Lesions vary widely in size.

Some flush to mucosa.

Some plaques

Some polypoid/confluent

No pt to intestinal obstruction

Contrast studies (-)

Esophagus rarely

1/35	20/36	4/36	19/36	11/36
Esoph	Stomach	Duod	Colon	Rectum

No sig bleeding from bx.

12/86 oral pharyngeal KS

9/117 to oral also had ~~to~~ intestinal lesions

± KS limited
5 SX, OE.
Ext. KS 5 SX, OE
Ext KS 5 SX, OE

(4)

SKIN & LN ⊕ KS ⇒ ⊕ involve.

But can't predict where ⊕ involvement will be.

- When contrast is ⊕ it's good but usually very late.

- Fever, constitutional symptoms ⇒ extensive disease.

No perforation, bleeding, obstruction

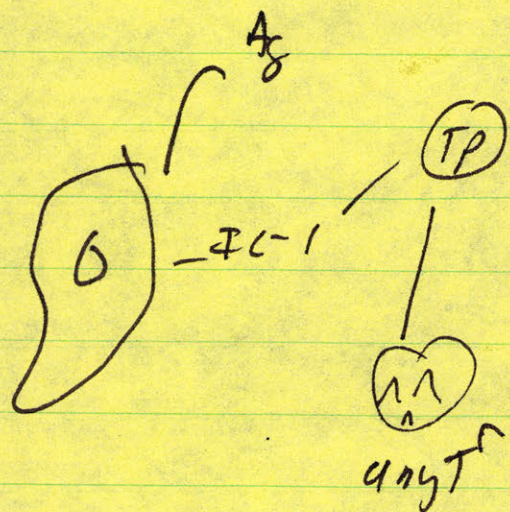
Diarrhea, hypoalbuminemia common.

Cytomegalovirus - in GI tract -

Can get CMV ulcerations.

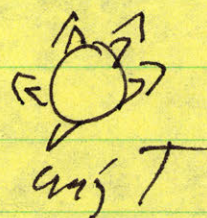
6/86 KS pts had CMV in GI tract.

IL-2 = T cell growth factor



NK can make IL-2

but requires it to grow.



ARDS has ↓ IL-2 prod & can at least in part be corrected $\bar{c}$ in vitro IL-2.

Goldstein- RIA for thymosin α_1

Thymosin - family of molecules

Thymic peptides may act at pituitary, hypoth.,

$\alpha_1 \rightarrow$ ACTH, glucocorticoids

$\beta_4 \rightarrow$ LH, LRF

Thymosin fraction 5 includes

FTS

THF

Thymopoietin

$T\alpha_1$ - amplifies helper T cells.

Thymosin α_1 , unlike lymphokines circulates, therefore is non toxic.

75% of 100 guys have $T\alpha_1$ (only 11 $\pm$ AIDS)

Hypotheses re. $[T\alpha_1] \uparrow$

- end organ failure

- abnormal α_1 ($\downarrow$ biolog. effect)

- may non-specifically be elevated in ill persons

Thymus cells shut light up $\pm \alpha_1$, ab also tight up $\pm$ HTLV-III Ab.

①

Prognosis of KS-

80% 3yr. survival if no OI.

100% mortality ± OI

? Predict which group.

GI - 50%

LN - 2/3 - sometimes exclusively LN

A vs. B symptoms is real prognostic break

B pts do as poorly as those ± coexisting
OI.

2 OIs 18/19 dead in bars.

metra - LNS in wives of ^{shaking}
B's _{hemophiliacs.}

splenomegaly - 20%

chorioret A.

Molluscum contagiosum

AIgG, A (one pt ± monoclonal)

polyarthritis of AIgG

marrow

↑ plasma

↓ plasma

(↓ shift

lymphoprolifer

Leukemia

AN follicular hyperplasia

Explosive follicular hyperplasia $\rightarrow$ 2% KS

Involution $\rightarrow$ KS 5
Lymph 5

mixed follicular hyperplasia, involution KS 1
Lymph 1

Often have neg. NK activity, $\downarrow$ PWM, E. coli

Neg NK & $\downarrow$ blastogenesis predicts OI etc for 21/29.

41% HLA Dr5

All 6 who $\rightarrow$ KS have HLA Dr5.

⑥ Response - Stress duration of response (measured from start of therapy), & survival (measured from dx)
Of two low dose non-responders, one is responding to high dose.

Stress NO OI. • IMMUNE EFFECTS

UCLA data.

11 patients

5 low dose 1 pr after 1 to high dose (almost CR)

6 high dose 3 "impressive" PR

All responders had only cutaneous disease.

2 OI (one PCP, one cryptosporidiosis) both on low dose.

No OI on high dose.

mention - No effect of IFN on H/S, candida blastogenesis, minimal increase in delayed cutaneous reactions.

In Summary - we are encouraged by our experience to date with α interferon. we feel that Interferon may be a viable alternative to chemotherapy but admit that these results are ~~at best~~ very preliminary. we are in the process of expanding this experience & are

Beginning in September 1981 we began in the KS Clinic at UCSF & at the San Francisco General Hospital a prospective chemotherapy trial in KS. Using criteria similar to those described by Dr Laubenstein 19 patients were treated with a single drug - in our case vinblastine - & 8 ^{patients} with the combination of adriamycin, bleomycin & vinblastine. The results of this experience are summarized on the first slide

- ① chemo summary -
- ② KS protocol - mention study primarily designed to eval. antineoplastic activity & thus extensive serial immunologic ~~pa~~ testing was not included.
- ③ characteristics (I) - mention UCSF only
- ④ characteristics (II) - mumps, ppd skin tests all (-)
- ⑤ Extent of disease - stress all stages ^{included} but lack of advanced pts. at UCSF trial.
- ⑥ Toxicity - essentially no toxicity from low dose.
- ⑦ Lab toxicity - Expected f modest toxicity on WBC, platelets, transaminase.
- ⑧ Response.

exploring other approaches including the recent
transplant of one of our SF patients at UCLA, ~~performed~~
~~this week, while~~ ~~Thank you~~ It is

Thank you

Intro. - ~~It should be indicated after hearing~~ ~~to that as~~

Kaposi Sarcoma is clearly a manifestation of AIDS the acquired immune deficiency syndrome. Thus the therapy of KS no matter how successful ~~may~~ may not alter the longer term prognosis for individual patients.

Nevertheless we as clinicians have had to respond to the all too common occurrence of a frequently disseminated & occasionally rapidly progressive visible malignancy in young patients.

Thus we have used available agents — both chemotherapy & others ~~which~~ ^{which} we realize are only palliative not curative. Clearly we must find the underlying cause or causes of AIDS.

Before presenting our experience ~~in~~ ⁱⁿ this therapy I'd like to express my ~~great~~ ^{support} gratitude to Marcus Conant, John Ziegler & Don Abrams for their invaluable ~~assistance~~ ^{support} & ~~encouragement~~ & to Mike Gottlieb & Jerry Groopman at UCLA for their continued example of open & unselfish collaboration.

①

Wed 3/17 A.M.

SIEGEL → A.F.K.

FRIEDMAN - KIRN - 1200 cases (classified) to 1960

- Endemic African

- Renal transplant.

1/80 - Antibiotics & Chemotherapy - Sym. in Karpis (KS)
African KS high of predom.

Incident rates diff. in Africa so have

prev rates	
Zaire	12.8%
Rwanda	9.1%
Burundi	
French Equat	5.0%
Uganda	4.2%

incid
Isolated areas (islands)
have ↓ incid rate.

In Uganda incid ↑ in
west states bordering
Zaire. (5x difference)

In Uganda wet areas higher but not
in other wet areas of tropical world.

In Uganda	with ♀'s & age
0-9	M/F ≈ 1.7
20-29	3.6
60-69	14.0

KS. α ? oncocirciasis

KS. α ? virus

- ① Geog. dist.
- ② Variable presentation
- ③ 2^o prim. tumor ⇒ persist
tumor marker
- ④ multifocal

CLASSIFICATION
Encloleat
cut. medula
Plasma
Aggressive
florid —
Infiltrative —
LN —
USC
etc

Nod 54
Floria 29
Infil 11
LN 3
USC 3

grows from deep fasciae, ulcers, bleeds
bone
medullarium included

bone involvement may be neurotic ? tumor pressure

KS is assoc. w leprosy.

? Cellular immunity in African KS

Controls (act age matched 1.01 - 2.29)
= 2 amb med stud ?? extent, therapy.

ICS pts w aggro 10/11 had ↓ H/sr/h's
the 'sport' still had ↓ helper.

In KSpts NO IgM to CMV or EBV.

Pathology - Prolif of small abnormally shaped vessels surrounding preexisting normal vessels.

Inflam. infiltrate contains plasma cells.
Endothelial cells thin.

Spindle cells in infiltrate. → will for burn of abnormal vessels.

Nodule — no abnormal vessel.

See fascicles of spindle cells ± RBCs.

No evid. of metastatic potential on skin lesions — in that sense not neoplasm.

Patch → Plaque → Nodules.
ABN. VESSELS. ○○○○ ○○○○○○○○○○ SPINDLES
RBC

Biopsy oldest most nodular lesion & if ulcerated or in setting of stasis, Biopsy deep.

(4)

HARWOOD / TORONTO KS in trans ph

1st case 1969

Now 23 case in English literature in detail.

Age = 42

mr. f = 1.6

Jewish, med. t., African.

Rare in Anglo-Saxons

7/23 d. KS

2 Puln ot KS

3 GI bleed

2 GI UI.

4/23 d. .

~~Indians~~

1/1400 Toronto

2/209 Capetown

14%

1/193 Den

~ 200 X increase MC

average time 16 months (4-53 mo)

22/23 on immuno + steroid.

5/11 - CR - retained kidney

2/11 - CR - lost kidney

4/11 - no response.

? H/S in
endemic
on tx
is KS a
malis.

5

XRT used for localized disease including

oral cavity
13 Locally controlled

2 failed 1 pr

1 uncontrolled

⇒ higher doses needed to control KS in
renal transplant

↓↓ PWM, Con A etc.

% of ↓ immun α KS

remission, immune studies improved.

(6)

LAUBENSTEIN - ESP. EPIDEMIO K.S.
STAGING, EFFECT OF DISEASE.

SKIN - PHOTOS. BIOPSY.
 LN - RX, CT ABD/PELVIS
 GI - ENDOSC., CONTRAS
 LUNG - BRONCA WIDEN CXR (-)
 LIVER - SCAN
 BONE - SCAN IF $\neq$ AKI (P)

STAGE I - 10 pts
 II - Cut. Locally aggressive - 0 pts.
 III - Gen metastatic. $\pm$ LN
 IV - Visceral. Poor prog $\bar{c}$ lung involve
 Diffic. to differentiate from PCP.

(Prog. IVB - 100% d. @ 28 mo.

✓P	CR	12	37.5%	Duration > 14 mo.
	PR	13	40.6%	
	NR	5	16.6%	
	±	2	6.3%	
	Tot	32		

CR	5	(15.5%)	BV.
PR	17	(63%)	
NR	5	(18%)	
±	0		
to:	27		

(7)

FalcebuVP-16 n = 34

PCP 2

MAI 1

CMV 1

ASV

n = 29

PCP 7 26%

MM 4 13%

CMV 2 6.9%

CMV 6 24%

Survival of K5 5 01 is 80% at 3+ yrs

EOL is 100% fatal at 36 mo.

Thymopentin - 10 pts 5 response

Plasma pheresis

 α , γ interferon

Safai -

Disc. tx of classical KS $\in$ electron beam
is OK.

$\therefore$ Interferon therapy - Crown et al.

21 abt. f pts

$\rightarrow 36 \times 10^6$
 54×10^6

9 pts
9 pts.

Daily IM $\times 28$ d. $\rightarrow$
3x wk $\times$ 4+ wks.

12 on low - 3×10^6 / day.

37 entered 3 not eval. 3 TETE
31 eval

CR	5	16.1%
PR	5	16.1
$\pm$	5	16.1
$\rightarrow$ prog	6	19.5
prog	10	32.2

H/S $\uparrow$ 8 .63 — .96
 $\downarrow$ 2 Time wk 3
 $\rightarrow$ 2

is ratio of response

9

most had $\downarrow$ NK at start of IFN
— no correl. of NK $\bar{c}$ elin response

PHA did $\uparrow$ $\bar{c}$ CR somewhat.

Thymus α_1 — no response in 5 pts

IL-2 —
Isoprinosine — Saturday

OLINGNEY — ^{cycling} VCR $\rightarrow$ BLZ0 $\rightarrow$ ACT.

CURRAN - CDC



Last 4 months > 100 cases / month despite
↓ reporting

			% mortality	
2/10/83			KS	21
#	deaths	%	⊗	
1051	406	46%	PCP	44
1161			Both	51
			Other OR	46

City			
NY	489	46.5%	
SE	128	12%	35 slabs
LA	71	6.8%	15 roundles
Wash	40	3.8%	
Newark	30	2.9%	
Other	295	28%	

95% ♂ 80% homo sex or bi sex.

Hep		Friend		Ar	
HbsAg	2				
SAB, cAb	76				
only cAb	15				
TOL	93	89	85	92	
HepA Ig1	86	63	56	54	* = 56.

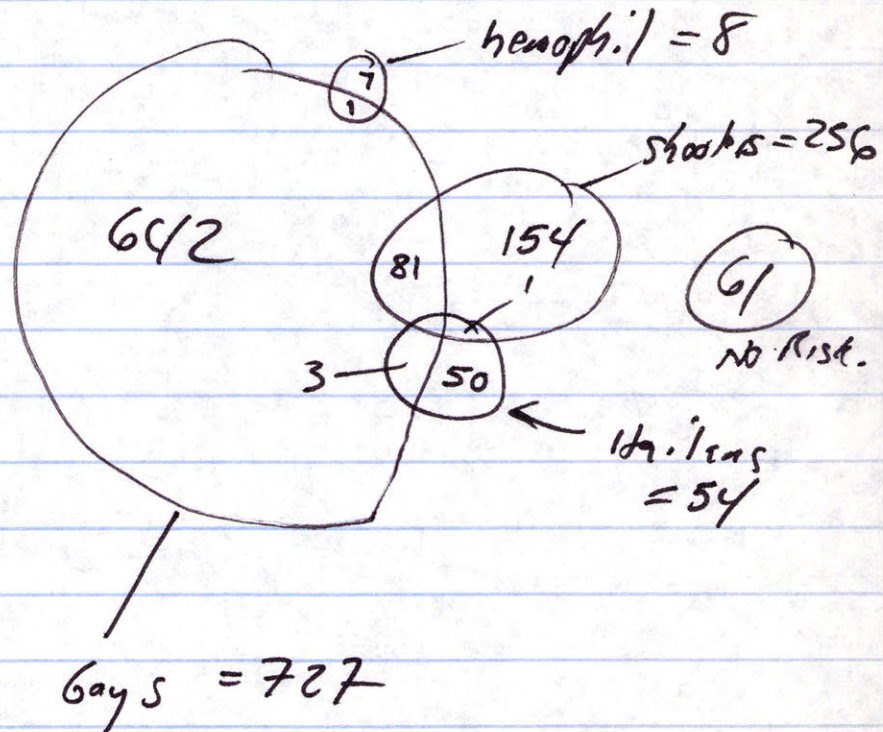
Dugas

6 - 36 mo

14 - 22 mo average time to AIDS.

12 AIDS in hemophilia (currently ~.1% of hemophiliacs)
 (Med. age hemophiliacs - 37)

1 gay man.



1. SX SX
2. partners of 1
3. Sex active gays
4. Partners of 3
- 5.

Blood Products / AIDS



? contaminated blood supply
Reviews recs of different
groups.

? ~~contaminated~~

- a.i.d. that infect. → AIDS

- Recipient develops AIDS
no other risk factors
approp incub
donor = AIDS

- Donor devel aids
recipient later devel AIDS

- transmission transmitter AIDS in epidemic areas

Primate AIDS — New England

780 monkeys

AIDS in
monkeys

31 CMV

13 Monkey

5 Herpes

4 PCP

3 MARS

2 SV40

infection in monkeys

Hexamita - chicken parasite.
Rarely hematogenous

William - D gay lifestyles

SF sex studies 1969 → 5000 selected
1978 published.

Gays diverse

Marmor - Epidemic of K.S. may be diff than other
AIDS.

20 ex + KS @ NYU 3/79 - 8/81
2 gay controls from private M.D.
Questionnaire ID, sex, drugs
diff/mo

Active, passive.

Rel. risk fellatio higher - swallow semen
anal - " " partner ejaculate
(RR = 11.3)

Sim. risk for Hep B.
R. Risk. of hep B higher in SF > LA > Chicago

? amyl A's use permeability has replaced
AIDS agent

vs.
Amyl use is $\propto$ sex activities at highest
risk for AIDS

$\therefore$ Conditions during rectal sex
Good + Low H/S $\leftarrow$
nitrate

Running out
sig risk factor

permeable sex

* partners

* anonymous partners

Risk factors in
endemic areas

- 1st part

- fecal exp via fishing

- rect recip of semen

- (+) A simplex type 2-) + ??

Risk factors in non-endemic areas

- contact in endemic areas

- (+) Syph serol.

- rect trauma via fishing

- rect recipient of semen

Conant - A patterns in sex transmitted disease



Rubenstein

Levine -

Two hypotheses -

A. single cause - prob. viral
B. MULT. DISEASES, CAUSES.

$T_H \downarrow$

$T_S \uparrow$ (Funct $\pm \downarrow$)

NK $\downarrow$ $M\phi \downarrow$

va γ IFN $\uparrow$ and labile IFN ($\therefore$ = SCF)

α Thymosin $\uparrow$

Angiogenesis - ? GVH

anti Sperm. Ab.

serum inhib factors (? binds IL-2)

Viruses often cause $\downarrow$ immune

esp retroviruses cause prolonged immune suppression.

Viruses affect on immunity:

** CMV $T_S \uparrow$ ($\pm T_S \downarrow$) $M\phi_S \uparrow$ B $\uparrow$ (CIC, Anti Ab $\uparrow$)

** EBV B $\uparrow$ (Polyclon AntiAb) $\rightarrow T_S \uparrow$ ($\pm T_S \downarrow$) NK $\pm$, mem. T $\uparrow$

FeLV $T_S \uparrow \uparrow$ (2' p15 interact at cell surf) thymic atrophy

RCAN(helper) $T_S \uparrow \uparrow$ (")

HTLV $T_S \uparrow$ (Infects T_{AC} / OKT_4^+ cells; $T_H \rightarrow T_S$ phenor)

Simian foamy virus . $T_H \downarrow$, $T_S \uparrow$ $M\phi \downarrow$ IFN $\downarrow$ Herpes reactivation.

MuLV $T_H \downarrow$ (depleted) $T_S \uparrow$ (relative)

HBV $T_S \downarrow$ (hepatic) immune complex

B lymph - grows in B cells

parvovirus - $\uparrow$ plasma cells.

Flu; fuler - Infect $m\phi \rightarrow$ suppress. factors
($\pm$ angiogenesis factor $\uparrow$)

Many need retrovirus, $\pm$ (immune) followed by
 $\&$ EBV $\rightarrow$ polyclonal B activation

Conjunct: ID

DiGeorge

(facial ab, hypopara, CHD)

congenital

$T_{\downarrow}$ ($T_S \downarrow > T_H \downarrow$) B me

Thym. hypoplas

No Cancer

Bruton

Depleted B cells. Tnl

Some ATs

Bacterial infect

↑ Cancer risk. . p long latency

— Non Hodgkins, AML.

Common Variable

B — limb comprom

some $\downarrow$ T cell ($T_H \downarrow > T_S \downarrow$) $\rightarrow$ B $\downarrow$

Infections like AIDS + bacterial.

auto antibodies

Over 5% 16 high incid of RA
(8:5%) incl gastric ca

SCID.

B & T ↓↓

Stem cell or 1° T cell defect. → ↓B

Wide variety of infect

Can get GVH p blood

? GVH at birth may be 1° cause
onset 1 yr

15% get cancer lymph, AML

Atax-Tel/an (Carroll diag., persist AFP)

B & T dysfunct

↓ Ig A, E

Ig G m, Ig M ↑ (variant)

Bact infect- (sino-pulmonary)

Spont chromosome breaks

↓ DNA repair.

12% get Ca if 9 + yrs. (wide variety
⇒ ? chromosome breaks)Wiscott - AlderB- & T dysfunct
in M.D. (2° to 1° defect
↓ antigen processing)

↑ Ig A, E

Ig G ±

Ig M ↓

Infection - wide

Ca risk 15-30% including 1° CNS lymphomas

EBV assoc. lymphoprolif.

Polyclonal B prolif
Follicular EBV prolif
ATs $\rightarrow$ hypo gammaglob.

No ATs $\rightarrow$ Lymphoma

Renal Trans

chem $\uparrow$ TH/S. = graft neg

$\downarrow$ TH/S = OI/KS

6% devel RA (100x A) onset 1/2 - 2 1/2 yrs

B cell NHL (EBV+)

1° CNS

KS ($\downarrow$ if immunosup D/c)

Hypoth 1° immuno supp $\rightarrow$ 2° react of CMV/EBV
 $\rightarrow$ TH/S $\downarrow$, polyclonal B prolif $\rightarrow$
OI/KS

Immune dysreg / cancer hypothesis.

Im. Surveil - (clones aut. elim by Ab, cytotoxic
NK, $\text{m}\phi$). Shouldn't $\rightarrow$ just
lymphoretic

$\text{T}_\text{S}^\text{A}$ - might $\rightarrow$ 2 $^\circ$ B prolifer $\rightarrow$ monoclonal
B cell.

$\text{T}_\text{S}^\text{V}$ - antigen driven B

$\text{T}_\text{H}^\text{V}$ - AB feedback $\downarrow \rightarrow$ B prolifer etc

B_A -

Exog. oncogenic virus - Immune Supp. + directly
oncogenic

aVIT - angiogenesis factor $\uparrow \rightarrow$ KS

Zolla - Porner

AIDS - Underlying disease.

Hypothesis -

1° B disorder. B Tropic virus.

B cells stim T_S which are not able
to down reg. B but do $\downarrow T_H$.

Immunoglob levels in KS

$I_{\Sigma}G$ A, A, mal.

pts $\in$ OI have $A I_{\Sigma} A$ more than
 $I_{\Sigma}G$.

Hyper gammu also seen $\in$ 'health' gay men.

Circ. B lymph cult $\bar{S}$ stim prod $2-3 \times$
 $I_{\Sigma}G$ than $ml.$ B cells.

Auto antibodies - also suggest B prolif.

anti platelet

anti T cell / anti sperm.

$\downarrow$ PWM responsiveness esp. OI. KS less so.

Prodromal AIDS - follicular hypoplasia.

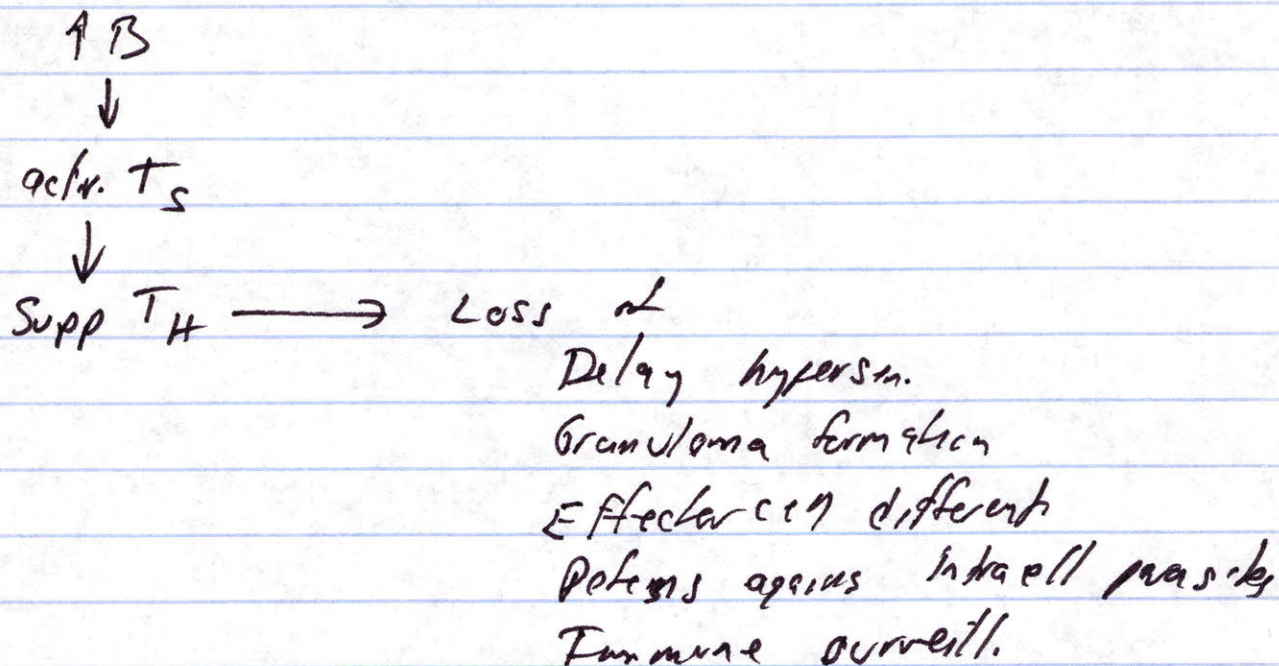
OI have absent germ centers $\Rightarrow$
burn out B cells.

All lymphomas = B cells.

Circ. B Σ microglob $\uparrow$ (freq. seen in B
cell malig., infections etc)

⇒ AIDS is lymphoprolif disorder.

IgG EBV ↑ (occ. 100x usual) (up to 1:80,000)
⇒ reactivation of EBV.



Fauci

Immune AIDS

↓ T_H
rel ↑ T_G

In vivo supp of T-cell funct

Intact B-cell immunity

Variable T & B cells in AIDS

H/S worst $\approx$ OI

$$KS = LNS \sim .7$$

Functional -

PWM esp. affected

($\Rightarrow$? 1° LPS_{ind} = T)

T_H cells very abnormal — when added to
ml. cells don't stim Ig prod.

Has not been able to clone T_H

T_G cells from pts
suppress normally

Hyperactivity of B cell is usually not able
to be further stimulated.

See profound defect in B cell prol. in
response to T cell independent B cell
mitogen (SAC)

ICCH antibody - blunted response in AIDS.
(also in 'healthy gays')
In vitro response - virtually nonexistent.

Transplant - int. lymphocytes 15-20 billion/cu.
See blip in H/S followed by repeat
drop.

Landerson - Haitian Study

	<u>US n=59</u>	<u>Haiti n=22</u>	<u>(No control groups)</u>
age	30	29	
♂	84%	82%	
% dead	63%	68%	

Haitians usually ~~don't~~ get KS

Difficult to find Haitians < 1979.

In NYC cases $\bar{p}$ 1980

Reports of KS > 01 in Haiti (unlike US)
Prob function underex of OI in Haiti

FL	25
NYC	21
Mon h	8
oh	5

COR reports to
end of 1/83

Port Au Prince	17
other	5
	81

	Cases	Haiti
	US	
KS	2	9
PCP	24	1
KS + PCP	1	0
Cand	3	
Prtylococ.	5	
Toxo	18	
other OI	6	

Immunol. parameters in patients like Homosexuals.

Several patients have developed TB
 before AIDS. (Not yet considered
 OI by CDC)

HLs ratios in patients w/ non-pulm. TB are
 low.

EFFECTOR CELLS IN AIDS -

↓ NK ~ 60% negative activity. Correlates
 w/ drug use.

Little w/ addition of αIFN.
 LNS have higher (ref. ul) NK but
 still see little augmentation w/ IFN.

Some LNS pts may recover NK activity
 spontaneously.

OKT10 cells & - pts cells may serve
 as NK targets

KARPATKIN

Crit

Wt

↑ mag

No ↑ spleen

No asic. disease

⊖ ANA

Rsp to splenect, steroids

Pts	cont
Age = 33	31
16,363 ± 2.9	235 ± 10

No correl. & drugs.

pl-IgG	5/6 (1.7)	2/10 (1.1)
--------	--------------	---------------

# lymph	1.6 x 10 ³ 5/9	2.5 x 10 ³ 4/16
---------	------------------------------	-------------------------------

IgG	1.78	1.37
-----	------	------

CIC (134 PCG)	.05 6/7	.01 4/9
---------------	------------	------------

H/S	.54	norm cont 1.75 Hemo cont 1.21
-----	-----	----------------------------------

No dif. in
Herpes S. serol
CMV titers
EBV
Hepatitis

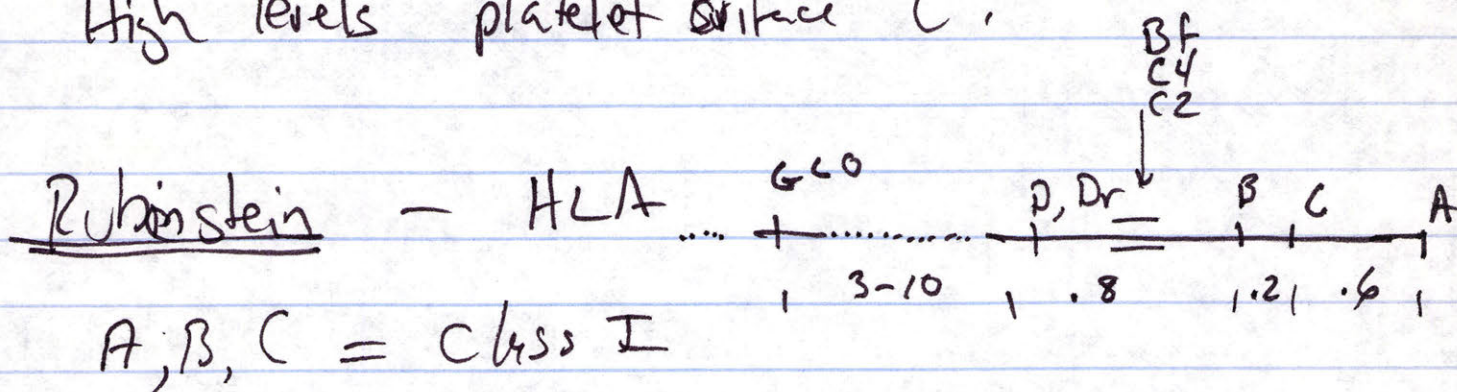
Gay IDP has more IgG / plts.

CIC elevated

Immune complexes bound to plts.

No correlation of (CIC) = platelet count.

High levels platelet surface C'.



D, Dr = Class II

	DRS	
	+	-
KS	30	30

$$\chi^2 = 9.44$$

GG Cont	31	85
---------	----	----

	DRS	
	+	-
KS	30	30
NS	16	64

NS

HLA in LUS is ident to KS etc.
 ϵ DR5 ~ 43-46%. C/w ~ 23% in controls.

B_W35, CW4 also elevated. Are same as elevated in classical LES.

DR2 may be elevated in N. Europeans.

HLA loci flanking DR are not assoc. to HIV.

Possible mechanisms of HLA assoc

1) Pop. stratification e.g. Jews, Italians
 (No good evidence)

2) HLA is cause of susceptible
 virus receptor
 Antigenic cross reactivity.

3.) Linkage disequilibrium & suscept locus
 - close linkage + recent population admix
 - Epistatic interaction,
 eg. immune response genes
 - facilitate ↓ immune
 - A sens. to pathogens

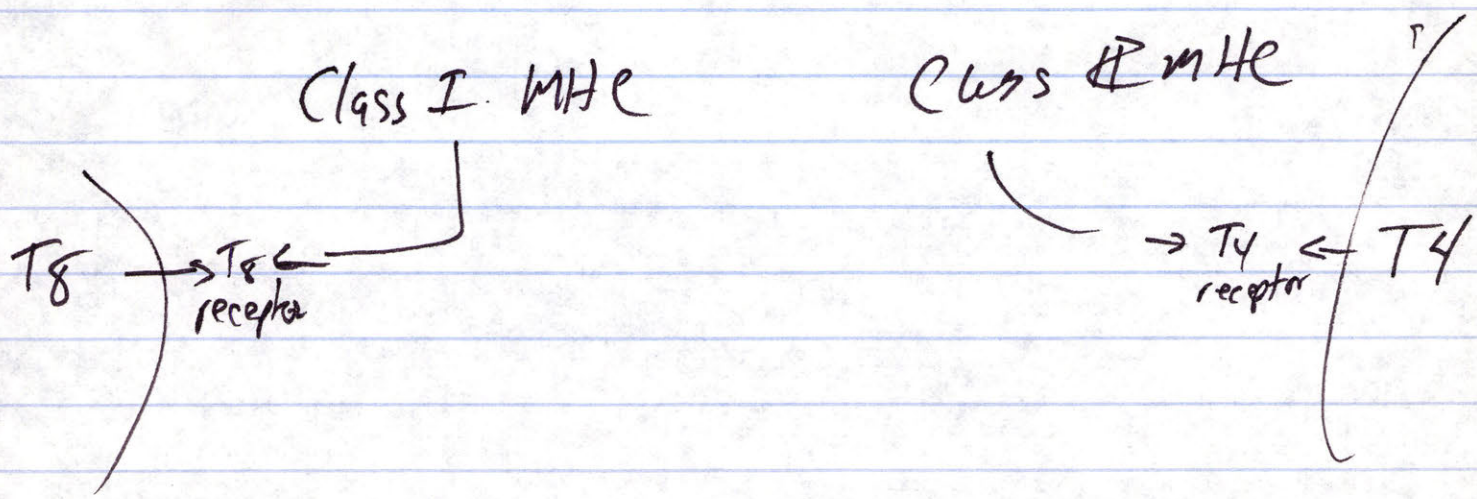
ARDS
Bw 44
8 (9%)
8 (9%)
Bw 44, DR7, Bf7
412 (8%)
6 (2.3%)

⇒ Linkage important

H/S $\propto$ PWM response

Schlossman - Neither H or S work well.
T₃ coexpresses T_H / T₈ (See HTLV)
could be both AdS

Clearly at least two pop of T_H⁺ cells
1 → activate B cells. etc T_H⁺ JRA⁻ TQ1⁻
1 → suppress T₈⁺ T_H⁺ JRA⁺ TQ1⁺



~~Real~~ Surface structures have functional roles
eg. T₉ is transferrin receptor.

1. SCID — Mat. arrest Thymocytes

2. Com. Var ID — No inducers
activation: suppressing
↓ H/s
non funct ind

non funct

CPromoters Capen

antigen specific & non-spec
suppression

INFECTION - ETIO / THEN OF AI

PAGANO - Viruses of Human cancers.

? RNA - HTLV

DNA - Papilloma - warts ? vulva, ? cervix.
? Papovavirus - human & Simian (SV40)

? Adeno

Herpes

? HSV II

? CMV

EBV

HBV

Clues to viral etiol

Unusual disease phenotype

High Incid infection / Low incid disease

Persist. or latent infection

Epidemicity

Virus reactivation

Co factors

Properties of oncogenic virus

DNA or RNA

Circ. genome or provirus.

Viral genes retained

Virus expression restricted

Stimulation of host macromolecular synthesis

Non-lytic cellular interactions

Tissue proliferative effects

EBV assoc. lymphoprolif

1° ID

Duncans

W. Scott Ald.

T. A

comb. ID.

2° ID

Allograft recipients
AIDS.

Proliferative phenotypes

Fatal IM. (Duncans)

Burkitts (Aner.)

Hist. lymph.

Immun. Sarco.

Humoral ID $\bar{c}$ EBV chronic INF

Plasmacytoma

Hist. med Reticulosis

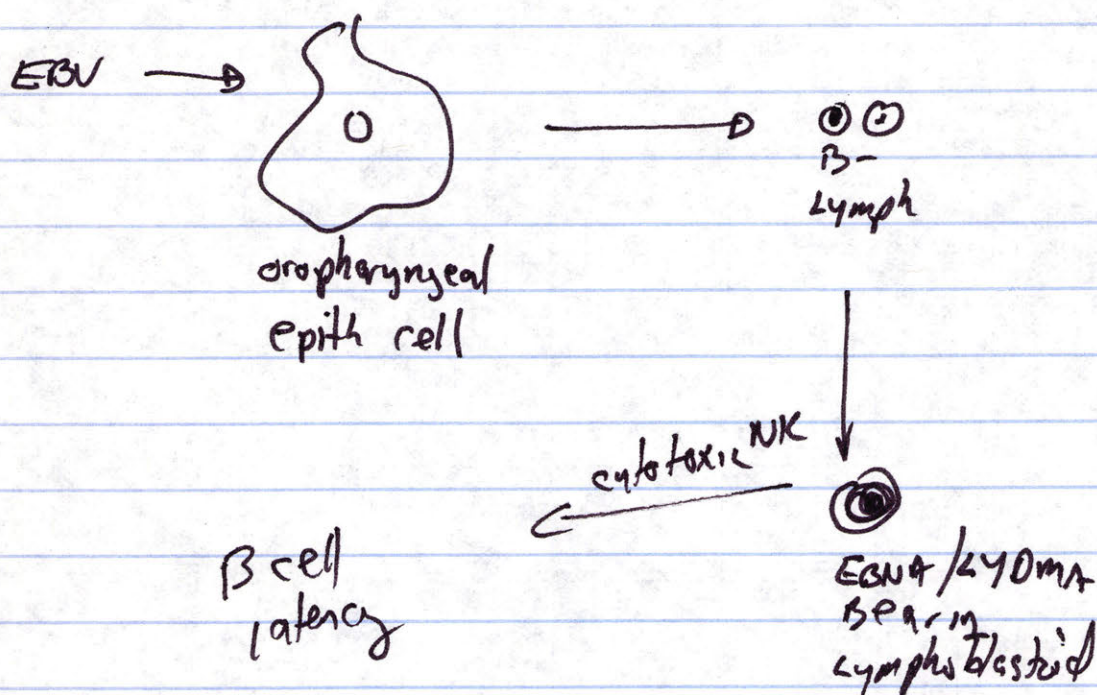
EBV serol

VCA Ab $\uparrow$

EA " +

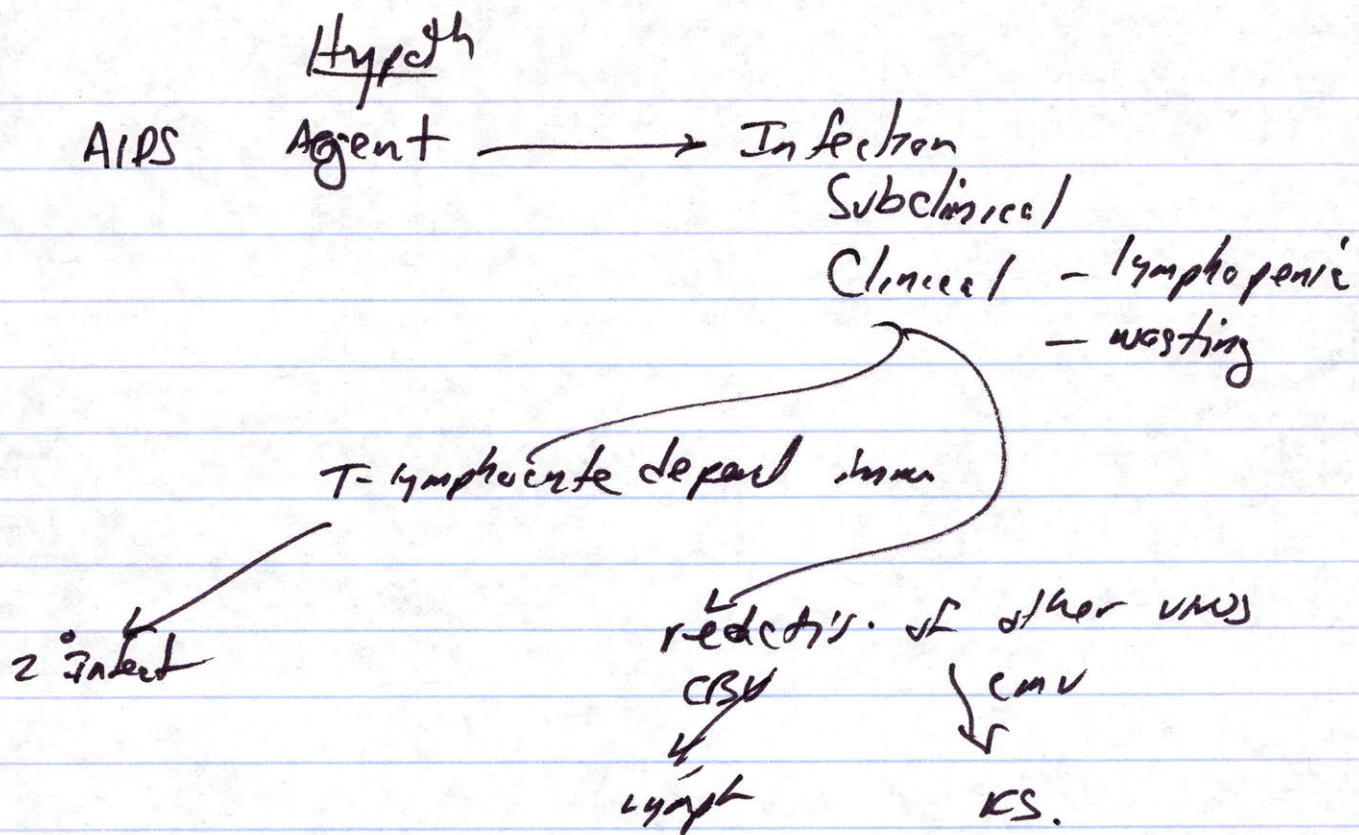
EBNA undetectable

Rising VCA = no EBNA is unfavorable sign -



therapy of EBV & Lymphoprolif

- Poly clonal
- antiviral drugs.
 - No anti cellular drugs.
 - Low dose XRT
 - T-cell restoration
 - Anti EBV Surface monoclonal Rx
- Monoclonal
- antiviral drugs
 - T-cell restorat.
 - anti-idiotypic serotherapy.



KS virus

Common virus (b/c cases in kidney transplant)

Infection silent, early

Latent $\rightarrow$ reactiv.

Target cell (secondary): vasc. endothel. stem cell

CMV? (Not AIDS virus)

Endothelial prolifer. potential

Immuno regulated

CO-Factor in Africa.

AIDS AGENT

- New : DNA or RNA - Prob not mutation.
as shifts in virulence rare.
- Transmission
multimodal
non-respiratory
not vector born
- contagiousness limited (A₁ adaptation)
- Silent infection probable
- 1° target cell unknown.
- Effectors on T-helper cells indirect, 2°
- Symptoms of infection, 2°
- Uremia non-cell-associated
- Simian origin? Caribbean.

Hoang - CMV

Role of CMV

- Causal association
- Non-Causal association.

Biochem Δ_p CMV

Stim. host DNA, RNA synth

Stim enz. synt

thymid kinase

DNA Polymerase-

↓

CMV can transform hamster embryonic fibroblasts

" HEL. T CMV

" HEL T CMV DNA

Transform 3T3 T fragment.

CMV strains all different unless from same pl. $\rightarrow$ No single CMV strain.

MqSUR — Pneumocystis

Spectrum of OI is unusual — extremely frequent c/w other ID. states.

Some OI not common in AIDS eg nocardia even tho common in transplants.

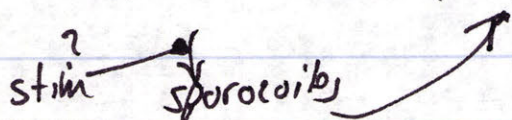
Incidence PCP in AIDS striking — 55% of all AIDS have PCP.

Of all OI, PCP is 290% cause of infection.

Biology

PCP is extracellular.

Cyst form. , trophozoite. = invasive form



Some evid of respir spread

- Mem. sk. outbreak
- Nude mice

Control of PCP.

- Humoral resp.
- Macrophage will engulf only $\bar{P}$ Ab
- ? T cell response.

Only 3 cases of PCP in 'healthy' persons prior to current outbreak.

Is AIDS PCP different than in other setting.

Present - Duration

Sever

No diff

Phys. findings

Rachol - varied - including effusions.

Pathol - Eosinophilic miter etc - No diff

Resp to tx -

Survival ~ 50-60% , Longer to respond in AIDS

Adverse effects. -

Outcome TCD

	<u>AIDS</u>	<u>other Adults</u>	<u>Kids</u>
Sr 12 ⁺ 16sp	62	54	77
a/ne > 30d.	<u>78%</u>	61	75
a/ne > 90d	56	56	69
relapse	<u>11%</u> *	0	11

* prob. higher.

Dx- Cult. $\pm$

Serology -

Problem of

Skephersm.

special stains is that only
see cyst forms.

Ghosts vs. living bugs.

Gram stain can show Sporozoites in
cyst but still not trophozoites.cyst wallSporozoitesTrophozoites

Therapy - Rat model

Regimen:	TMP/S	-	$\frac{\% \text{ PCP}}{36\%}$
	Pentamidine	-	86%

TMP/S - static

Pentam - ~~epi~~cidal

Kombin - Kluge 1978 - TMP/S + Pent worse.

Rate Response

	<u>Pentam</u>	<u>TM</u>
Temp	4 (1-8)	4 (1-25)
CXR	9 (4-20)	12 (1-15)
$PaO_2 < 85$	8 (1-21)	9 (3-27)
$RR < 30$	7 (1-12)	10 (4-33)

$\Rightarrow$ Don't expect resp. $\propto$ $< 4d$.

Prevention - No immun. effect
 TMP/S completely prevents PCP in kids
 = ALL

14 days therapy +
 ? Assessing efficacy

Prevention -

? Resp spread in clinics.

? efficacy

Some have devel PCP on prophylaxis

Few pts tolerate TMP/S.

- Neutropenia
- Fatigue
- N/V

Greene - M.A.IOT in AIDS

Fungal
Cryptococci
Coccidioid

Bacterium
MAI
MTB

Legionella
Salmonella
Actinomyces
M. Kansasii

~~Stage 01~~ 8+

Presenting symp

- Pulm. Syndrome
- CNS syndrome
- GI syndrome
- FVO

42 consic trans fs
 → dx in 37 (88%)
 No serious compl,
 14 pts PCP + oI
 Other oI 3 (7%)
 Non dx 5 (7%)

CNS Syndrome	<u>NDA</u>
Enceph	- CMV
Dementia	- PML.

Headache	Cyto. men
Photophobia	MTB
Neural sig	MAI

Seizures	- Toxo
AIIP	- CNS lymphoma
Focal sigs	

CMV Retinitis -

Toxoplasmosis - mult necrot masses $\bar{c}$ enhance
 Serol tests unreliable (include CSF)
 Cran. ct & bx of wall - needle no good

Cryptococcus meningitis -

⊕ index IHC 15/15
↓ cells in CSF 14/15

TX CNS

Toxoplasmosis | Pyrameth. ^{100mg} load → 50 qd
Sulfadiazine 1.5g po qid
Clind. 600-1200 mg/d

Cryptococcus | Amphot. 0.6 mg/kg/d IV
SFC 100-150 mg/kg/d

GI syndrome, Low vol diarrhea, wat., no stool pain

⇒ Major no pathogen

High vol. diarrhea -
⇒ cryptosporidiosis - salinamycin > rifampin
pyralium

Low vol., tenes., blood

⇒ CMV

FUO — when 1st manifest of AIDS w/ny
often unclear.

When in setting of prior QT,
usually $\Rightarrow$ new QT

MAIC esp common.

Group III — non photochromogen

18 pts. — 14 $\approx$ KS

— 4 other QT

Lives — pen cytopenias (rapid)
abn. LFTs

Acid fast stain on all pts.

Best tissues — B. Marrow

— LN

— Liver

Begin presumptive tx. serotypes 4, 8

Therapy — sub optimal.

Quinymycin

INH, amcy, 3LP / Pth
Amc

— 5/33 response to quinymycin in NY
coop trials.

antilep. (100mg/d.)
Clofazimine now — being tried

HTLV -

T-LCL
Cura

ATL
Jab

↑ WBC

↑ OKT4 but may act as suppressors.

HTLV - gp 50-54 (Sim. to bov. Leuc. vir)



HTLV is resp for 90% Japan T-cell lymphomas. Is spread horiz., low infectivity. Infects OKT4.

Retrovirus etiol of AIDS

- AIDS is disease of OKT4⁺ cells & so is HTLV
- Animal models of retrovir. → neoplas, & hypoplasia
- AID in Hiti first

Diffe. in estab. assoc
antibody pos
loss of infected cell.

INTERFERON in AIDS -

IFN in autoimmunity - % $\uparrow$ in IFN

SLE	50
RA	50
Scleroderma	60
Sjogrens	77
Aphthous	0
NL	3

IFN in pathogen SLE

- [serum] α disease activity
- IFN $\rightarrow$ worse disease
- IFN $\rightarrow$ newborn mice $\rightarrow$ glomerulonephritis sim to SLE

IFN nomenclature

old system

Leucocyte

Fibroblast

Immune

Le

F

I

α

β

γ

new

(numerous subtypes)

SLE IFN

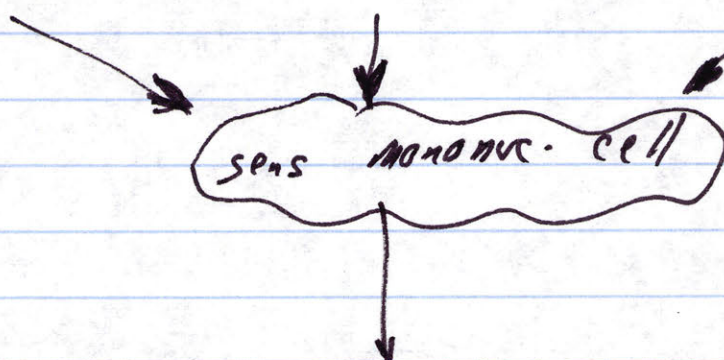
- bound by antibody to IFN α

IFN stim. in SLE

Host
antigen

Imm. Comp

Anti lymphocyt
ab



IFN α

Antibody react $\bar{c}$ lymphocytes $\rightarrow$ test for IFN.

E IFN

Harris - 0/22

Gays - 2/25

LMS - 10/35 — = SLE IFN.

ICS - 17/27 — (acid labile)

? - response to causative agent
- " " reported infections

- 2^o autoimmune

Role

- No fund. significance

- Beneficial

- Detrimental

- ↑ phago, cytotoxic
- ↑ ↑ Fc recept
- ↑ NK activ.
- ↑ ADCC
- ↓ Ig prod (or ↑)
- ↑ ILA exp mφ, [β2 microglobulin.]
- ↑ or ↓ allograft reject, delayed hypersen.

Rationale for IFN tx

- ↑ tumor regression
- ↑ immune competence
- ↓ viral infection

? Dilemma

- ? adverse effects on immune compet.
- prelim evid of response

Inverse correl of (IFN) & mitogen response.

Hemophiliacs & IFN anti AIDS.