Jesse A. Stoff, M.D.

GOALS

- Discussion of the immune system and immunology.
- Identification of factors affecting immune system performance.
- Orientation to effectiveness of *immune modulation* and *immune reconstitution*.
- Introduction to the application of *immune modulation and reconstitution.*

: Lancet 2000 Nov 25;356(9244):1795-9

Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population.

Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K.

Saitama Cancer Centre Research Institute, Japan.

BACKGROUND: One of the most critical questions in immunosurveillance is whether differences between individuals with regards to natural immunological host defense can predict future development of cancer. Although this question has so far remained open, there are clear indications of significant roles of several naturally cytotoxic lymphocytes in preventing the development of cancer. We began a prospective cohort study among a Japanese general population in 1986, using various immunological and biochemical markers. METHODS: Natural cytotoxic activity of peripheral-blood mononuclear cells was assessed by isotope-release assay in 3625 residents of a Japanese population mostly older than 40 years of age, between 1986 and 1990. Immunological and biochemical markers were also measured, and participants were given a questionnaire on lifestyle. We did an 11-year follow-up survey of the cohort members looking at cancer incidence and death from all causes, and analyzed the association between cytotoxic activity of peripheral-blood lymphocytes assessed at baseline and cancer incidence found in the subsequent follow-up. FINDINGS: 154 cancer cases were used in the analysis. When we categorized the cytotoxic activity of peripheral-blood lymphocytes by tertiles, age-adjusted relative risk of cancer incidence (all sites) was 0.72 (95% CI 0.45-1.16) for men with high cytotoxic activity, and 0.62 (0.38-1.03) for men with medium cytotoxic activity, taking the risk of those with low cytotoxic activity as reference. For women with high cytotoxic activity relative risk was 0.52 (0.28-0.95), and for those with medium cytotoxic activity 0.56 (0.31-1.01). For both sexes with high and medium cytotoxic activity risk was 0.63 (0.43-0.92) and 0.59 (0.40-0.87), respectively. INTERPRETATION: Our results indicate that medium and high cytotoxic activity of peripheral-blood lymphocytes is associated with reduced cancer risk, whereas low activity is associated with increased cancer risk suggesting a role for natural immunological host defense mechanisms against cancer.

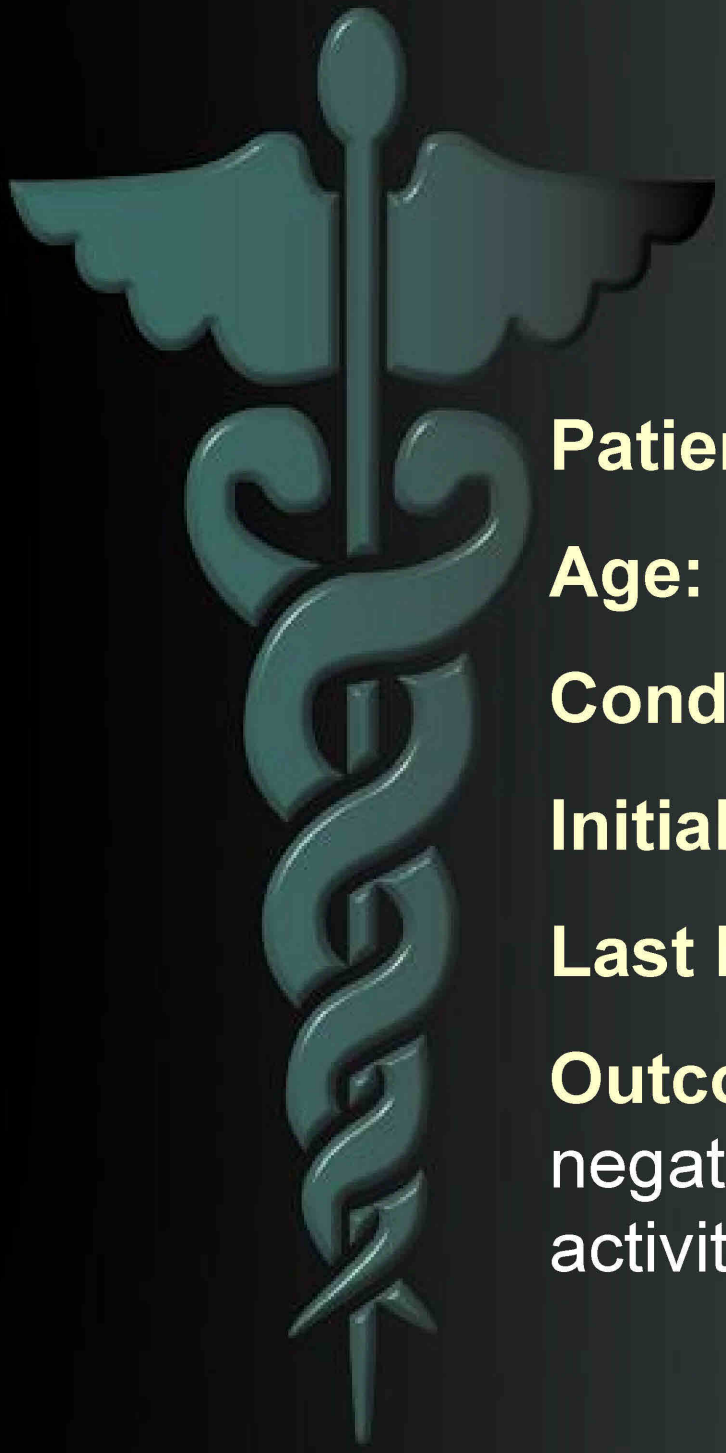
: Lancet 2000 Sep 2;356(9232):802-7

Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial.

Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, Shimada K, Sakamoto M, Hirohashi S, Ohashi Y, Kakizoe T.

Department of Surgery, National Cancer Centre Research Institute, University of Tokyo, Japan. takayamat-2su@h.u-tokyo.ac.jp

BACKGROUND: Postsurgical recurrence of hepatocellular carcinoma (HCC) is frequent and fatal. Adoptive immunotherapy is active against HCC. We assessed whether postoperative immunotherapy could lower the frequency of recurrence.
METHODS: Between 1992 and 1995, we did a randomized trial in which 150 patients who had undergone curative resection for HCC were assigned adoptive immunotherapy (n=76) or no adjuvant treatment (n=74). Autologous lymphocytes activated vitro with recombinant interleukin-2 and antibody to CD3 were infused five times during the first 6 months. Primary endpoints were time to first recurrence and recurrence-free survival and analyses were by intention to treat.
FINDINGS: 76 patients received 370 (97%) of 380 scheduled lymphocyte infusions (mean cell number per patient 7.1x10(10) [SD 2.1]; CD3 and HLA-DR cells 78% [16]), and none had grade 3 or 4 adverse events. After a median follow-up of 4.4 years (range 0.2-6.7), adoptive immunotherapy decreased the frequency of recurrence by 18% compared with controls (45 [59%] vs 57 [77%]) [corrected] patients. Time to first recurrence in the immunotherapy group was significantly longer than that in the control group (48% [37-59] vs 33% [22-43] at 3 years, 38% [22-54] vs 22% [11-34] at 5 years; p=0.008). The immunotherapy group had significantly longer recurrence-free survival (p=0.01).
INTERPRETATION: Adoptive immunotherapy is a safe, feasible treatment that can lower recurrence and improve recurrence-free outcomes after surgery for HCC.



Typical Patient "*Outcomes*"

Patient Tim

Age: 66

Condition: Prostate Cancer

Initial NK Cell Activity Level: 13

Last NK Cell Activity Level: 76

Outcome: Bone scans and x-rays all negative for any sign of cancer or metastatic activity after 21 months.

SPECIALTY LABORATORIES, INC.
OncQuest
2211 MICHIGAN AVENUE
SANTA MONICA, CA 90404-3900
(310)828-6543 (800)421-4449

ACCOUNT NUMBER	S.L.I. ACCESSION #
16334	9738548

PATIENT NAME: [redacted] TIM

ORDER #	D.O.B	GENDER
9044	07/05/31 66 Y	Male

REFERRING PHYSICIAN: Stoff MD,Jesse A

PATIENT I.D. #	DRAWN
950427002KIT	

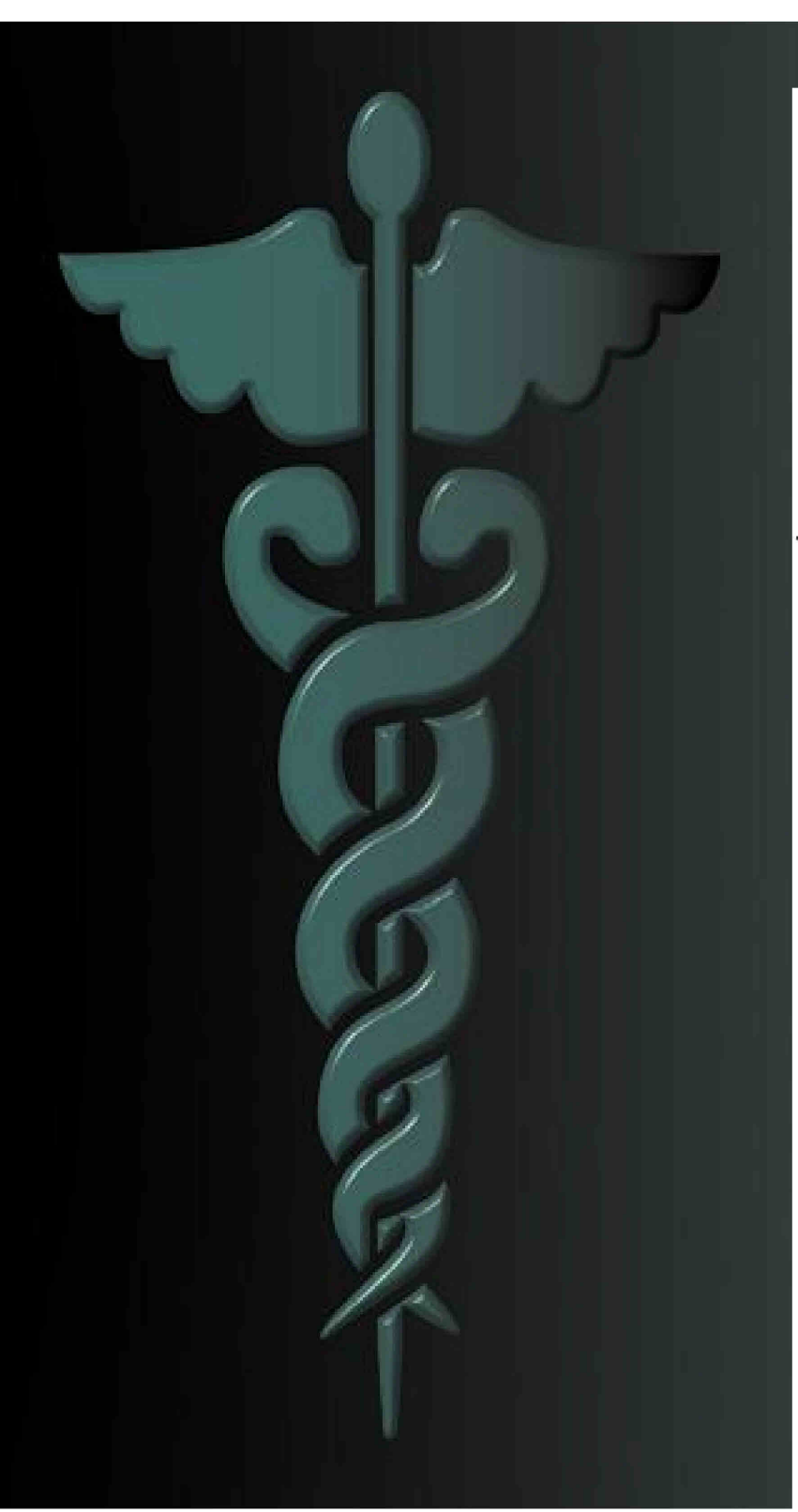
RECEIVED	REPORTED
11/05/97 10:46 AM	11/12/97 10:02 PM

INTEGRAMED
2122 N. Craycroft
Tucson, AZ 85712

Test Name	Result	Reference Range
FREE PSA	82.10	See below ng/mL
TOTAL PSA	1066.0	Less than 4.0 ng/mL
% FREE PSA	8	See below %
PROSTATIC ACID PHOSPHATASE	5.1	Less than 3.5 ng/mL

Final

James B. Peter, M.D.,Ph.D.



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OncQuest
2211 MICHIGAN AVENUE
SANTA MONICA, CA 90404-3900
(310)828-6543 (800)421-4449

ACCOUNT NUMBER	S.L.I. ACCESSION #
16334	6576181

PATIENT NAME: [redacted] TIM

ORDER #	D.O.B	GENDER
9824	07/05/31 66 Y	Male

REFERRING PHYSICIAN: Stoff MD,Jesse A

PATIENT I.D. #	DRAWN
950427002KIT	

RECEIVED	REPORTED
02/24/98 3:04 PM	02/27/98 4:57 AM

INTEGRAMED
2122 N. Craycroft
Tucson, AZ 85712

Test Name	Result	Reference Range
NATURAL KILLER CELL FUNCTION	52	20-250 LU
PROSTATIC ACID PHOSPHATASE	0.7	Less than 3.5 ng/mL
PSA Serum	1.4	Less than 4.0 ng/mL

Final

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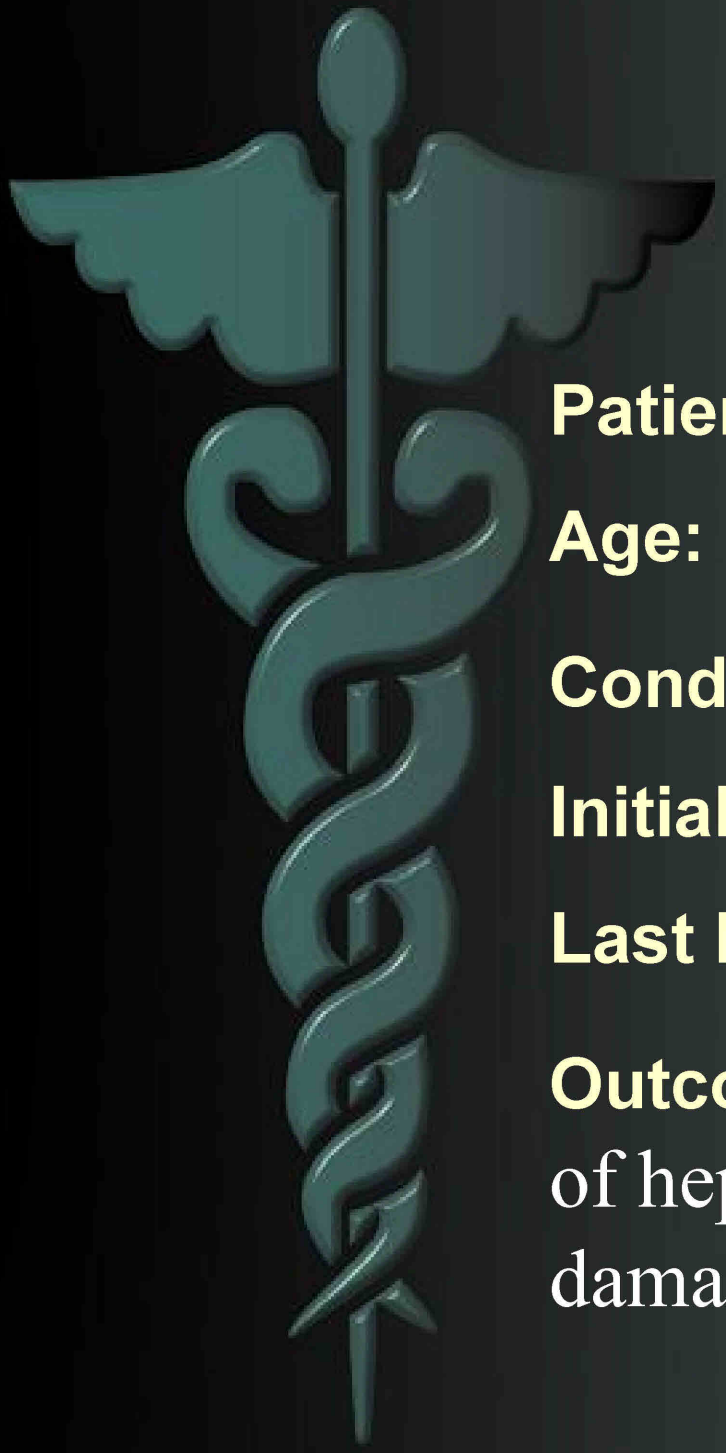

Typical Patient "*Outcomes*"

Patient Gwen

Age: 52

Condition: Hepatitis C, 2b

Initial NK Cell Activity Level: 8

Last NK Cell Activity Level: 115

Outcome: HCV PCR negative for any sign of hepatitis or ongoing inflammatory damage to the liver after 6 months.

Send to:

KAISER FOUNDATION HOSPITAL
ATTN:LAB
X 401 BICENTENNIAL WAY
SANTA ROSA, CA 95401

Quest Diagnostics
33608 Ortega Hwy., San Juan Capistrano, California 92675
CLIENT SERVICES - (800) 553-5445
Directors: L.P. Espinoza MD, D.A. Fisher MD, L.M. Herman MD, R. Horton MD, O.W. Jones MD, K.A. Lynch MD, J.C. Nelson MD, W.B. Paxton MD PhD, R.E. Reitz MD

Patient Name	Patient ID No.			Date	Time
[redacted]	2927235 2927285			Collected 08/03/1998	NOT GIVEN
Accession No.	Age	Sex	Sample ID No.	Other ID No.	Received 08/05/1998 09:17
82412649	NG	FEMALE	NOT GIVEN		Reported 08/26/1998 12:33
Remarks		Referring Physician			Status: FINAL
		PERMUTT			

Test	Result (* = Out of Range)	Units	Reference Range
HEPATITIS C GENOTYPING	GENOTYPE 2b		

Hepatitis C viral genotypes are determined by DNA sequencing and phylogenetic analysis after reverse transcription and amplification of the NS5B region of the HCV genome. There are 6 major Genotypes (1-6) and many subtypes (e.g. 1a, 1b, 1c, etc.). The subtypes detected by this assay include 1a, 1b, 2a, 2b, 3a, 3b, 4a, 5a, and 6a. Genotypes 1, 2 and 3 predominate in Western countries and the Far East. Although HCV genotype may be an independent predictor of response to alpha interferon therapy with patients having genotypes 2 and 3 being more likely to have a sustained response than those infected by genotypes 1a or 1b, HCV genotyping should be looked upon as a research tool (MANAGEMENT OF HEPATITIS C, NIH Consensus Statement Online 1997 March 24-26; 15 (3) in press).

HEPATITIS B VIRAL, PCR QUANTITATION	NEGATIVE <100	Copies/mL	

A positive result indicates the presence of virus-specific nucleic acid sequence at or above 1 copy/10 uL specimen using respective primer sets.

Positive controls indicate sensitivity of 1-10 copies/10 uL specimen.
Negative controls indicate no specific bands.

This test performed at NATIONAL GENETICS INSTITUTE
2311 PONTIUS AVENUE
LOS ANGELES, CA 90064

HEPATITIS C RNA BY PCR

HCV RNA, PCR QUANTITATION:	POSITIVE 3,700,000	Copies/mL	

A positive result indicates the presence of virus-specific nucleic acid sequence at or above 1 copy/ 10 ul specimen using respective primer sets.

Positive controls indicate sensitivity of 1-10 copies/10 ul specimen.
Negative controls indicate no specific bands.

This test performed at NATIONAL GENETICS INSTITUTE
2311 PONTIUS AVENUE
LOS ANGELES, CA 90064

Please mail to pt

SPECIALTY LABORATORIES, INC.
OncQuest
2211 MICHIGAN AVENUE
SANTA MONICA, CA 90404-3900
(310)828-6543 (800)421-4449

ACCOUNT NUMBER	S.L.I. ACCESSION #
16334	098-1139413

PATIENT NAME: [redacted]

ORDER #	D.O.B	GENDER
12757	05/22/46 52 Y	Female

REFERRING PHYSICIAN: Stoff MD,Jesse A

PATIENT I.D. #	DRAWN
SCA955KIT	01/19/99 2:38 PM

RECEIVED	REPORTED
02/10/99 12:47 AM	02/16/99 10:28 PM

INTEGRAMED
3402 E. BROADWAY
TUCSON, AZ 85716

Test Name	Result	Reference Range
Hepatitis C Virus RNA UltraQuant	< 200	< 200 copies/mL

This test result or one or more of its components was developed and its performance characteristics determined by Specialty Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

HEPATITIS C VIRUS RNA ULTRAQUANT, PCR: HCV RNA is detectable within one week of exposure to HCV. Patients with higher concentrations of HCV RNA are more infectious and more resistant to interferon therapy. The use of interferon is associated with a decline in HCV RNA. Decline of HCV RNA to undetectable concentrations is associated with a sustained response, even after the discontinuation of interferon therapy.

WBC Total Count	**3.6**	4.0-11.0 thou/cu mm
RBC Total Count	4.30	4.00-5.50 mil/cu mm
Hemoglobin	13.6	11.5-15.0 g/dL
Hematocrit	39.6	37.0-47.0 %
MCV	92	80-96 fL
MCH	31	26-34 pg
MCHC	34	31-37 g/dL
Platelet Count	177	150-400 thou/cu mm
Segmented Neutrophils	54	50-70 %
Basophils	0	< 2 %
Eosinophils	5	< 6 %
Lymphocytes	25	20-40 %
Monocytes	**16**	< 8 %
RBC Morphology	Normal	Normal
Uric Acid	4.0	2.3-6.4 mg/dL
GGT	10	< 46 U/L
Phosphorus Inorganic	3.4	2.5-4.5 mg/dL
Alanine Transaminase (ALT)	20	< 41 U/L

Continued

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DEFINITIONS

Immune Reconstitution

is the therapeutic process of repairing structural and functional damage to the immune system.

Immune Modulation

is the process of re-establishing the balanced regulation of immune function by restoring the cytokine communication pathways.

The Mission Of The Immune System

- Recognize
- Respond
- Remember

Factors That Affect Immune Function

- Poor Nutrition
- Infection
- Trauma
- Toxin
- Stress

Examining Immune Integrity

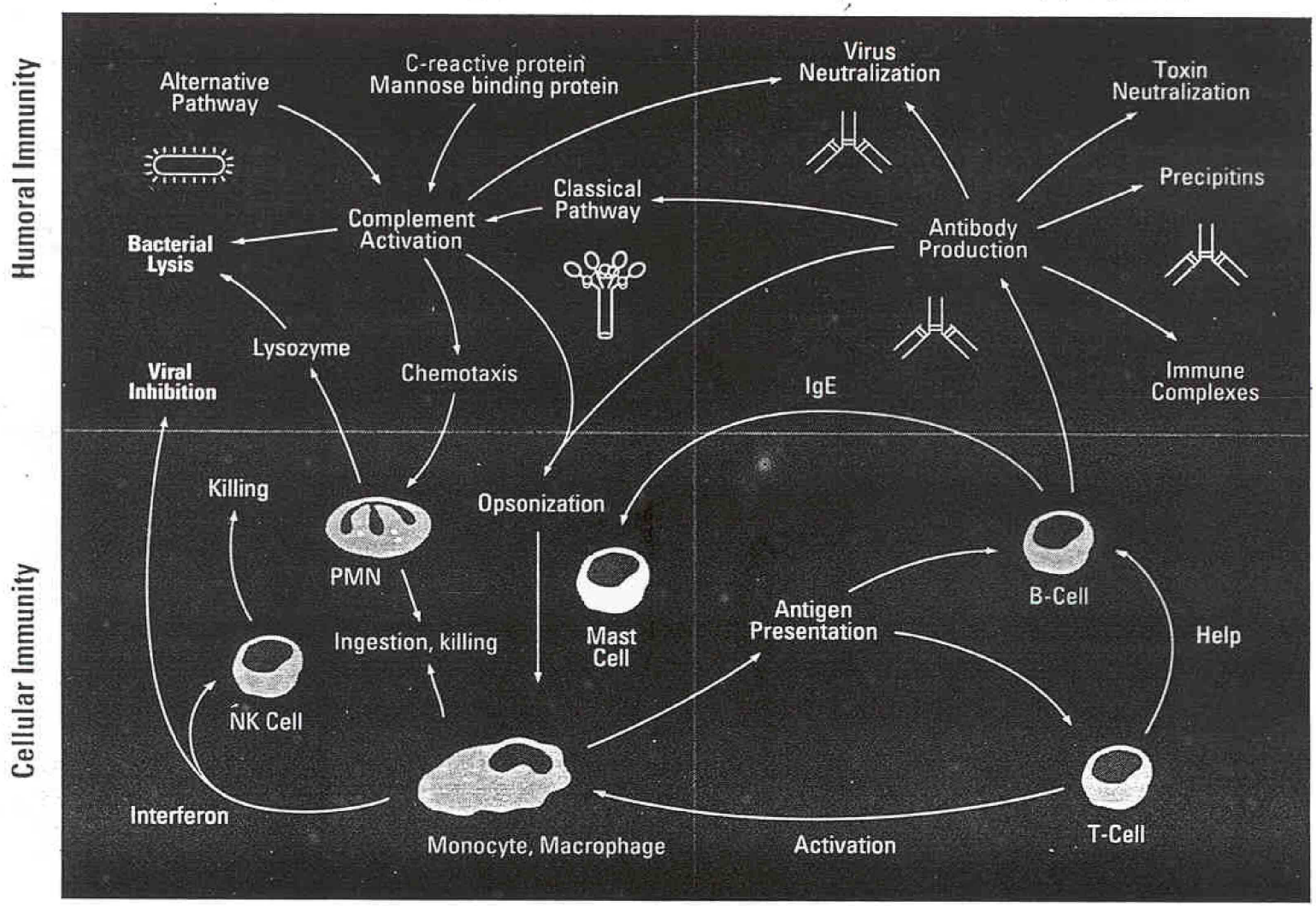
Step 1

- Patient history
- T & B Subset
- NK Cell activity
- Disease specific tests
- Others as indicated

Examining Immune Integrity

Step 2

- Biochemistry testing
- Endocrine testing
- GI testing
- Infection testing
- Nutrition testing


Non-Specific Immunity (Innate)
Specific Immunity (Acquired)
Humoral Immunity
Cellular Immunity
Alternative Pathway
C-reactive protein
Mannose binding protein
Virus Neutralization
Toxin Neutralization
Classical Pathway
Complement Activation
Antibody Production
Precipitins
Bacterial Lysis
Lysozyme
Chemotaxis
Viral Inhibition
IgE
Immune Complexes
Killing
Opsonization
PMN
B-Cell
Antigen Presentation
Help
Ingestion, killing
Mast Cell
NK Cell
Interferon
Monocyte, Macrophage
Activation
T-Cell

- Trigger
- Fuels

Thank you!