Preventing HIV-induced Cardiac Dysfunction
Novel Insights from the SIV/Macaque Model

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Leading research in human and animal disease
Disclosures

Pfizer provided Maraviroc for these studies

Patent pending: Compositions and Methods for Treating or Preventing Cardiac and Neurological Disorders Using Chemokine Receptor Antagonists. JL Mankowski, First Inventor. Patent will be held by Johns Hopkins University
AN INVESTIGATION

INTO THE

PARASITES

IN THE

PORK SUPPLY OF MONTREAL.

BY

WILLIAM OSLER, M.D., M.R.C.P., Lond.,
Professor of the Institutes of Medicine, McGill University; Lecturer on Helminthology, Montreal Veterinary College.

AND

A. W. CLEMENT (LAWRENCE, MASS.),
Student Montreal Veterinary College.

MONTREAL:
PRINTED BY THE GAZETTE PRINTING COMPANY.
1883.
glands. No hair follicles are seen. For the most part the
cyst is surrounded by a narrow band of connective tissue or
ovarian stroma, but at some points the epithelial cells have
penetrated to the surface and cell-masses are found in the
mesosalpinx and even between the layers of muscle-bundles in
the tube-wall. The broad ligament also contains metas-
tases, cell-nests being found in the lymph-spaces, and, in one
place, in a large vein. The tubal mucosa is normal and no
tumor elements are found on the upper surface of the tube-wall.

Left side.—The tumor is similar to that on the opposite
side. The corpus luteum observed macroscopically presents
the usual features and shows commencing organization.

Diagnosis.—Carcinoma ovarii duplex associated with a
small dermoid cyst in the right ovary. Corpus luteum in the
left ovary. Practically normal uterine mucosa. Peri-
salpingitis. Subperitoneal cysts.

References.
VII, S. 169.
3. Heschl: Prager Vierteljahrschr., 1860, Bd. LXVIII,
S. 57.

PULMONARY TUBERCULOSIS, WITH DIFFUSE PNEUMONIC CONSOLIDATION, IN A LION.

BY W. G. MACCALLUM, M. D., AND A. W. CLEMENT, V. S., Baltimore, Md.

While in Birmingham, Ala., in November, 1899, one of the
lions belonging to the Hagenbeck menagerie, a large adult-
male of the black-maned sort, which had been captured in
South Africa and had been in captivity ten years, fell ill. The
keeper noticed that the lion was not well and frequently
refused food. On the removal of the menagerie to Baltimore
it grew worse, developed a slight grunting cough, became very
much thinner than normal, and, after an illness of about four
weeks altogether, died.

The autopsy was performed the next day. The body was
that of an adult male lion, said by the keeper to be about four-
teen years old. The subcutaneous and omental fat were very
intervening lung-substance was gray or grayish-yellow, and
somewhat gelatinous and translucent. The lower lobes were
more firmly and uniformly consolidated, the firmness being
due to a diffuse consolidation rather than to the translucent
nodules which were more sparsely scattered throughout these
lobes. The cut surface was, as in the upper lobe, grayish-yel-
low and somewhat translucent. In the posterior portion of
the lobe, there were two well-defined cavities communicating
with one another by a narrow channel, and marked off from
the surrounding lung by the fibrous thickening of their walls.
These cavities communicated with the bronchi; their walls
were fairly smooth and covered with a purulent material.
Visna Virus Infection of American Lambs

Abstract. Random-bred fetal and 4-week-old American lambs, inoculated intra-cerebrally with visna virus, developed a persistent infection in the brain and sometimes in the lung. The pathologic changes present in these lambs were similar to the early lesions of visna in Icelandic sheep, thus providing a possible model for the study of virus-induced demyelinating disease.

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Sequence Homology and Morphologic Similarity of HTLV-III and Visna Virus, a Pathogenic Lentivirus

Abstract. A study was conducted of the genetic relation between human T-cell lymphotropic retroviruses and visna virus. The human T-cell lymphotropic viruses include those associated with T-cell malignancies (HTLV-I and HTLV-II) as well as the etiologic agent of the acquired immune deficiency syndrome (HTLV-III). Visna virus, a slowly replicating and pathogenic but nononcogenic retrovirus of sheep, is a member of the subfamily Lentivirinae. Results obtained by molecular hybridization and heteroduplex analysis indicated that a greater extent of nucleotide sequence homology exists between HTLV-III and visna virus than between HTLV-III and any of the other viruses. The homology observed under conditions of low stringency spanned the entire genome, but was strongest in the gag/pol region. The morphogenesis and fine structure of HTLV-III and visna virus also demonstrated striking similarities. The data provide strong evidence for a close taxonomic and thus evolutionary relation between HTLV-III and the Lentivirinae subfamily.

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PREVENT HIV WITH ABC

Abstain from sex, or...
Be faithful to one partner, or...
Correctly use condoms every time.

Message brought to you by: San Pedro AIDS Commission and U.S. Embassy

For Information on HIV/AIDS, Please Call 206-2085
Natural Hosts of SIV
African Primates

Abnormal Hosts
Asian Macaques

Moderate viral loads
No clinical disease

High viral loads
Clinical disease
HIV organ specific disease

- Lymphocytes
- Macrophages

HIV
SIV

Immunosuppression AIDS

Organ specific disease

- CNS disease: HAND
- Peripheral neuropathy
- Cardiomyopathy
- Pneumonia
- Nephropathy
HIV-associated cardiac dysfunction

- Overt clinical cardiac manifestations: ~20%
- Association of myocarditis with function decline undefined
- LV diastolic dysfunction
  - 60% of asymptomatic HIV+
  - HAART
Diastolic dysfunction

- Functional abnormalities that exist during left ventricular relaxation and filling
- At risk for development of heart failure and reduced survival
Assessing Cardiac Phenotype in SIV

Mitral Inflow Doppler Imaging

Tissue Doppler Imaging

LV
LA

Septal TDI

Lateral TDI
Assessing Cardiac Phenotype in SIV

Control

SIV
SIV-associated Diastolic Dysfunction

- Change in MV DT (msec): P < 0.001
- Change in E/A: P = 0.027
- Change in lateral myoRT (msec): P = 0.002
- Change in septal myoRT (msec): P = 0.041
SIV-associated Diastolic Dysfunction

A

B

C

D

P = 0.042

P = 0.020

dp/dt min

Tau fit

Control
SIV

Control
SIV
Macrophage Immune Activation in Myocardium

Control

SIV

CD68

A

B

CD163

C

D
Macrophage Immune Activation in the Myocardium

\[ \text{CD68 Immunostaining (\%ROI)} \]

\[ \text{CD163 Immunostaining (\%ROI)} \]

- P = 0.019
- P = 0.0005
Myocardial SIV RNA and Diastolic Dysfunction
SIV/Macaque Model: Clinical Conclusions

- Diastolic dysfunction develops in SIV-infected macaques
- Diastolic dysfunction not correlated with macrophage activation
- SIV RNA in heart strongly correlated with cardiac dysfunction
T-cell-line-tropic strain of HIV-1

HIV (X4)

α-chemokine receptor (CXCr4)

CD4

Sdf-1

CD4+ target cell

Macrophage-tropic strain of HIV-1

HIV (R5)

β-chemokine receptor (CCr5)

CD4

β-chemokine (Rantes, Mip-1α, Mip-1β)

CD4+ target cell

Adapted from Fig. 3 of A. S. Fauci, Nature 384:529–533, 1996, with permission.
Maraviroc
(UK-427,857)

T-cell-line-tropic strain of HIV-1

Macrophage-tropic strain of HIV-1

Adapted from Fig. 3 of A. S. Fauci, *Nature* **384**:529–533, 1996, with permission.
In vitro assessment of functional CCR5 expression on cardiomyocytes

- Isolation of rhesus ventricular cardiomyocytes
- Single cell recordings of sarcomeric contraction and calcium transients measured over time in cells exposed to CCL5
- Cells subsequently exposed to Maraviroc, sarcomeric contraction and calcium transients measured over time
% Change in Sarcomeric Contraction

-60 -40 -20 0

CCL5 CCL5+MVC

P = 0.002
n = 17

SIV SIV+MVC

P = 0.059
n = 4

CCL5 CCL5+MVC

P = 0.002
n = 17

SIV SIV+MVC

P = 0.059
n = 4
## Maraviroc Study Design

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of animals</th>
<th>Days post-inoculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIV + Maraviroc</td>
<td>6</td>
<td>180</td>
</tr>
<tr>
<td>SIV</td>
<td>22</td>
<td>180</td>
</tr>
<tr>
<td>Uninfected</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

Maraviroc dose = 200 mg PO BID, started day 24 p.i.
CCR5 Inhibition Modulates Viral Load
CCR5 Inhibition Preserves Diastolic Function
Conclusions

• SIV/macaque model established for HIV-associated cardiac disease

• Addition of CCL5 or SIV to isolated cardiomyocytes decreased contractility which was reversed by maraviroc

• Maraviroc monotherapy is cardioprotective in the SIV macaque model
Animal Models of Disease

• Model development- basis for translational research
• Foundation for pathogenesis studies – when and where
• Molecular mechanism discovery
• Improving diagnosis
• Platform for novel therapeutic and preventive approaches
• Cornerstone for team science – fostering interdisciplinary research emphasizing an integrative comparative approach
Johns Hopkins University School of Medicine

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