Chemical AIDS

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Part IV

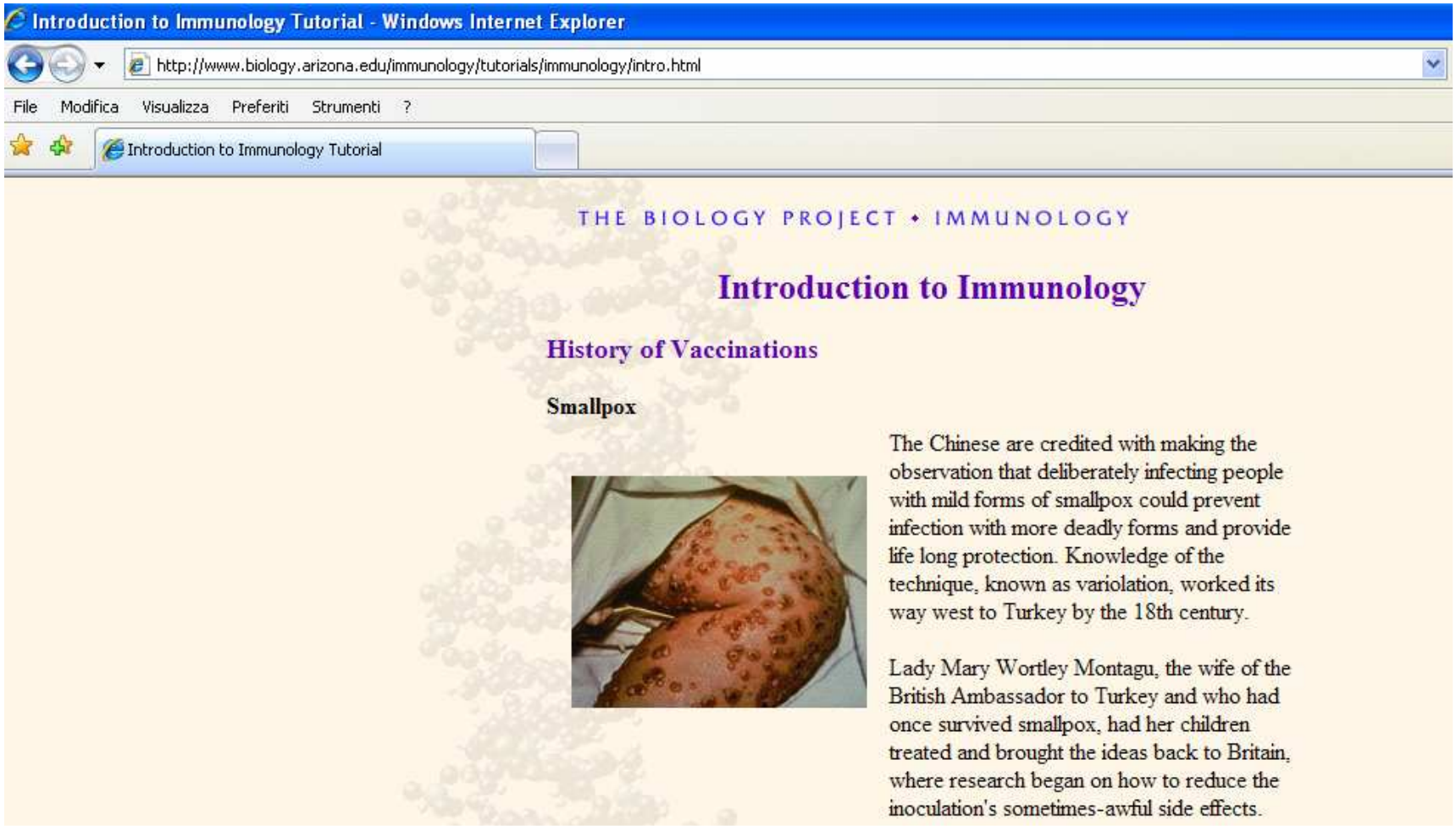
HIV≠AIDS?

Then what?

"AIDS", just like "cancer" is too generic a word. Just like there are many pathways leading to different types of cancers, there are many different pathways leading to immune system impairment.

A brief overview

- Of the immune system



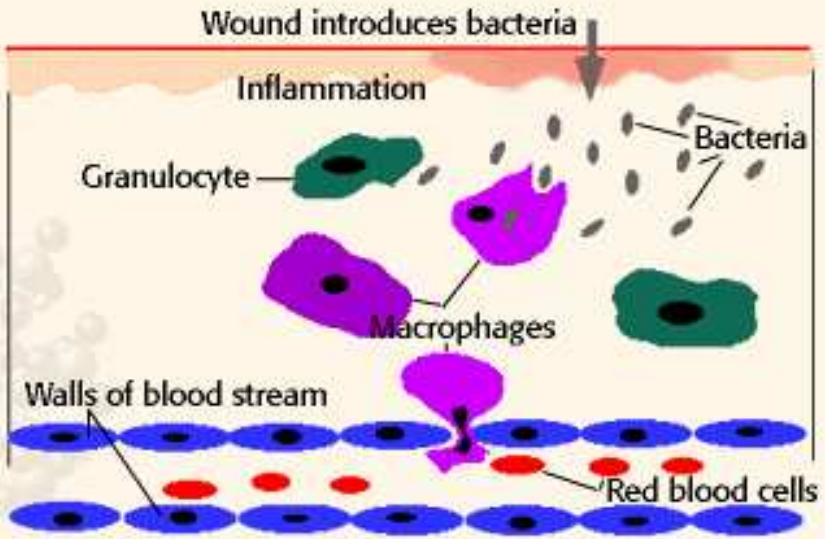
Key Concepts of Immunity

- The immune systems has evolved to protect us from common pathogens.
- Innate immunity is the immediate response to commonly shared microbe antigens (LPS, teichoic acid, patterns of sugars).
- Innate immunity includes physical, chemical and mechanical barriers to entry, phagocytes to engulf and digest extracellular pathogens, and interferons and NK cells to block virus replication and kill virus-infected cells.
- Inflammation attracts leukocytes to the infection site, where innate immune responses occur.

Innate defenses begin to act very soon after the appearance of a pathogen in the body. Innate defenses are nonspecific – they target any pathogen. Innate defenses include:

- Skin, which excludes most pathogens from entering the body
- Cilia in mucous membranes, which sweep out airborne pathogens and dust
- Tears, nasal secretions and saliva, which contain bacteria-destroying enzymes
- Specialized phagocytic cells (*"phago-"=eating, "cyte"=cell*) which migrate to affected areas and engulf pathogens.

Phagocytic cells include granulocytes (or neutrophils), macrophages, and dendritic cells that are part of the white blood cell fraction. Pathogens and infected cells produce chemokines, peptides that increase the permeability of blood vessels. This permits a migration of white blood cells toward the wound, causing the redness and inflammation associated with infection.



Some types of lifestyle

- Target innate defenses
- Next slide courtesy of

Intestinal Dysbiosis and “AIDS”

Tony Lance

RA 2009

Oakland, California

November 6-8, 2009

- Sexual lubricants, many of which are hyperosmolar, are known to damage the intestinal epithelium and presumably affect gut flora.

  - A 2008 study found that many commercially available lubricants dried out the lining of the colon. Astroglide, the top-selling brand worldwide and one targeted to gay men, was described as “highly hyperosmotic” and “…resulted in severe irritation and tissue damage.”

Adaptive immunity

- Adaptive immunity is the slower response to specific antigens which vary from pathogen to pathogen.
- Adaptive immunity includes antibody, cytotoxic T cells, and inflammatory (macrophage-activating) helper T cells.
- An active immune response is made to antigen exposure, either naturally acquired during infection or artificially acquired by vaccination. Passive immunity is acquired from another individual in the form of antibodies. Humoral immunity is due to antibody production, while cellular immunity is due to cytotoxic and inflammatory T cell activity.
- Innate immune mechanisms including inflammation and phagocytosis are essential for the efficient functioning of the adaptive immune system.

The immune system

- The immune system is composed of circulating leukocytes and lymphoid organs.
- Hematopoiesis, the differentiation of stem cells into mature leukocytes, occurs in the bone marrow. T cell maturation is completed in the thymus. Bone marrow and thymus are the primary (central) lymphoid organs.
- The secondary (peripheral) lymphoid organs bring together antigen and leukocytes to initiate adaptive immune responses. Secondary lymphoid organs include the lymph nodes, spleen, Peyer's patches, tonsils and adenoids, appendix, and collections of lymphoid cells in mucous membranes.
- Leukocytes recirculate between lymphoid organs and the blood via the lymphatic vessels, which also collect antigen from the tissues.

Phagocytes

- Phagocytes include monocyte/macrophages, granulocytes (neutrophils, eosinophils, basophils) and dendritic cells. They have receptors for common pathogen antigens and for complement-coated and antibody-coated antigen. In addition to engulfing and destroying pathogens, macrophages and dendritic cells can make cytokines that regulate immune responses and can process and present antigen to T cells.

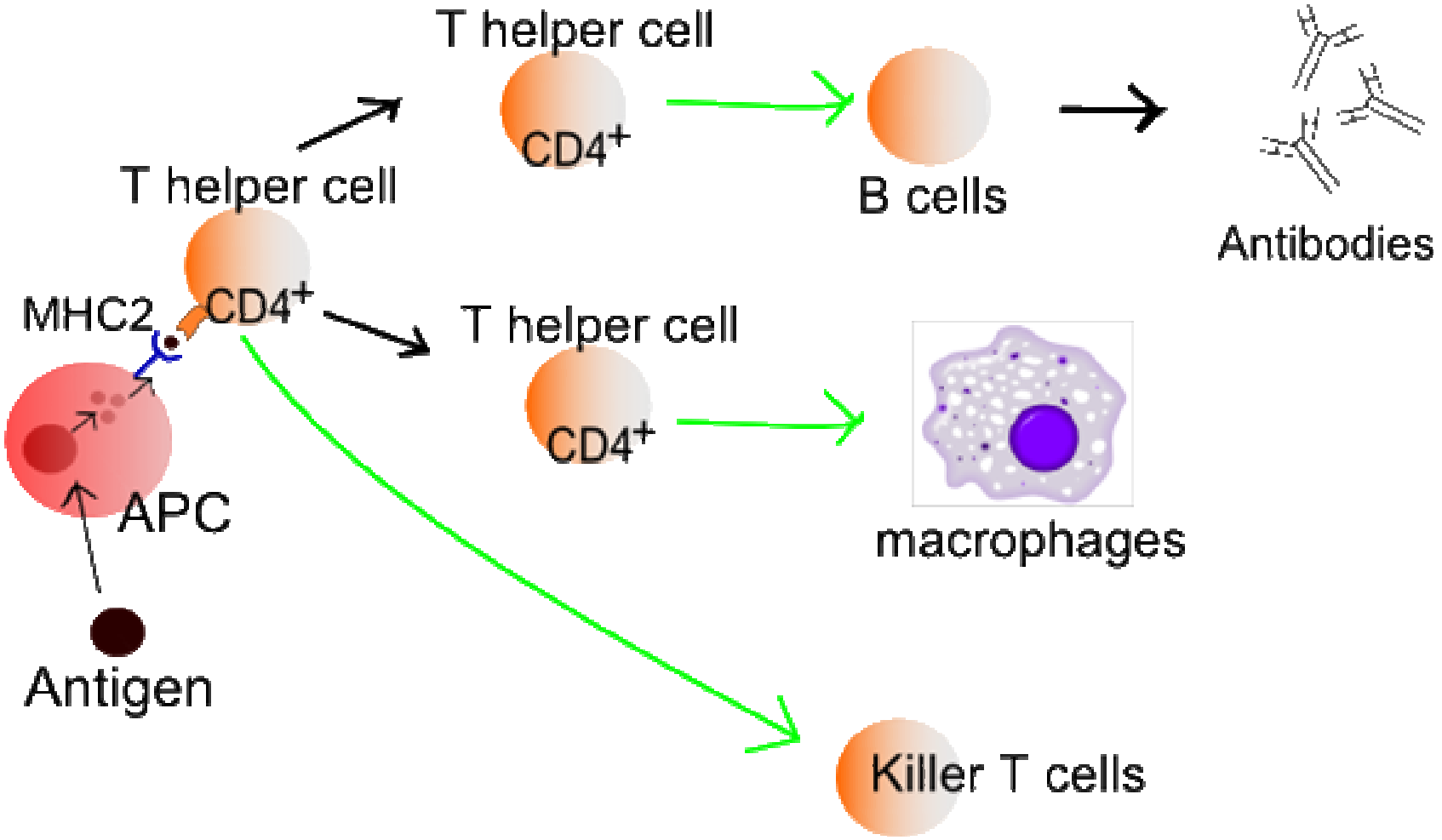
Lymphocytes

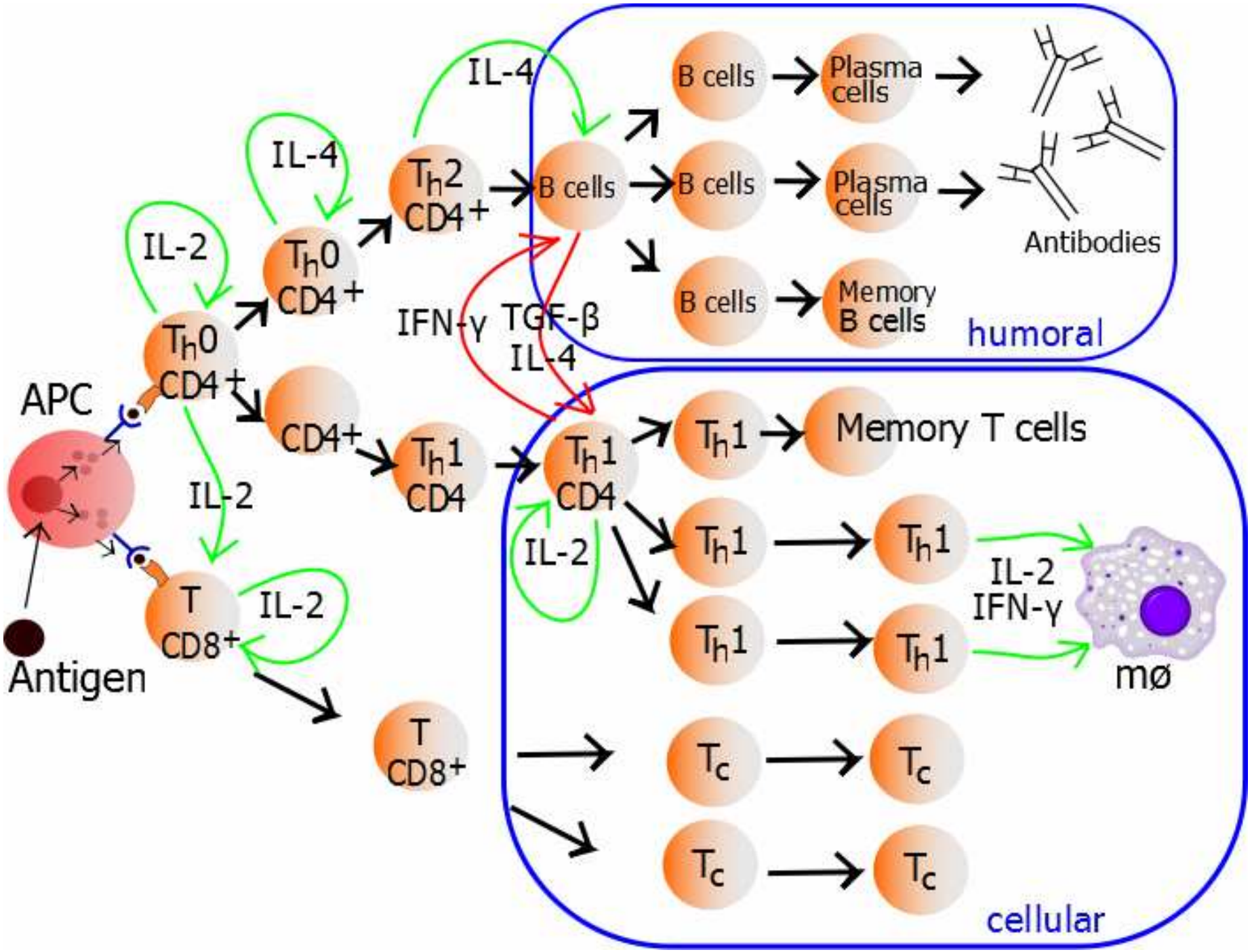
- Lymphocytes include B cells, T cells, and Natural Killer (NK) cells. B and T cells have specific antigen receptors which are generated during lymphocyte development by a specialized gene-splicing process. BCR bind native antigen, but TCR bind only to antigen peptides presented on MHC. NK cells do not have antigen-specific receptors, but recognize altered MHC on virus-infected and cancer cells.

T helper cells

- T helper cells (also known as Th cells) are a sub-group of lymphocytes that play an important role in establishing and maximizing the capabilities of the immune system. These cells are unusual in that they have no cytotoxic or phagocytic activity; they cannot kill infected host (also known as somatic) cells or pathogens, and without other immune cells they would usually be considered useless against an infection. Th cells are involved in activating and directing other immune cells, and are particularly important in the immune system. They are essential in determining B cell antibody class switching, in the activation and growth of cytotoxic T cells, and in maximizing bactericidal activity of phagocytes such as macrophages. It is this diversity in function and their role in influencing other cells that gives T helper cells their name.

Mature Th cells are believed to always express the surface protein CD4. T cells expressing CD4 are also known as CD4+ T cells.

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IL-2
Antigen
T CD8+
IFN-γ
TGF-β
IL-4
B cells
B cells
B cells
B cells
Plasma cells
Plasma cells
Memory B cells
Antibodies
humoral
T_h1 CD4
IL-2
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Memory T cells
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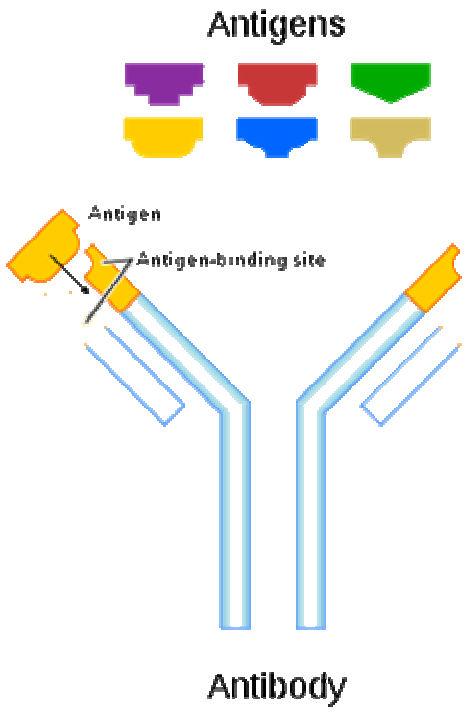
Cytokines

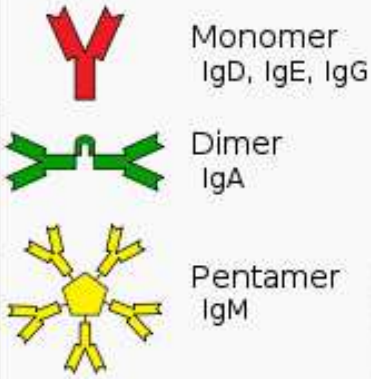
- Cytokines are chemical messengers made by leukocytes, primarily T cells, macrophages and dendritic cells.
- Antigen stimulation plus other signals stimulate specific lymphocytes to proliferate and differentiate into clones of effector cells and memory cells.

Antibodies

- B cells are activated to become antibody-producing plasma cells. Antibodies are specific antigen-binding proteins that neutralize and opsonize antigen and activate complement to promote inflammation and phagocytosis. Different antibody isotypes have specialized locations and functions.
- Antibody is composed of disulfide-bonded heavy and light chains in a Y shape, with two identical antigen-binding regions at the ends of the top of the Y. The antigen-binding regions of antibody differ in their amino acid sequence from one molecule to the next and are called variable regions. The stem of the Y (the constant region) has one of five possible structures (isotypes: IgA, IgD, IgE, IgG, and IgM) that determine the effector functions of the antibody.



Antibody isotypes of mammals

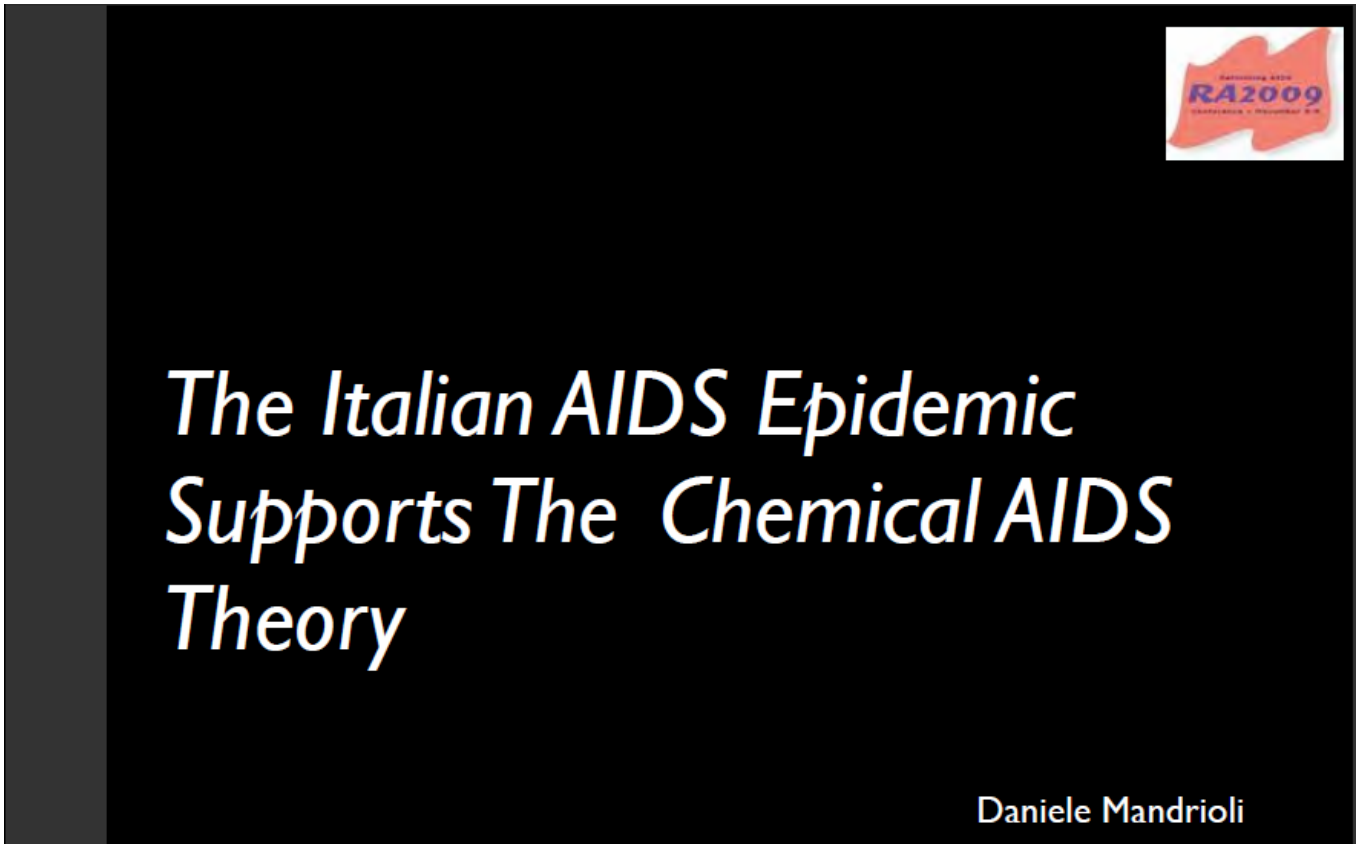
Name	Types	Description	Antibody Complexes
IgA	2	Found in mucosal areas, such as the gut, respiratory tract and urogenital tract, and prevents colonization by pathogens.[10] Also found in saliva, tears, and breast milk.	
IgD	1	Functions mainly as an antigen receptor on B cells that have not been exposed to antigens.[11] It has been shown to activate basophils and mast cells to produce antimicrobial factors.[12]	
IgE	1	Binds to allergens and triggers histamine release from mast cells and basophils, and is involved in allergy. Also protects against parasitic worms.[6]	
IgG	4	In its four forms, provides the majority of antibody-based immunity against invading pathogens.[6] The only antibody capable of crossing the placenta to give passive immunity to fetus.	
IgM	1	Expressed on the surface of B cells and in a secreted form with very high avidity. Eliminates pathogens in the early stages of B cell mediated (humoral) immunity before there is sufficient IgG.[6][11]	

Out of the innumerable

- Causes that impair immune system function, here we shall focus on four major points:
- 1. Drugs.
- 2. Malnutrition
- 3. Oxidative stress
- 4 Semen

DRUGS

- The next slides are courtesy of Dr. Daniele Mandrioli



Evolution of the AIDS epidemic among the different Risk Groups

Tabella 7 - Distribuzione dei casi di AIDS in adulti per modalità di trasmissione e per anno di diagnosi

Modalità di trasmissione		Anno di diagnosi <1996	1996-97	1998-99	2000-01	2002-03	2004-05	2006-07	Totale	Maschi	Femmine
Contatti omo/bisessuali	n.	5.079	1.250	768	674	638	611	555	9.575	9.575	0
	%	*15,6*	*15,0*	*16,9*	*18,0*	*18,5*	*19,7*	*21,8*	*16,4*	*21,1*	*0,0*
Uso iniettivo di droghe	n.	21.167	4.737	2.063	1.415	1.196	953	680	32.211	25.664	6.547
	%	64,9	56,7	45,4	37,8	34,6	30,7	26,7	*55,2*	56,5	50,6
Uso iniettivo di droghe/ contatti omosessuali	n.	726	116	32	28	21	22	19	964	964	0
	%	*2,2*	*1,4*	*0,7*	*0,7*	*0,6*	*0,7*	*0,7*	*1,7*	*2,1*	*0,0*
Emofilico	n.	282	33	8	10	4	6	2	345	335	10
	%	*0,9*	*0,4*	*0,2*	*0,3*	*0,1*	*0,2*	*0,1*	*0,6*	*0,7*	*0,1*
Trasfuso	n.	330	50	23	10	9	8	4	434	248	186
	%	*1,0*	*0,6*	*0,5*	*0,3*	*0,3*	*0,3*	*0,2*	*0,7*	*0,5*	*1,4*
Contatti eterosessuali	n.	4.541	1.732	1.312	1.365	1.373	1.299	1.119	12.741	7.173	5.568
	%	*13,9*	*20,7*	*28,9*	*36,5*	*39,8*	*41,8*	*43,9*	*21,8*	*15,8*	*43,0*
Altro/non determinato	n.	472	431	337	241	212	210	168	2.071	1.442	629
	%	*1,4*	*5,2*	*7,4*	*6,4*	*6,1*	*6,8*	*6,6*	*3,5*	*3,2*	*4,9*
Totale	n.	32.597	8.349	4.543	3.743	3.453	3.109	2.547	58.341	45.401	12.940

HEROIN

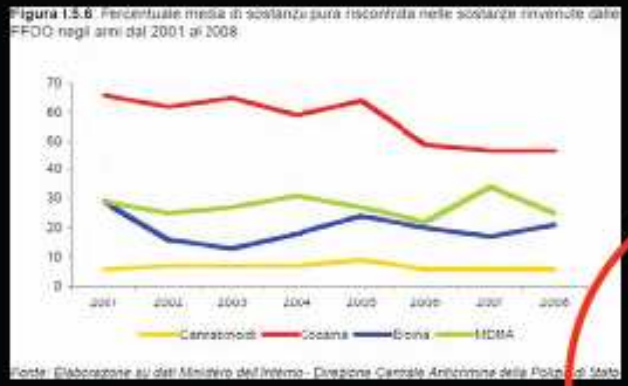
MEDICAL CONSEQUENCES OF CHRONIC HEROIN INJECTION USE INCLUDE SCARREDAND/OR COLLAPSED VEINS, **BACTERIAL INFECTIONS** OF THE BLOOD VESSELS AND HEART VALVES, ABSCESSES (BOILS) AND OTHER SOFT-TISSUE INFECTIONS, AND **LIVER OR KIDNEY DISEASE.** LUNG COMPLICATIONS (INCLUDING VARIOUS TYPES OF **PNEUMONIA AND TUBERCULOSIS**) MAY RESULT FROM THE POOR HEALTH CONDITION OF THE ABUSER AS WELL AS FROM HEROIN'S DEPRESSING EFFECTS ON RESPIRATION.

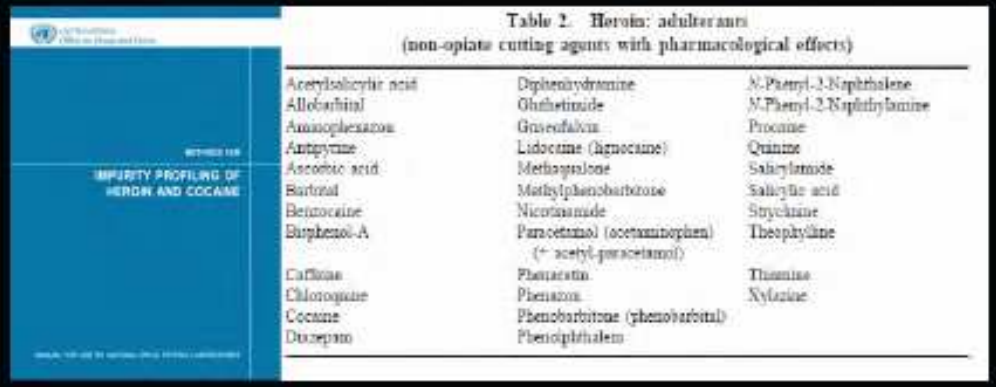
MANY OF THE **ADDITIVES IN STREET HEROIN** MAY INCLUDE SUBSTANCES THAT DO NOT READILY DISSOLVE AND RESULT IN CLOGGING THE BLOOD VESSELS THAT LEAD TO THE LUNGS, LIVER, KIDNEYS, OR BRAIN. THIS CAN CAUSE **INFECTION OR EVEN DEATH OF SMALL PATCHES OF CELLS IN VITAL ORGANS.**

HEROIN ABUSE DURING PREGNANCY AND ITS MANY ASSOCIATED ENVIRONMENTAL FACTORS (E.G., LACK OF PRENATAL CARE) HAVE BEEN ASSOCIATED WITH ADVERSE CONSEQUENCES INCLUDING **LOW BIRTH WEIGHT**, AN IMPORTANT RISK FACTOR FOR LATER DEVELOPMENTAL DELAY

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

(IM)PURE HEROIN

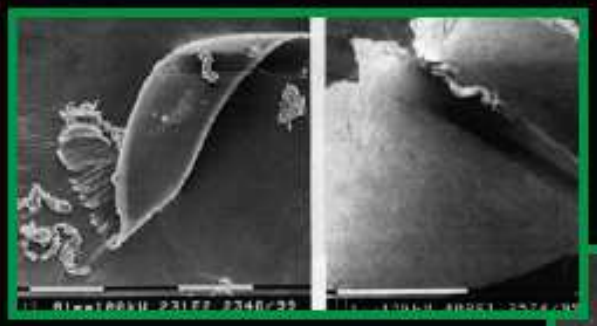


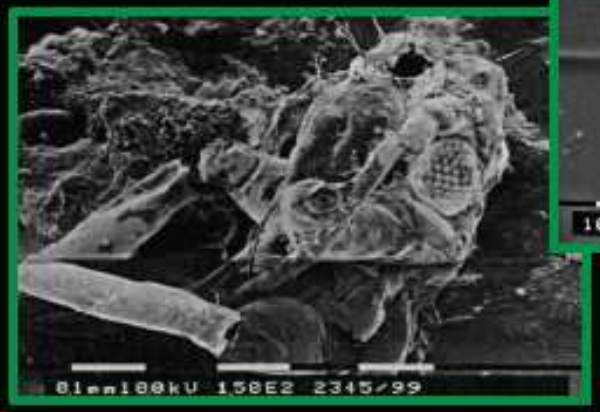


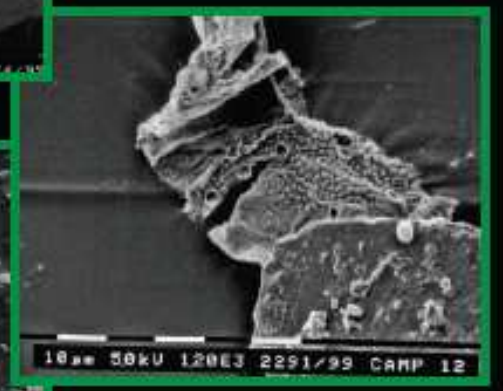
IMPURITY PROFILING OF HEROIN AND COCAINE

Table 2. Heroin: adulterants (non-opiate cutting agents with pharmacological effects)

Acetylsalicylic acid	Diphenhydramine	N-Phenyl-2-Naphthalene
Allobarbital	Glthetimide	N-Phenyl-2-Naphthylamine
Aminophenazon	Griseofulvin	Procaine
Antipyrine	Lidocaine (lignocaine)	Quinine
Ascorbic acid	Methaqualone	Salicylamide
Barbital	Methylphenobarbitone	Salicylic acid
Benzocaine	Nicotinamide	Strychnine
Bisphenol-A	Paracetamol (acetaminophen) (+ acetyl-paracetamol)	Theophylline
Caffeine	Phenacetin	Thiamine
Chloroquine	Phenazon	Xylazine
Cocaine	Phenobarbitone (phenobarbital)	
Diazepam	Phenolphthalein	







FONTS

Parlament Report on Drug Addiction in Italy- 2008

DPA, Dipartimento Politiche Antidroga

Narcotics Control Bureau by the Italian Government

Drug Addiction Services Report- 2007

Italian Ministry of Health

AIDS Cases and HIV Infections Report- 2007

Italian National Health Service

HEROIN

Population treated by the Drug Addiction Services (SerT)

Tab. 1 - UTENTI DEI SERVIZI PUBBLICI PER LE TOSSICODIPENDENZE

REGIONE	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
PIEMONTE	10.455	10.347	10.320	12.022	12.723	13.248	13.718	13.083	14.081	13.562	13.583	14.553	13.315	11.577	14.103	14.859	14.561
VALLE D'AOSTA	286	306	292	294	289	341	337	338	375	331	334	315	302	291	295	297	268
LOMBARDIA	16.157	17.848	17.847	18.762	19.309	20.666	19.511	20.868	22.034	21.913	22.955	24.148	15.309	25.951	26.096	25.774	26.118
PROV.AUT.BOLZANO	1.060	1.050	1.004	756	304	301	348	962	1.037	1.052	308	916	820	735	724	738	801
PROV.AUT.TRENTO	480	621	613	646	657	686	509	596	683	748	808	788	757	799	858	868	907
VENETO	8.415	8.076	8.928	9.821	9.692	10.438	10.589	11.032	11.747	10.832	11.112	12.487	12.589	13.452	11.476	13.151	13.408
FRIULI V.GIULIA	1.743	1.919	1.894	2.119	2.398	2.264	2.421	2.591	2.626	2.753	2.863	2.815	2.659	2.962	3.152	3.247	2.617
LIGURIA	3.724	4.118	2.914	1.172	3.068	2.244	6.138	5.546	5.684	5.744	6.192	6.605	7.076	5.731	6.091	9.491	5.974
EMILIA ROMAGNA	6.979	7.558	7.677	8.289	8.654	8.943	8.787	8.943	9.422	9.738	10.010	10.636	10.692	11.204	11.435	11.482	12.370
TOSCANA	6.673	6.682	7.986	9.326	9.982	9.811	9.243	9.673	10.229	10.621	9.285	11.895	12.043	11.044	10.111	12.956	13.224
UMBRIA	1.299	2.052	1.742	2.082	2.701	2.811	3.102	1.897	2.198	3.277	3.328	3.129	3.093	3.037	3.396	2.859	3.187
MARCHE	1.848	2.202	2.134	2.549	2.614	3.869	3.722	4.110	4.116	3.870	3.503	4.431	4.111	4.321	4.836	3.960	4.509
LAZIO	9.698	10.108	9.175	9.273	11.021	9.864	11.403	11.013	11.345	11.724	10.921	12.066	14.887	13.282	13.791	13.133	11.849
ABRUZZO	829	1.450	2.051	2.801	3.443	3.149	3.331	3.171	2.732	3.334	3.845	4.047	3.976	3.980	3.876	4.820	5.305
MOLISE	242	268	258	405	461	535	552	534	579	397	400	389	707	412	834	974	970
CAMPANIA	5.294	7.750	7.005	9.476	9.925	11.625	12.377	11.327	12.828	13.831	15.887	16.523	17.341	19.999	17.937	18.587	19.718
PUGLIA	9.057	10.595	10.828	10.446	11.033	11.539	14.335	13.178	12.400	13.039	12.023	12.301	12.200	12.483	11.602	12.082	12.680
BASILICATA	719	822	812	796	796	982	922	893	927	844	991	1.038	1.024	1.080	1.170	1.178	1.454
CALABRIA	1.084	1.307	1.787	2.024	2.677	3.491	3.323	4.294	3.646	4.401	4.708	4.936	4.416	4.301	4.557	4.536	4.458
SICILIA	3.813	4.951	4.943	5.874	6.896	7.843	8.263	8.103	8.597	9.959	10.112	9.894	11.196	10.453	10.503	11.241	12.341
SARDEGNA	3.102	3.775	4.532	5.002	5.158	5.439	5.108	5.506	5.365	5.186	5.232	5.140	5.000	5.386	5.178	5.119	5.574
ITALIA	92.853	103.805	104.743	113.735	123.731	129.894	138.218	137.667	143.651	147.146	150.400	159.051	163.516	162.230	162.005	171.353	172.303

M/F ratio in the population treated by the SerT

HEROIN

Deaths for acute drug intoxication in Italy and Europe

Tabella I.3.26: Decessi per intossicazione acuta di stupefacenti in Europa e in Italia. Anni 1985 – 2005 (Anno base 1985=100)

Anno	Decessi	Italia	Europa
1985	242	100	100
1986	292	120,7	110,2
1987	543	224,4	154,7
1988	809	334,3	207,9
1989	974	402,5	277,9
1990	1.161	479,8	369,3
1991	1.383	571,5	480,6
1992	1.217	502,9	461,7
1993	888	366,9	419,2
1994	867	358,3	436,2
1995	1.195	493,8	470,6
1996	1.566	647,1	533,7
1997	1.160	479,3	485,1
1998	1.081	446,7	514,4
1999	1.002	414,0	547,3
2000	1.016	419,8	579,5
2001	625	340,9	559,4
2002	520	214,9	475,1
2003	517	213,6	441,7
2004	653	269,8	469,3
2005	653	269,8	478,7

Fonte: Elaborazione su dati del Ministero dell'Interno - DCSA e Osservatorio Europeo delle Droghe e delle Tossicodipendenze - Bollettino Statistico 2008

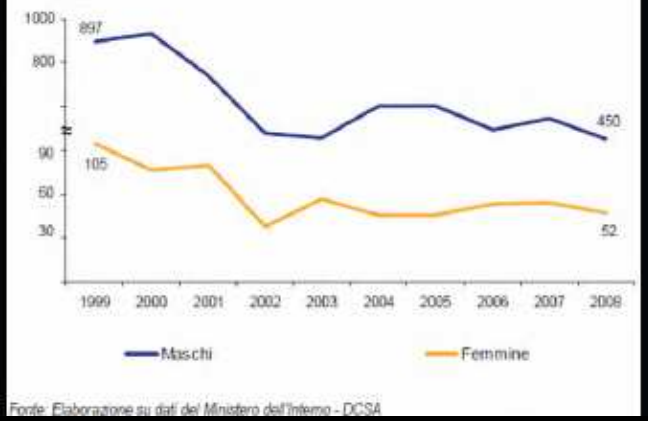
Death for acute drug intoxication in Italy (M/F)

Tabella I.3.27: Decessi per intossicazione acuta di stupefacenti secondo il genere. Anni 1999 - 2008

Classe di età	Maschi	Femmine	Totale
1999	897	105	1.002
2000	931	85	1.016
2001	737	88	825
2002	478	42	520
2003	454	63	517
2004	602	51	653
2005	602	51	653
2006	492	59	551
2007	546	60	606
2008	450	52	502

Fonte: Elaborazione su dati del Ministero dell'Interno – DCSA

Figura I.3.27: Trend dei decessi per overdose, secondo il genere e l'anno di decesso. Anni 1999 - 2008



Fonte: Elaborazione su dati del Ministero dell'Interno - DCSA

AIDS CASES

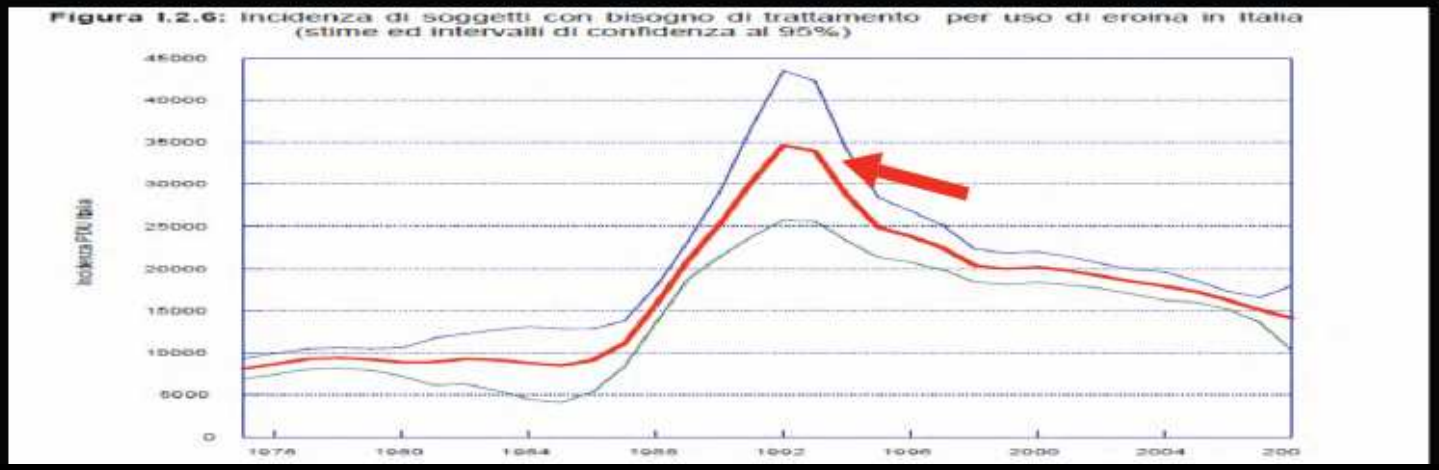
Semestral Incidence

HEROIN

Figura 1 - Casi di AIDS in Italia per semestre di diagnosi, corretti per ritardo di notifica e tasso annuale di incidenza al 31 dicembre 2007

HEROIN ABUSERS

Incidence of heroin abusers that need to be treated (estimation, confidence 95%)



AIDS CASES

Semestral Incidence

HEROIN

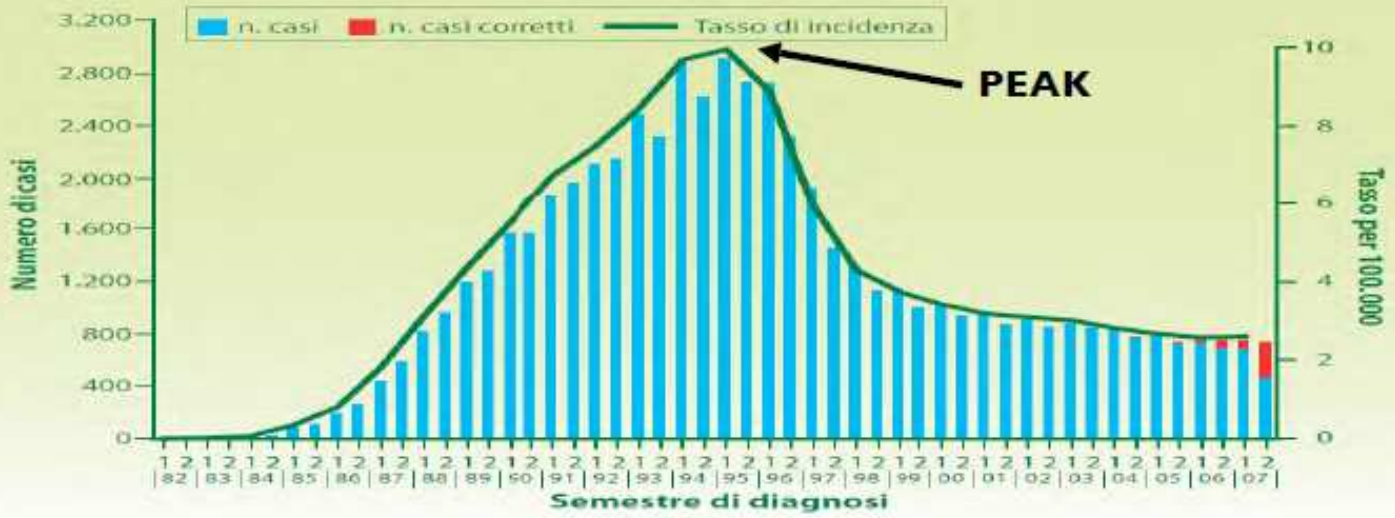
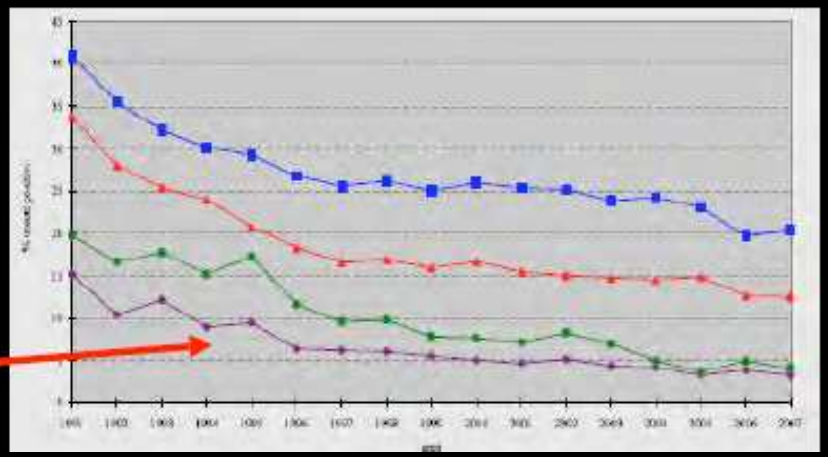


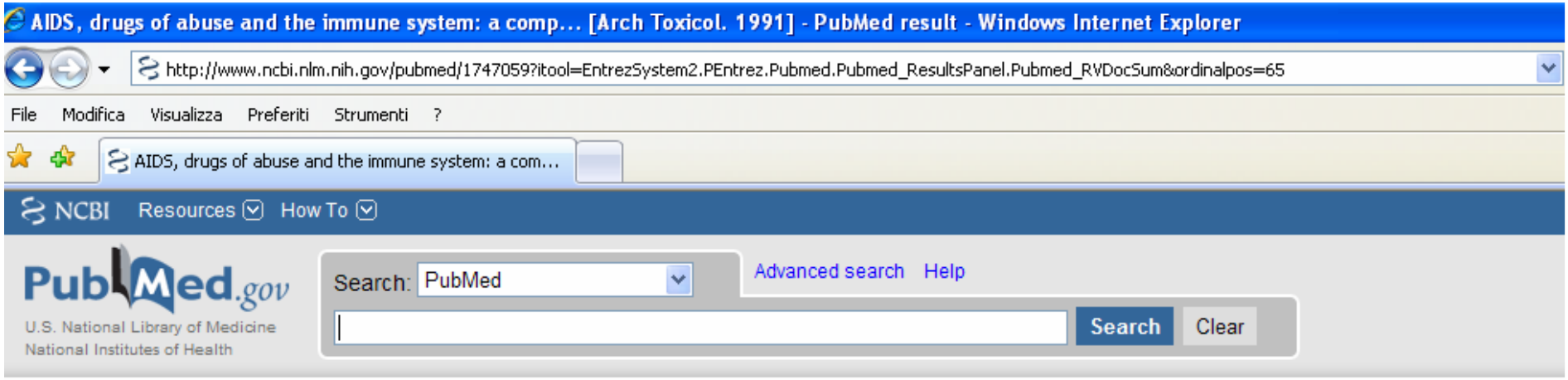
Figura 1 - Casi di AIDS in Italia per semestre di diagnosi, corretti per ritardo di notifica e tasso annuale di incidenza al 31 dicembre 2007

HIV+ TESTS: PREVALENCE AND INCIDENCE AMONG DRUG ABUSERS

Percentage of the SerT Population



NO PEAK



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Arch Toxicol. 1991;65(8):609-17.

AIDS, drugs of abuse and the immune system: a complex immunotoxicological network.

Pillai R, Nair BS, Watson RR.

Department of Family and Community Medicine, University of Arizona Health Sciences Center, Tucson 85724.

Two of the most interesting questions often asked about AIDS is why many people do not become immunodeficient or get complicating disease when first infected with Human Immunodeficiency Virus (HIV) and what are the "risk factors" making some individuals more susceptible to the disease. A large majority of people with AIDS have a well established history of drug and alcohol abuse. Both drugs of abuse and alcohol have immunotoxic properties as evidenced by a number of studies. These include marked changes in the cellular, humoral and other components of the immune defense mechanism. Such a compromise of the immune system can render it susceptible to the development of AIDS after HIV infection. This paper reviews the evidence suggesting possible links between substance abuse and its immunotoxicology, and their possible roles in the pathogenesis of AIDS.

PMID: 1747059 [PubMed - indexed for MEDLINE]

⊕ Publication Types, MeSH Terms, Substances, Grant Support

⊕ LinkOut - more resources

Immunotoxicology of Opioids, Inhalants, and Other Drugs of Abuse

Robert V. House, Peter T. Thomas, and Hemendra N. Bhargava

INTRODUCTION

Drug abuse is a problem of increasing worldwide significance. In addition to the obvious socioeconomic problems associated with the use of so-called street drugs, the abuse of ethical pharmaceuticals may also result in serious untoward health effects depending upon a wide range of variables (Chiang and Goldfrank 1990). One possible medical complication of drug abuse is modulation of the immune system, or immunotoxicity (Pillai and Watson 1990). The immune system is a highly regulated organ system that presents a variety of potential targets for modulation by drugs. This modulation may take the form of immunosuppression, leading to an enhanced susceptibility to infection or neoplasia; conversely, it may take the form of immunostimulation, resulting in hypersensitivity (allergy) or autoimmunity (Luster and Rosenthal 1993). Closely associated with drug abuse in recent years has been the emergence of the acquired

Other drugs

- **Khansari, Nemat; Whitten, H. D.; Fudenberg, H. Hugh**
  Phencyclidine-induced immunodepression
  Science v225 p76-8 July 6 1984
  SUBJECTS: Ketamine Phencyclidine
  Immunosuppressive agents

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Infection. 2007 Dec;35(6):469-73. Epub 2007 Oct 4.

"Recreational" drug abuse associated with failure to mount a proper antibody response after a generalised orthopoxvirus infection.

Huemer HP, Himmelreich A, Hönlinger B, Pavlic M, Eisendle K, Höpfl R, Rabl W, Czerny CP.

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Infections with orthopoxviruses usually lead to cross-protection among all species of the family. This has been a prerequisite for successful eradication of smallpox. Here we report the rare case of a 17-year-old male, who survived a generalised cowpox virus infection of unusual severity but surprisingly did not show a proper seroconversion. Only a very weak antibody production was observed in early and late serum samples, which initially appeared to be cowpox virus specific in immunofluorescence. No neutralising antibodies were detected and in Western blotting antibody specificity was restricted to the orthopoxvirus H3L protein only. The patient had been hospitalised for alcohol and cannabis intoxication 2 months prior to the orthopoxvirus infection and high levels of cannabinoids have been found repeatedly in the urine and upon one occasion also benzodiazepines. As these substances are known to interfere with antibody production and no immunodeficiencies were detected, drug-induced immunosuppression can be suspected as the most likely cause. Therefore a possible link between "soft" drug use and sufficient immunosuppression to warrant alterations in vaccine policies using live virus vaccines like smallpox vaccine should be further studied.

PMID: 17917699 [PubMed - indexed for MEDLINE]


ROOM
ODORISOR
BUZZ
AROMA
BANG!
AROMA
Gold
HAZE
ROOM
ODORISOR
Popi's

POPPERS

ANIMAL RESEARCH RAISES THE POSSIBILITY THAT THERE MAY BE A LINK BETWEEN ABUSE OF NITRITE INHALANTS AND THE DEVELOPMENT AND PROGRESSION OF INFECTIOUS DISEASES AND TUMORS. THE RESEARCH INDICATES THAT INHALING NITRITES DEPLETES MANY CELLS IN THE IMMUNE SYSTEM AND IMPAIRS IMMUNE SYSTEM MECHANISMS THAT FIGHT INFECTIOUS DISEASES. A RECENT STUDY FOUND THAT EVEN A RELATIVELY SMALL NUMBER OF EXPOSURES TO BUTYL NITRITE CAN PRODUCE DRAMATIC INCREASES IN TUMOR INCIDENCE AND GROWTH RATES IN ANIMALS.

Table 3. CDC 1983*: Drug use by American male homosexuals with AIDS and at risk for AIDS.

Drugs	Percentage users among 50 AIDS cases and 120 at risk for AIDS
Nitrite inhalants	96
Ethylchloride	35–50
Cocaine	50–60
Amphetamines	50–70
Phenylcyclidine	40
LSD	40–60
Metaqualone	40–60
Barbiturates	25
Marijuana	90
Heroin	10
Drug-free	None reported

*(Jaffe *et al* 1983).

- *just a couple of weeks ago I had a conversation with my (gay) neighbor – he is also from the UK and even went to the same gay nightclub in Coventry despite him being from Liverpool. We were reminiscing about the ever-present amyl nitrite fumes!*
  … there was most probably synergy between poppers and something else possibly rapamycin, aka sirolimus (because it was initially used in the treatment and prophylaxis of CHLAMYDIA) as it would certainly fit the timeframe. Since its immunosuppressive effects (and the full data sheet USED to read like a shopping list for AIDS but has strangely and recently been rewritten) became known (hence the name and indication change) it was no longer used as a "general" antibiotic.

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Surgery
Volume 146, Issue 3, September 2009, Pages 526-527

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Letter to the Editor

Rapamycin—rather than FK506—might promote allograft tolerance induced by $CD4^+CD25^+$ regulatory T cells

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Reference

1. Elison EC. Assessing the vital signs of regional surgical societies: what is the prognosis? Surgery 2008;144:483-91.

doi:10.1016/j.surg.2009.04.017

Rapamycin—rather than FK506—might promote allograft tolerance induced by $CD4^{+}CD25^{+}$ regulatory T cells

To the Editors:

We read with interest the article by Li-Yong Pu et al[1] suggesting that adoptive transfusion of ex vivo donor alloantigen–stimulated $CD4^{+}CD25^{+}$ regulatory T cells (Tregs) combined with short-term FK506 treatment may represent a new strategy for preventing rejection after liver transplantation. We agree that, to be acceptable in the clinical setting, a Tregs-based therapy should be compatible with the transient use of standard immuno- of Tregs with unaltered immunosuppressive function were observed in the spleens and thymus of rapamycin-treated mice.[11] Baan et al[12] also demonstrated that rapamycin, in contrast to calcineurin inhibitors, preserves the expression of Foxp3 in human Tregs as well as their function in cardiac transplantation. Very strikingly, accumulated clinical evidence demonstrated that rapamycin could slow progression of cardiac transplantation vasculopathy because of its potent antiproliferative and antimigratory properties on vascular smooth muscle cells.[13-15] In addition to its inhibitory effect on intimal hyperplasia,[16] rapamycin may decrease chronic allograft vasculopathy and prevent development of chronic rejection.

In our opinion, after considering the cumulative results of the studies described above, rapamycin—rather than FK506—may be one of the most promising immunosuppressants in promoting allograft tolerance mediated by Tregs-based therapy.

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REVIEWS OF MODERN PHYSICS VOLUME 21, NUMBER 3 JULY, 1949

An Example of a New Type of Cosmological Solutions of Einstein's Field Equations of Gravitation

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1. THE MAIN PROPERTIES OF THE NEW SOLUTION

ALL cosmological solutions with non-vanishing density of matter known at present[1] have the common property that, in a certain sense, they contain an "absolute" time coordinate,[2] owing to the fact that there exists a one-parametric system of three-spaces everywhere orthogonal on the world lines of matter. It is easily seen that the non-existence of such a system of three-spaces is equivalent with a rotation of matter relative to the compass of inertia. In this paper I am proposing a solution (with a cosmological term $\neq 0$) which exhibits such a rotation. This solution, or rather the four-dimensional space S which it defines, has the further properties:

(1) S is homogeneous, i.e., for any two points P, Q of S there exists a transformation of S into itself which carries P into Q. In terms of physics this means that the solution is stationary and spatially homogeneous.

(2) There exists a one-parametric group of transformations of S into itself which carries each world line of matter into itself, so that any two world lines of matter are equidistant.

(3) S has rotational symmetry, i.e., for each point P of S there exists a one parametric group of transformations of S into itself which carries P into itself.

(4) The totality of time-like and null vectors can be divided into $+$- and $-$-vectors in such a way that: (a) If ξ is a $+$-vector, $-\xi$ is a $-$-vector, (b) a limit of $+$- (or $-$-) vectors, if $\neq 0$, is again a $+$- (or $-$-) vector. That is, a positive direction of time can consistently be introduced in the whole solution.

and this holds both for an open and a closed time coordinate.

(6) Every world line of matter occurring in the solution is an open line of infinite length, which never approaches any of it's preceding points again; but there also exist closed time-like lines.[3] In particular, if P, Q are any two points on a world line of matter,[4] and P precedes Q on this line, there exists a time-like line connecting P and Q on which Q precedes P; i.e., it is theoretically possible in these worlds to travel into the past, or otherwise influence the past.

(7) There exist no three-spaces which are everywhere space-like and intersect each world line of matter in one point.

(8) If $\sum$ is any system of mutually exclusive three-spaces, each of which intersects every world line of matter in one point,[5] then there exists a transformation which carries S and the positive direction of time into itself, but does *not* carry $\sum$ into itself; i.e., an *absolute* time does not exist, even if it is not required to agree in direction with the times of all possible observers (where "absolute" means: definable without reference to individual objects, such as, e.g., a particular galactic system).

(9) Matter everywhere rotates relative to the compass of inertia with the angular velocity: $2(\pi\kappa\rho)^{\frac{1}{2}}$, where ρ is the mean density of matter and κ Newton's gravitational constant.

2. DEFINITION OF THE LINEAR ELEMENT AND PROOF THAT IT SATISFIES THE FIELD EQUATIONS