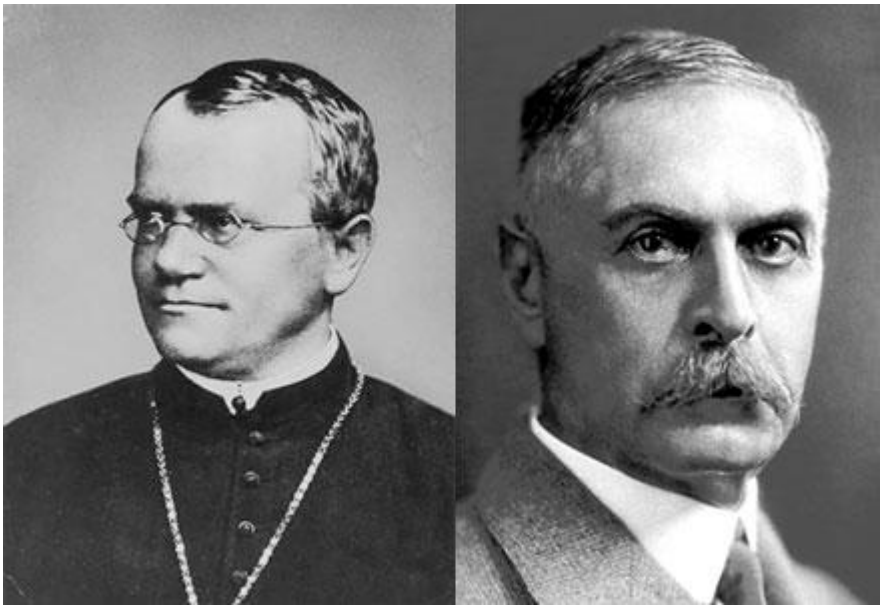
History of MHC – 1901 – 1970

1901
1901
20th Century Discoveries



The turn of the 20th century serves as a landmark due to two important events:

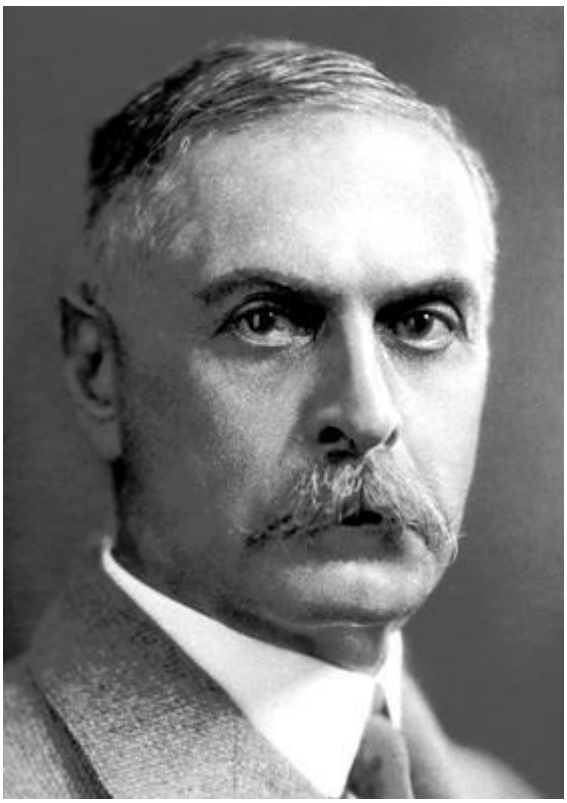
1. recognition of Gregory Mendel’s work of 1867 and his theory of inheritance, and
2. discovery in 1901 of the blood group system on erythrocytes by Karl Landsteiner, an Austrian scientist. This set the pace for search of a similar polymorphic system on leukocytes.

1920
1920
Discovery of the MHC

During the first decade of the 20th century, two important advances were made that paved the way to the discovery of the MHC in later years:

1. Loeb and Tyzzer discovered that the resistance and susceptibility to transplantable tumors are genetically determined by at least 15 genes.
2. Inbred strains of mice were developed by Little (DBA/1, DBA/2, C57BL), Bagg (BALB/c) and Strong (CBA and C3H) that facilitated the understanding of transplant biology.

1930
1930
1930 Nobel Prize



In 1930, Karl Landsteiner was awarded the Nobel Prize in Medicine and Physiology for the discovery of the human ABO blood system.

Nobel Prize 1930 – The Nobel Prize in Physiology or Medicine 1930 was awarded to Karl Landsteiner "for his discovery of human blood groups."

1936
1936
Antigen II

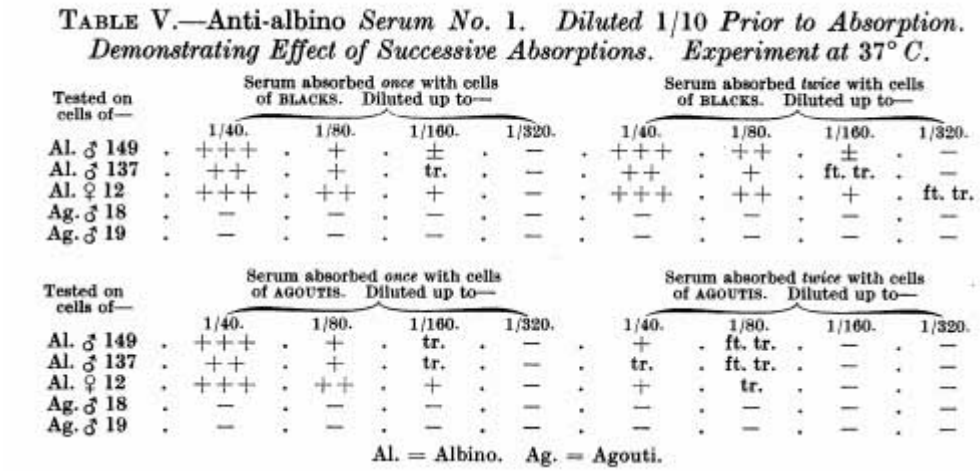


TABLE V.—Anti-albino *Serum No. 1. Diluted* 1/10 *Prior to Absorption. Demonstrating Effect of Successive Absorptions. Experiment at* 37° *C.*

Tested on cells of—	Serum absorbed *once* with cells of BLACKS. Diluted up to— 1/40.	1/80.	1/160.	1/320.	Serum absorbed *twice* with cells of BLACKS. Diluted up to— 1/40.	1/80.	1/160.	1/320.
Al. ♂ 149	+++	+	±	−	+++	++	±	−
Al. ♂ 137	++	+	tr.	−	++	+	ft. tr.	−
Al. ♀ 12	+++	++	+	−	+++	++	+	ft. tr.
Ag. ♂ 18	−	−	−	−	−	−	−	−
Ag. ♂ 19	−	−	−	−	−	−	−	−

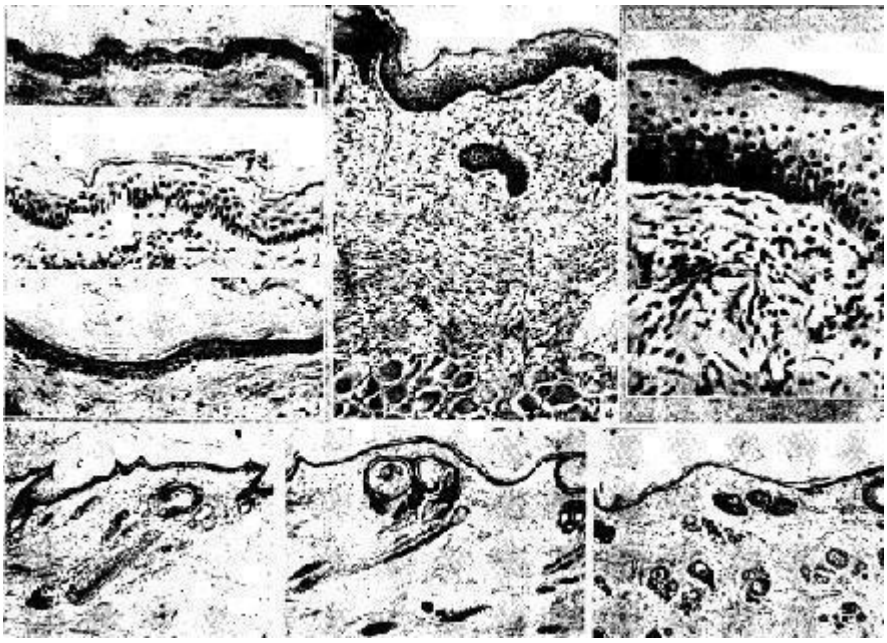
Tested on cells of—	Serum absorbed *once* with cells of AGOUTIS. Diluted up to— 1/40.	1/80.	1/160.	1/320.	Serum absorbed *twice* with cells of AGOUTIS. Diluted up to— 1/40.	1/80.	1/160.	1/320.
Al. ♂ 149	+++	+	tr.	−	+	ft. tr.	−	−
Al. ♂ 137	++	+	tr.	−	tr.	ft. tr.	−	−
Al. ♀ 12	+++	++	+	−	+	tr.	−	−
Ag. ♂ 18	−	−	−	−	−	−	−	−
Ag. ♂ 19	−	−	−	−	−	−	−	−

Al. = Albino. Ag. = Agouti.

Peter A. Gorer in 1936 discovered the antigen II on mouse erythrocytes (Br J Exp Pathol 17:42-50, 1936) and the very

next year he reported that this antigen is identical to the gene controlling susceptibility to a transplantable sarcoma (J Pathol Bacteriol 41:691-696, 1937).

1944
1944
Allografts



In 1944, Peter Medawar (J Anat 78:176, 1944) studying skin transplants in rabbits demonstrated that rejection of homografts (now named allografts) is the result of a specific and systemic immune response.

1948
1948
Gene H2

TABLE 5. THE SEGREGATION OF FUSED IN VARIOUS BACKCROSSES

tumour-susceptible grandparent	sex of F_1	fused	normal
A	♂	77	104
dba	♂	26	17
dba	♀	12	21

TABLE 6. LINKAGE OF H_2^d TO FUSED, TESTED WITH *dba* TUMOUR

	response to tumour		
phenotype of mouse	+	−	total
fused	5	33	38
normal	35	3	38
totals	40	36	76

TABLE 7. SURVIVAL TIMES OF BACKCROSS TO *P* STOCK

	survival time (weeks)							
	2	3	4	5	6	12	17	total
normal mice	2	18	9	5	1	0	0	35
fused mice	0	1	1	0	1	1	1	5
total	2	19	10	5	2	1	1	40

(2) *With* dba *tumour P* 1534

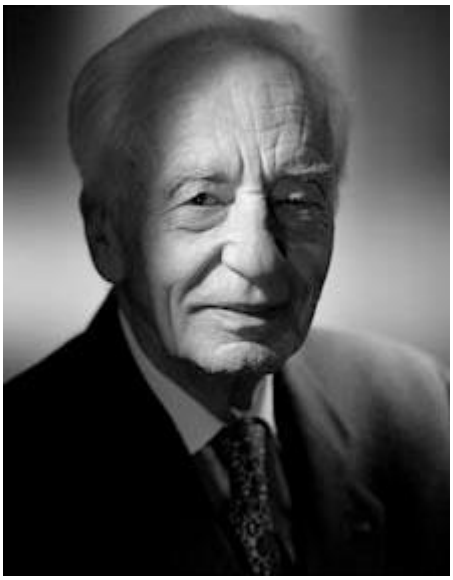
In 1948, Gorer, Lyman and George Snell published a landmark paper (Proc Royal Soc B 4:9i9, 1948) demonstrating that antigen II was identical to the antigen present on tumors of two strains of mice and was the major factor controlling graft acceptance. The gene coding for this antigen was named H_2, where´H´stands for Histocompatibility. The H-2 locus therefore came to be recognized as the Major Histocompatibility Antigen System.

1954
1954
Leuco-agglutinins

Jean Dausset in 1950s (Vox Sang 4:190, 1954; Acta Haematol 20: 156, 1958; and 20:185, 1958) was the first to describe antibodies to platelets in the sera of multitransfused patients that were able to agglutinate donor leukocytes. He

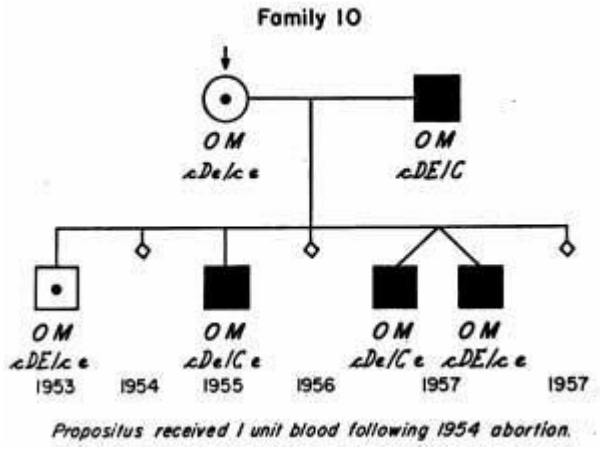
referred to them as leuco-agglutinins.

1958
1958
MAC – HLA-A2



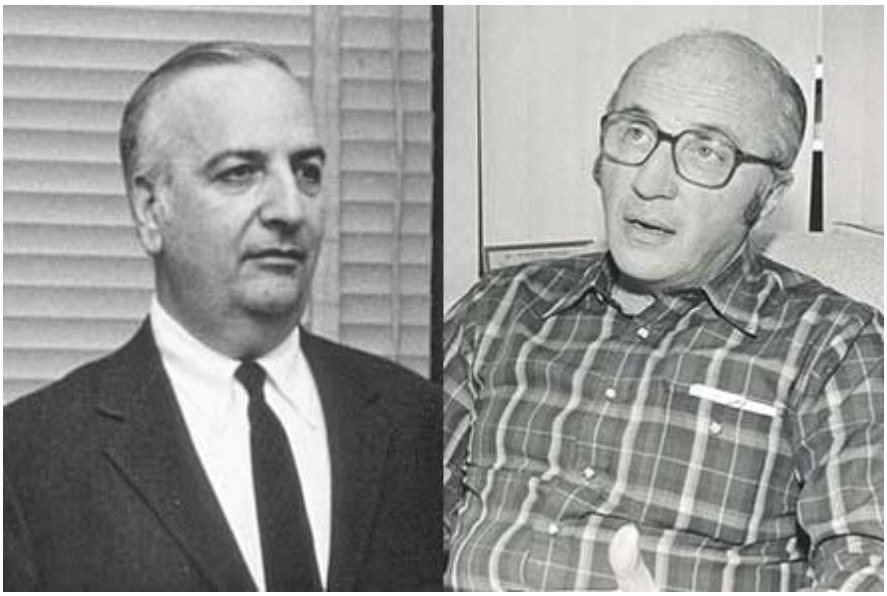
Jean Dausset (1916-2009) discovered the first HLA antigen in 1958, which he named “MAC”, the three letters based on the first names of three of his volunteers. Later it came to be recognized as HLA-A2.

1958
Anti-leukocyte antibodies



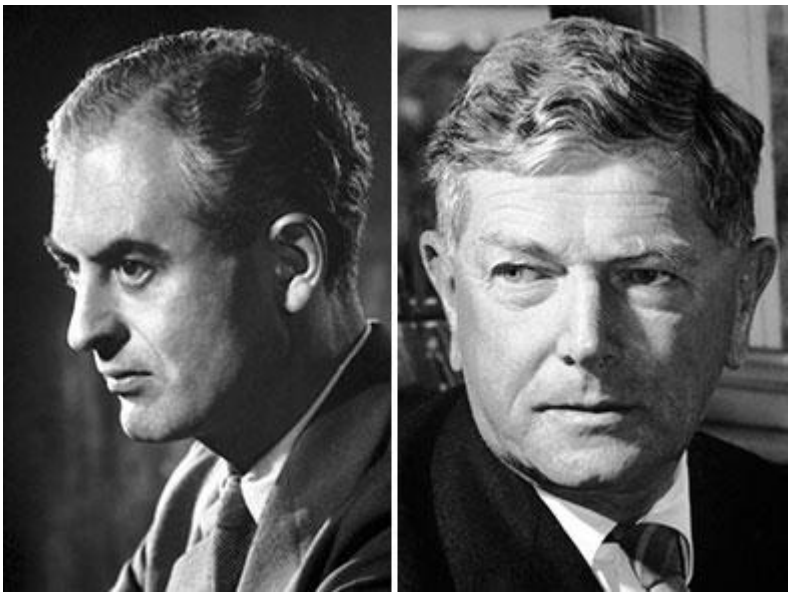
Rose Payne in the US (J Clin Invest 37:1756, 1958) and Jon van Rood in the Netherlands (Nature 151:1735, 1958) working independently reported the presence of anti-leukocyte antibodies in the sera of pregnant women. This set the momentum for the availability of mono or oligospecific HLA antisera to determine HLA antigens in an individual.

1960
1960
MHC immune responses



In the 1960s, studies done by Baruj Benacerraf and colleagues (Levine et al. J Exp Med 118:953, 1963) and Hugh McDevitt and coworkers (J Exp Med 126:969, 1967), amongst others, revealed that the MHC genes controlled specific immune responses through what they called Immune Response genes (Ir genes).

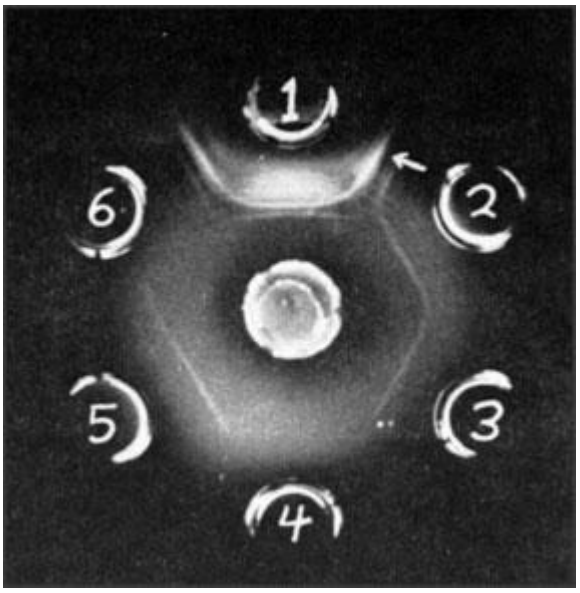
1960
Nobel Prize – 1960



In 1960, Peter Medawar received the Nobel Prize for his pioneering studies on tissue transplantation and immunological tolerance. The Prize was shared with McFarlane Burnet who postulated the Clonal Selection Theory of Acquired Immunity.

Nobel Prize 1960 – The Nobel Prize in Physiology or Medicine 1960 “for discovery of acquired immunological tolerance.”

1963
1963
C4 component of complement



In 1963, Shrefler and Owen (Genetics 48:9, 1053) discovered a mouse serum protein whose levels were genetically determined by genes located on the H-2 loci. They called it ´Ss´, later identified as the C4 component of complement.

1964
1964
MHC Workshops

In 1964, Bernard Amos organized the First International Histocompatibility Workshop (IHWS) at Duke University, North Carolina, USA, where participants compared various techniques for the detection of human leukocyte antigens. This led to the start of a very productive international collaborative program, which contributed significantly to further define the HLA loci with their multiple alleles. It also discussed the methods to be used for the detection of HLA alleles, and paved the way for studies on the anthropological significance of HLA polymorphism, clinical meaning of HLA and disease associations, and influence of donor-recipient HLA matching and antibody determination in organ and hematopoietic stem cell transplantation. Seventeen such workshops have already been organized, while the 18th IHWS is planned for May 2021 in Amsterdam.

1964
Complement Dependent Cytotoxicity (CDC) Assay

In 1964, Paul Terasaki and John McClelland (Nature 204:998, 1964) introduced the microlymphocytotoxicity test, known as complement dependent cytotoxicity assay or simply CDC, which became the standard serological assay for HLA typing and cross-matching in clinical tissue transplantation.

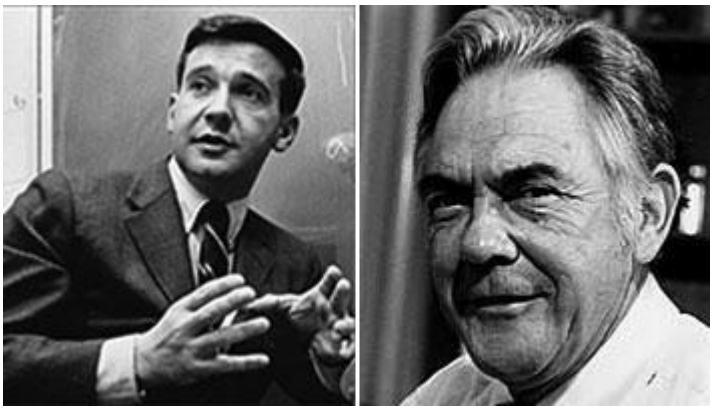
1964
MHC polymorphisms

TABLE III—EFFECT OF EXERCISE ON FIBRINOLYTIC ACTIVITY IN OBESE AND NORMAL SUBJECTS

Subject no.	Sex	Observed/standard weight ratio	Fibrinolytic activity (units)				
			Before exercise	Immediately after exercise	Increase	After 30 minutes' rest	Fall after rest
1	M	190	1·5	2·4	0·9	2·1	0·3
2	F	162	1·9	2·6	0·7	2·6	0·0
3	F	238	1·1	1·4	0·3	1·4	0·0
4	F	200	0·9	0·9	0·0	0·9	0·0
		Means	1·35	1·82	0·47	1·75	0·07
5	M	121	4·1	6·2	2·1	4·5	1·7
6	F	103	3·3	4·3	1·0	3·5	0·8
7	F	100	5·5	9·0	3·5	7·1	1·9
		Means	4·3	6·5	2·2	5·03	1·37

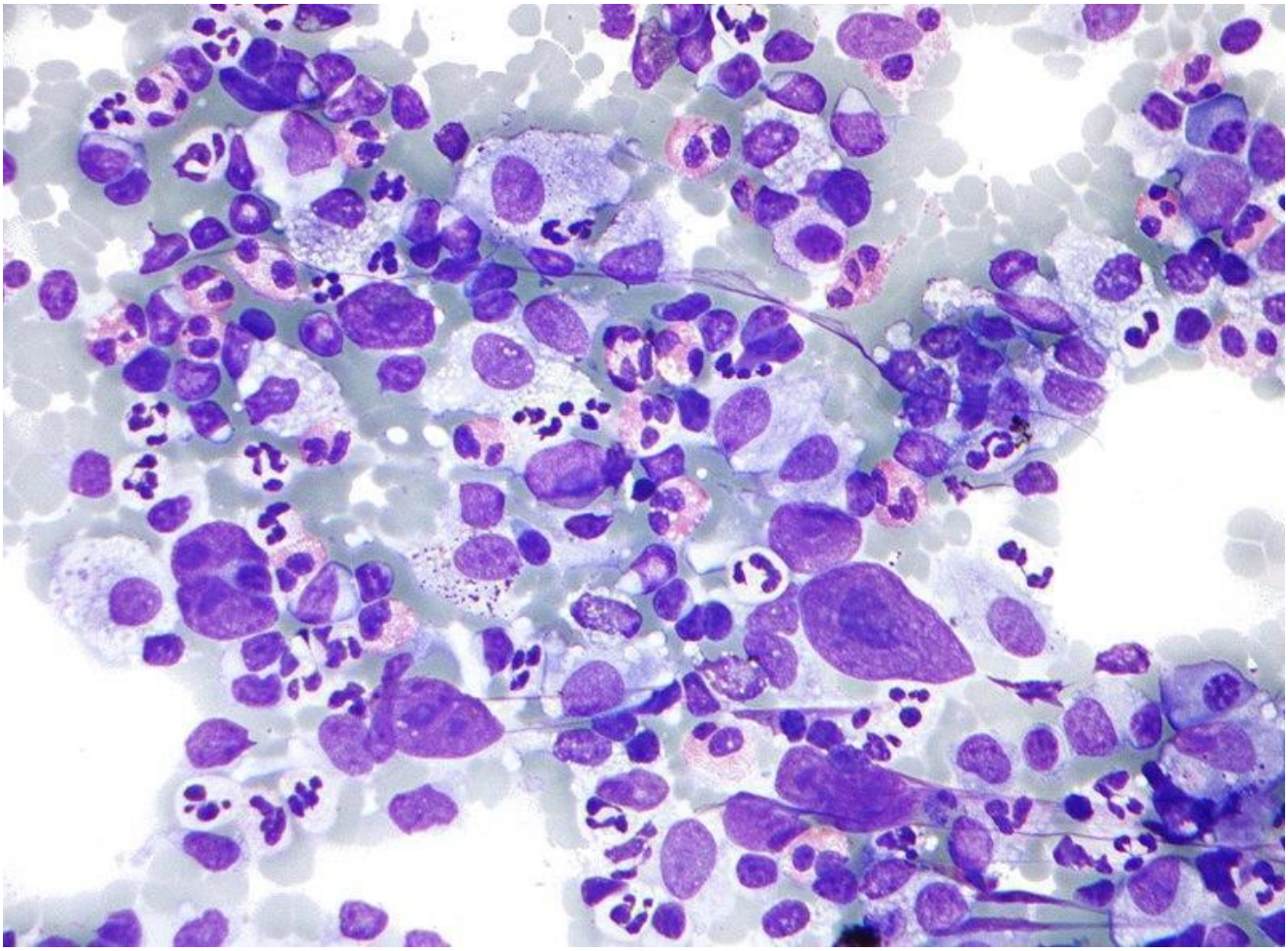
Also in 1964, Frank Lilly and colleagues (Lancet 2(7371):1207, 1964) reported an association between H-2 and susceptibility to viral leukemogenesis in the mouse system. This was the first publication of a possible association of MHC polymorphisms and disease susceptibility.

1967
1967
Mixed Lymphocyte Culture (MLC) reaction



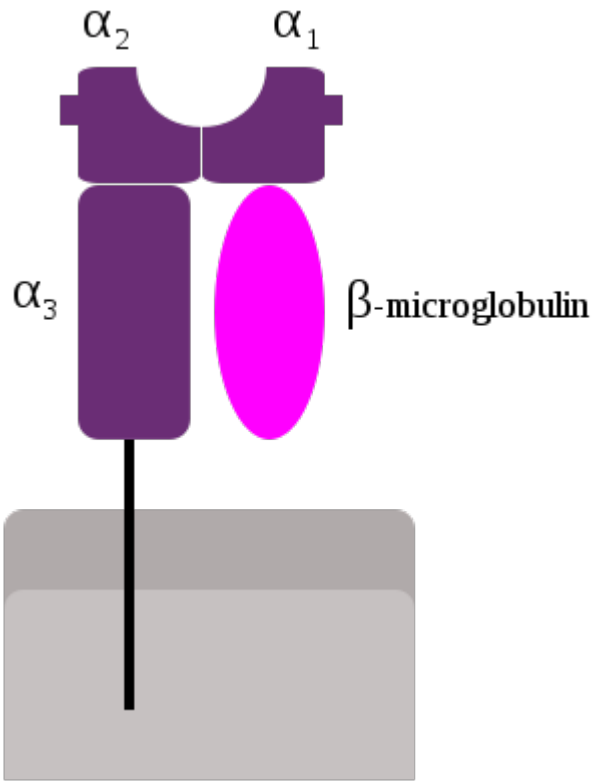
In 1967, Fritz Bach and Bernard Amos reported that HL-A genes control the Mixed Lymphocyte Culture (MLC) reaction.

1967
Hodgkin's Disease



The first report of an association between HLA and a human disease was by Amiel in 1967 (Histocompatibility Testing p79, 1967), who published a weak association of HLA-B5, B15 and BW35 with Hodgkin’s disease.

1968
1968
Class I alpha Chain



Class I α chain was first isolated in 1968 by Mann et al (Nature 217: 1180, 1968) and Nathenson and Shimada (Transplantation 6:662, 1968).

1968
Beta 2-Microglobulin

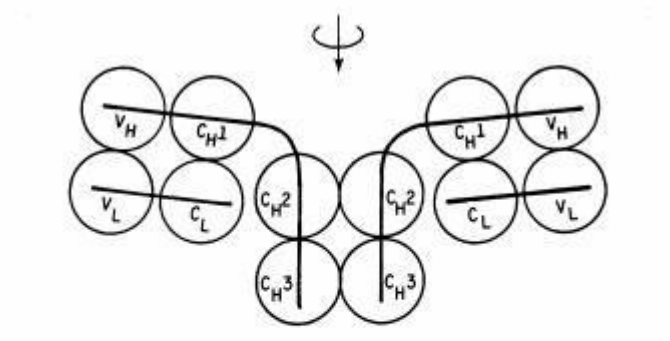
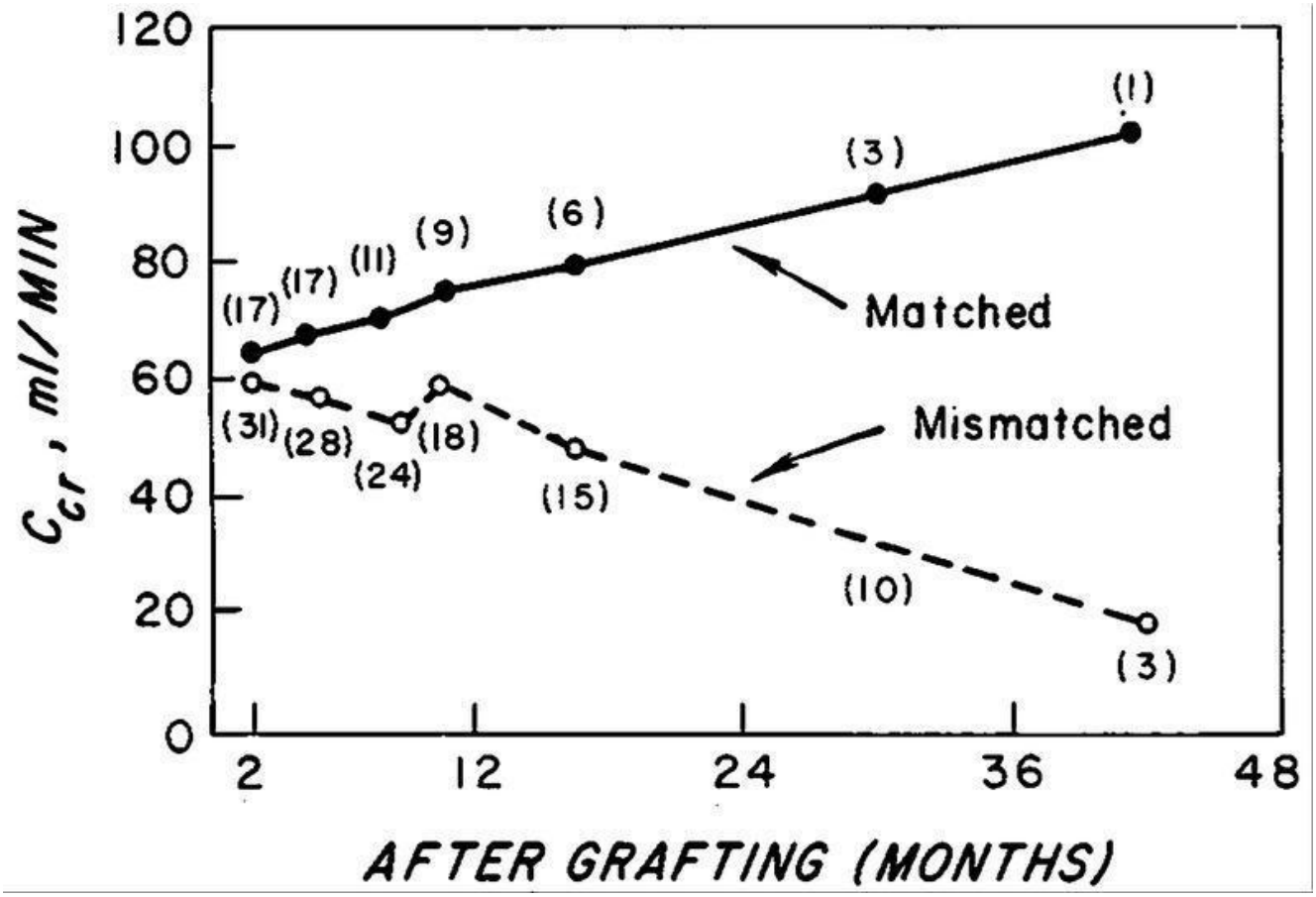


FIG. 1. Diagram of the overall structure of immunoglobulin G illustrating the domain hypothesis (1, 2). Light chain (V_L, C_L) and heavy chain (V_H, C_H1, C_H2, and C_H3) domains are denoted by *circles;* the dyad axis is indicated by Ψ. Each domain is connected to the succeeding domain by a less tightly folded region of the polypeptide chain. V-region domains mediate antigen-binding functions, while C-region domains mediate effector functions.

β2-microglobulin was first isolated by Bergard and Bearn (J Biol Chem 243:4095, 1968) from the urine of patients with cadmium-induced renal tubular damage. The complete protein sequence was published in 1972 by Peterson et al. (Proc Natl Acad Sci USA 69:1697, 1972) indicating that it belonged to the

Ig superfamily.

1968
HLA Matching



The first evidence that HLA matching improved renal graft survival was published in 1968 (Morris et al., Lancet 2(7572):803, 1968; Patel et al., N Engl J Med 279:501, 1968)

1968
HLA Antigens

Kissmeyer-Nielsen et al. (Nature 219:1116, 1968) defined the first series of HLA antigens assigned to the HLA-A and B loci.

1968
HLA Nomenclature Committee

In 1968, the World Health Organization (WHO) sponsored the establishment of an HLA Nomenclature Committee, which is still active and continues to revise the system.

1969
1969
HLA Compatibility

In 1969, Ceppellini et al. (Transplant Proc 1:385, 1969) provided experimental evidence in man that indicated that the survival of skin grafts depended on HLA compatibility between the donor and the recipient.

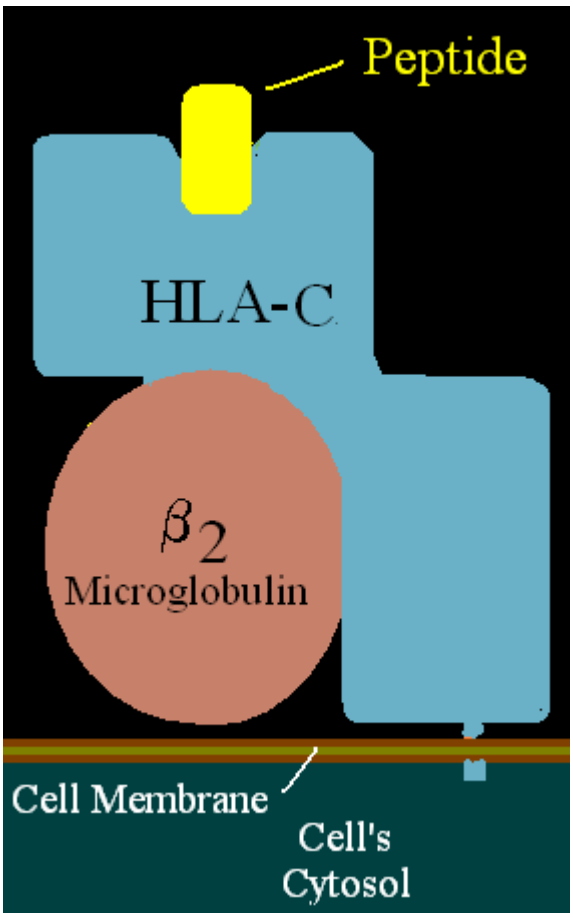
1969
Hyperacute Rejection

TABLE 2. *Classification of 248 Kidney Transplants Performed in 63 Recipients with and 163 without Preformed Antibodies According to the Duration of Graft Survival.*

GRAFT SURVIVAL	RECIPIENTS WITH ANTIBODIES			RECIPIENTS WITHOUT ANTIBODIES
	POSITIVE CROSSMATCH	NO CROSSMATCH	NEGATIVE CROSSMATCH	
Immediate failures	24 (80.0%)	6 (26.1%)	4 (14.8%)	4 (2.4%)
Failure within <3 mo	0	6	4	32
Failure after >3 mo	1	3	7	22
Survival for <3 mo	2	2	1	6
Survival after >3 mo	3	6	11	104
Totals	30	23	27	168

Patel and Terasaki (N Engl J Med 280:735, 1969) demonstrated that the presence of preformed cytotoxic antibodies in recipients of renal grafts was associated with hyperacute rejection.

1970
1970
HLA-C locus



Sandberg et al. (Histocompatibility Testing p163, 1970) assigned the first serologically defined antigens to the HLA-C locus.

1970
Two loci, K and D

Erik Thorsby (Eur J Immunol 1:57, 1970) and Snell et al. (Transplant Proc 3:183, 1971) independently proposed that the known H-2 genes were encoded by two loci, K and D.

1970

[De novo Donor-specific Antibodies]

TABLE 1. *Humoral Antibodies in Kidney Transplantation.*

GROUP	NO. OF TRANSPLANTS	ANTIBODIES			
		BEFORE OPERATION		AFTER OPERATION	
		against donor	*against other persons*	*against donor*	*against other persons*
A	5	−	−	−	−
B	7	−	+	−	+
C	16	−	+ or −	+	+
D	10	+	+	+	+

Jeannet et al., (N Engl J Med 282:111, 1970) reported that the development of *de novo* donor-specific antibodies early after kidney transplantation was associated with severe vascular rejection and poor allograft survival.

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