# HISTOCOMPATIBILITY STUDIES IN A CLOSELY BRED COLONY OF DOGS

## III. Genetic Definition of the DL-A System of Canine Histocompatibility, with Particular Reference to the Comparative Immunogenicity of the Major Transplantable Organs*

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A principal immunogenetic system of histocompatibility has been detected in every mammalian species studied thus far. The murine H-2 system (1) served as the primary model in this search, although Snell, Cherry, and Demant (2) have recently suggested that the H-2 specificities may also fit into the two-locus scheme proposed for the human HL-A system (3). Similar genetically defined systems have also been reported in rats (4, 5), guinea pigs (6), pigs (7), chimpanzees (8), and rhesus monkeys (9). In the canine species, Puza and associates (10), Rubinstein and Ferrebee (11), Cleton and his associates (12, 13), Cohen and Kozari (14), and Epstein et al. (15) have shown that immunization of dogs (particularly littermates) with buffy coat cells may stimulate the production of leukocyte group-specific antisera. Such antisera have been shown to be useful in the selection of donor-recipient pairs for bone marrow transplantation in littermates (15) as well as in unrelated dogs (16). In an extension of this serological approach, Rubinstein et al. (17) and Mollen and associates (18) produced a battery of typing sera capable of detecting 10 different leukocyte antigen specificities in a closely-bred colony of beagles maintained at the Mary Imogene Bassett Hospital in Cooperstown, N.Y. Histocompatibility studies in this colony have shown that skin (18), kidney (19), heart (20), lung, and liver (21) allografts transplanted across major leukocyte group incompatibilities are rejected more rapidly than transplants obtained from compatible donors.

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These observations, taken together with evidence that the leukocyte antigens detected in the Cooperstown Colony behave as mendelian autosomal dominants (21), suggested that such antigens were components of a major system of histocompatibility, for which the term DL-A was proposed in 1969 (20). The studies of Bos et al. (22), Westbroek et al. (23), Chandler et al. (24), and Blumenstock and associates (25) have provided further evidence to support the existence of such a major histocompatibility locus in the canine species. More recently, Templeton and Thomas (26) have also confirmed the existence of the DL-A locus through the use of the mixed leukocyte culture technique.

Although significant prolongations in allograft survival have been shown to occur in the Cooperstown Colony under conditions of DL-A compatibility (17–21), the results have also suggested the need for further genetic and serological studies of the antigenic components of the DL-A system. Further progress in the selection of donor-recipient combinations which would predictably be associated with long-term organ transplant survival appeared to be particularly dependent upon genetic studies of the transmission of the DL-A antigens within this particular canine colony (20). This type of analysis also appeared to be a prerequisite for an assessment of the comparative immunogenicity of the major transplantable organs under defined conditions of DL-A compatibility.

The present report provides a genetic definition of the principal antigenic components of the DL-A system and of the segregation of these components in 679 offspring of 141 consecutive matings within the Cooperstown Colony. In addition to such family studies, the results of population studies, based upon the incidence of currently detectable DL-A antigen(s) in 100 randomly selected mongrel dogs, will be presented and discussed. These observations serve as the basis for an assessment of the comparative immunogenicity of allografts of skin, kidney, heart, and liver in the Cooperstown Colony, performed under serologically and genetically defined conditions of donor-recipient compatibility.

## *Materials and Methods*

*Source of Experimental Animals, Production of Typing Sera, and Serological Techniques.*— The Cooperstown Colony is a closely-bred colony of dogs which originated 11 yr ago in the kennels of the Mary Imogene Bassett Hospital. The colony was initiated with 17 beagles obtained from a number of different kennels. Since then, 517 matings have produced 1302 offspring; 679 offspring of 141 matings in this colony and 100 randomly selected mongrel dogs were studied with a battery of 10 lymphocytotoxic DL-A typing antisera. As described previously (18), the sera were prepared by reciprocal exchanges of skin allografts and subcutaneous inoculations of blood leukocytes in five pairs of beagle littermates and in two nonlittermates. They were used to detect 10 different leukocyte antigen specificities (or sets of specificities), including antigen(s) *b, c, d, e, f, g, h, k, l,* and *m* (18). The DL-A phenotypes and presumed genotypes of the donors and recipients used to produce these antisera are outlined in Table I. The technique of lymphocytotoxicity of Epstein et al. (15) was employed, with removal of erythrocytes by sedimentation before nylon infiltration, in order to separate lymphocytes from polymorphonuclear leukocytes. Erythrocyte group antigens A, C, and D were detected with the typing sera and technique of Swisher (27).

In an attempt to assess further the specificity of the DL-A antisera, a number of such sera was absorbed with leukocytes obtained from mongrel dogs selected on the basis of their DL-A phenotypes. For this purpose, 0.5 ml of serial dilutions of each serum sample were absorbed by a standard technique (incubation for 2 hr at 37°C) with 100–200 $\times$ $10^6$ cells obtained from unrelated mongrel dogs whose cells were positive for the corresponding DL-A specificities. Each absorbed serum was then retested with lymphocytes obtained from the same beagle whose tissues had been used as the source of immunizing material for production of that particular antiserum. Where the original donor was not available, the absorbed sera were retested with lymphocytes obtained from six unrelated mongrel dogs whose cells were positive for that particular antigen.

TABLE I

*DL-A Phenotypes and Presumed Genotypes of the Cooperstown Colony Donors and Recipients Used to Produce a Battery of Leukocyte Typing Antisera*

| Leukocyte and skin allograft donors | | | Recipients | | | Relationship between donor and recipient | Antibodies produced by recipients |
|---|---|---|---|---|---|---|---|
| Dog No. | Phenotype | Presumed genotype | Dog No. | Phenotype | Presumed genotype | | |
| 1614 | bkhfmcd | bkhfm/bkcd | 1611 | gl | gl/gl | | anti-k |
| 1611 | gl | gl/gl | 1614 | bkhfmcd | bkhfm/bkcd | Littermates | anti-l |
| 1608 | bkhfmcd | bkhfm/bkcd | 1607 | bkcdgl | bkcd/gl | | anti-b |
| 1607 | bkcdgl | bkcd/gl | 1608 | bkhfmcd | bkhfm/bkcd | | anti-g |
| 1322 | bkcdgl | bkcd/gl | 1323 | gl | gl/X‡ | Littermates | anti-b |
| 1623 | bkhfmgl | bkhfm/gl | 1625 | gl | gl/X‡ | Littermates | anti-h |
| 1600 | egl | e/gl | 1599 | gl | gl/X‡ | Littermates | anti-e |
| 1651 | bkhfmgl | bkhfm/gl | 1649 | egl | e/gl | Littermates | anti-m |
| 1281 | NT* | — | 1280 | NT* | — | Littermates | anti-d |
| 1242 | NT* | — | 1086 | NT* | — | Nonlittermates | anti-c |

* NT = not tested.

‡ X = the possibility of homozygosity could not be ruled out by genetic analysis.

*Methods of Genetic Analysis; Population Studies.*—The leukocyte antigen(s) transmitted from parents to offspring were studied in 141 consecutive matings within the Cooperstown Colony, with special regard to the different leukocyte group antigen(s) detected in the members of each litter. A particular effort was made to ascertain whether the DL-A antigen(s) were governed by one single pair or by different pairs of chromosomes. The method of deduction of the DL-A haplotypes (i.e. specificities determined by the DL-A region of one single chromosome) was based upon the probability that the DL-A antigen(s) are determined by one single chromosomal region (21), thereby permitting the application to the DL-A system of the same methods of analysis which have been used previously for the definition of the HL-A system in man (3). As a result, the determination of the DL-A phenotypes within the most recent Cooperstown Colony generations permitted a deduction of the genetic components of the DL-A system present in the 17 original animals of this colony, and the subsequent tracing of these genotypes through the entire colony.

This combined genetic and serological approach provided a definition of the different DL-A haplotypes occurring within the Cooperstown Colony. It also permitted the recognition, in

each successive litter, of those siblings inheriting the same parental haplotyeps (i.e. DL-A identical siblings[1]), those sharing only one haplotype (i.e. DL-A haploidentical siblings), and those which differed by both haplotypes. Possible relationships between the segregation of the DL-A antigen(s) and the sex and erythrocyte antigens of the offspring were also sought.

In addition to these family studies, the incidence of the DL-A antigen(s) was determined in 100 randomly selected mongrel dogs. The frequency of positive and negative associations between the different DL-A antigen(s) was calculated by determination of positive or negative coefficients of correlation (28) between each of the antigen(s).

*Transplantation Techniques; Correlation of the Results with DL-A Genotypes of Donors and Recipients.*—The results of transplantation of skin, kidney, heart, and liver allografts in the Cooperstown Colony have been reported in part previously (19–21). In order to permit a more precise assessment of the comparative immunogenicity of these organs, the results were correlated in the present study with the DL-A genotypes of donors and recipients. For this purpose, the results of each transplantation procedure in littermates were placed into one of three categories; (*a*) allografts performed in DL-A identical siblings; (*b*) DL-A haploidentical siblings; (*c*) DL-A different siblings. Knowledge of the DL-A genotypes of nonlittermate donors and recipients of transplants of different organs also facilitated a more precise assessment of the role of DL-A compatibility in the latter group. It is this combined genetic and serological assessment of donor-recipient compatibility which provides the basis of the present analysis.

## RESULTS

The segregation of DL-A antigen(s) in the Cooperstown Colony is illustrated in the representative matings shown in Fig. 1. The results were consistent in 141 consecutive matings, producing 679 offspring; (*a*) the DL-A antigen specificities (or sets of specificities) were regularly transmitted en bloc from parents to offspring; (*b*) there was no instance of independent segregation of these antigen(s) in any of the matings studied; (*c*) there was no correlation between DL-A genotypes and the sex or Swisher erythrocyte group antigens of these dogs. These results are in keeping with the concept of the DL-A system as a single major immunogenetic system governed by a single region (or locus) located on an autosomal pair of chromosomes. As noted in Fig. 1, the standard mendelian dominant patterns anticipated under such genetic conditions occur in regularly reproducible fashion in the Cooperstown Colony.

The haplotypes deduced for the 17 original members of the Cooperstown Colony are outlined in Table II. Through methods of backcross analysis, 23 haplotypes derived from different serological patterns of DL-A antigen(s) (*gl, bkhfm, bkcd, e, be, fgl*) were identified. In two instances, genetic analysis indicated that individual haplotypes did not possess any of the currently known DL-A specificities; such cases are listed as "nul" in Table II. In nine other instances, listed as "X" in Table II, homozygosity could not be excluded by genetic analysis.

As noted in Fig. 2, 31 different DL-A phenotypes were detected in a population

[1] *Abbreviations used in this paper:* DL-A identical siblings, siblings inheriting the same parental haplotypes; DL-A haploidentical siblings, siblings sharing only one haplotype; MST, mean survival time.

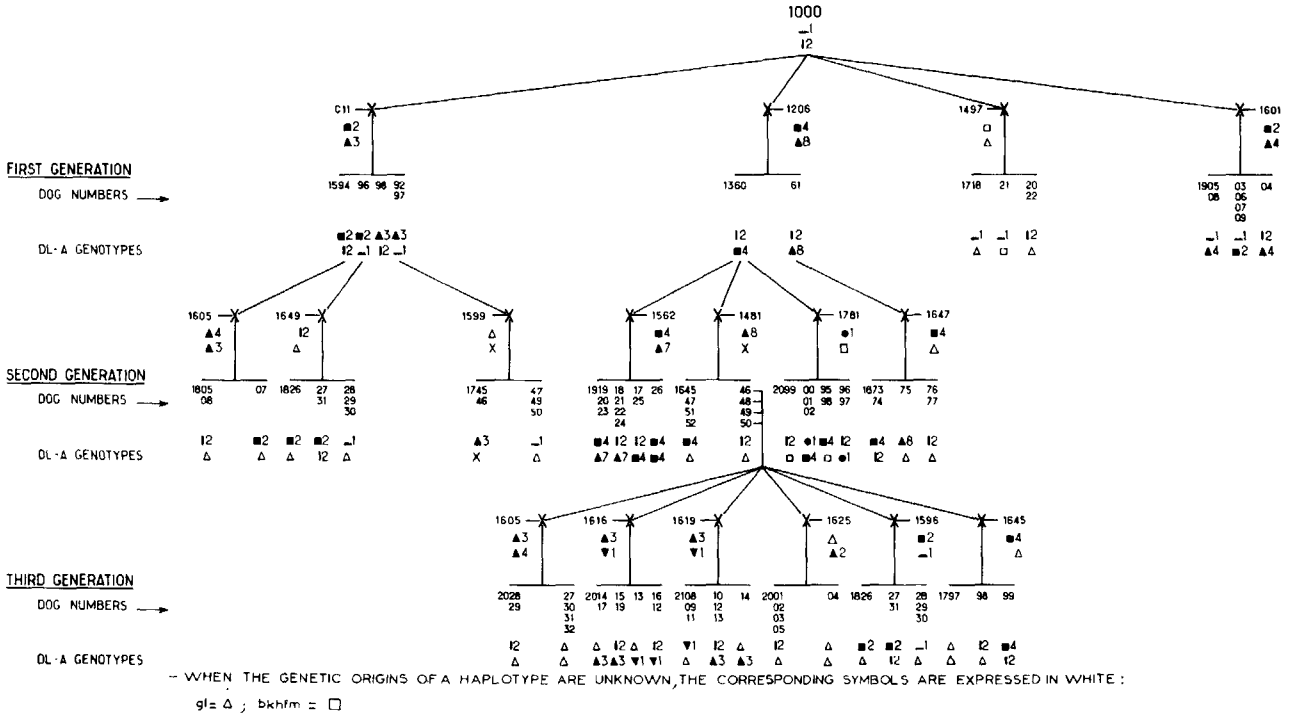


FIG. 1. Illustration of the segregation of the DL-A antigens in the Cooperstown Colony through three consecutive generations. The DL-A genotypes of the members of each litter are expressed in accordance to the symbols outlined in Table II.

of 100 randomly selected mongrel dogs. Antigenic "inclusions" (29) were observed with great frequency in this population. For example, dogs whose cells were positive for anti-*d* serum also reacted with anti-*c* serum; similarly, *c*-positive dogs were also *k* positive. Also, with the exception of four animals, dogs positive for *k* were also *b* positive. This group of antigen(s) (*b*, *c*, *d*, *k*) provided

TABLE II

*DL-A Genotypes of the Initial Members of the Cooperstown Beagle Colony*

| Dog No. | Relationship between individual beagles | Postulated genotypes | Symbols for each genotype* |
|---|---|---|---|
| C6 | Littermates | gl/"nul" | ▲1/"nul" |
| C7 | Littermates | gl/bkhfm | ▲2/■1 |
| C11 | Same sire as C6, C7 | gl/bkhfm | ▲3/■2 |
| 470 | None | bkcd/X | ●1/X |
| 684 | None | gl/X | ▲4/X |
| 709 | None | e/X | ▮1/X |
| 794 | None | gl/bkhfm | ▲5/■5 |
| 1000 | None | e/be | ▮2/▬1 |
| 1184 | None | be/X | ▬2/X |
| 1189 | Littermates | gl/X | ▲6/X |
| 1193 | Littermates | gl/fgl | ▲7,▼1 |
| 1196 | | bkcd/X | ●2/X |
| 1202 | Dam | bkhfm/X | ■3/X |
| 1206 | Offspring from Dam 1202 | bkhfm/gl | ■4/▲8 |
| 1208 | None | gl/X | ▲9/X |
| 1209 | None | gl/"nul" | ▲10/"nul" |
| 1284 | None | be/X | ▬3/X |

DL-A genotypes of the initial members of the Cooperstown Colony. The black symbols listed in the fourth column refer to the different haplotypes detected in the Cooperstown beagles (gl, bkhfm, bkcd, e, be, and fgl). The numbers opposite each haplotype refer to the individual origins of each of thise haplotypes, i.e., the different parental lines.

* gl = ▲, bkhfm = ■, bkcd = ●, e = ▮, be = ▬, fgl = ▼ — The black symbols refer to the six different haplotypes detected in the Cooperstown beagles. The numbers opposite to these haplotypes in the fourth column of this table refer to the different individual origins of each of these haplotypes.

one example of the occurrence of inclusions in the DL-A system. Similar associations were noted between antigen(s) *g* and *l*, and *f* and *m*.

Table III lists the incidence of reactivity to different DL-A typing sera in a population of mongrel dogs. This varied from 87% for *k* to 19% for *d*. As noted in Table IV, the calculated coefficients of correlation between the DL-A antigens detected in this population showed a number of statistically significant positive and negative associations between some of the antigen(s). There were

positive associations between *b* and *c*, *k*, *m;* between *c* and *k;* between *f*, *k*, and *m;* between *g* and *l*. There were negative associations between *d*, and *m*; between *d* and *e*; between *g*, *l*, and *b*, *m*, and *k*.

Absorption studies showed evidence of the presence of at least two different

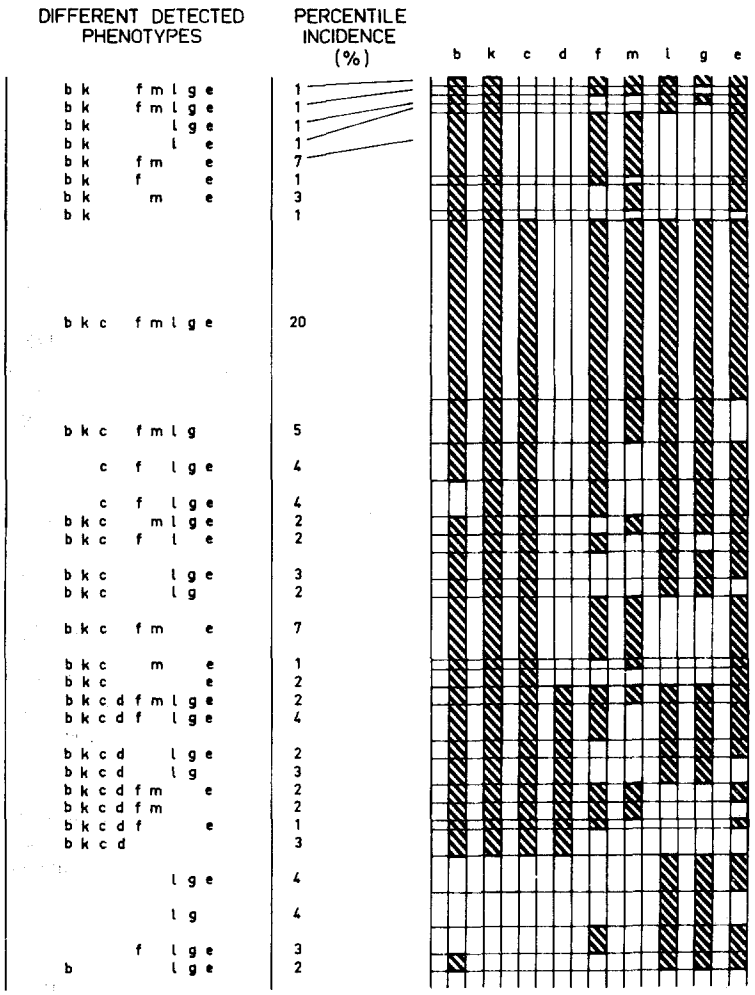


FIG. 2. Distribution of positive reactions obtained with DL-A typing antisera in a population of 100 mongrel dogs.

antibody specificities in all but one of the antisera composing the current DL-A typing battery. The anti-*e* antiserum was shown to be monospecific by this technique. The term DL-A antigen(s), as used in this report, therefore, refers to sets of frequently associated specificities, rather than to single antigenic determinants.

The results of skin, kidney, heart, and liver allografts performed between littermate dogs with defined DL-A genotypes are summarized in Table V. The mean survival time (MST) of allografts performed in DL-A identical donor–recipient combinations was 25.1 days for skin, 28.1 days for kidney, 47.1 days

TABLE III

*Incidence of Reactions Obtained with Nine DL-A Typing Antisera in a Population of 100 Mongrel Dogs*

| Typing serum utilized | Incidence of positive reactions |
|---|---|
| | % |
| Anti-b | 85 |
| Anti-c | 71 |
| Anti-d | 19 |
| Anti-e | 81 |
| Anti-f | 66 |
| Anti-g | 66 |
| Anti-k | 87 |
| Anti-l | 70 |
| Anti-m | 53 |

TABLE IV

*Coefficients of Correlation ($r$) × 100 between the DL-A Antigens (or Sets of Antigenic specificities) Detected in a Population of 100 Mongrel Dogs*

| | c | f | m | k | d | e | g | l |
|---|---|---|---|---|---|---|---|---|
| b | **41** | 17 | **45** | **75** | 20 | 08 | **−30** | **−28** |
| | c | 29 | 15 | **60** | −12 | −08 | 19 | 16 |
| | | f | **51** | **35** | 29 | 30 | −02 | −01 |
| | | | m | **41** | **−21** | 16 | **−21** | **−27** |
| | | | | k | 19 | 12 | **−28** | **−25** |
| | | | | | d | **−29** | −08 | −13 |
| | | | | | | e | 12 | 30 |
| | | | | | | | g | **91** |
| | | | | | | | | l |

Significant associations ($P \leq 0.001$ for positive associations and $P \leq 0.05$ for negative associations) are listed in bold face; negative associations between different antigen(s) are indicated by the sign "−" (28).

for heart, and 74.2 days for liver transplants. Under conditions of haploidentity, the MST was 21.8, 24.1, 25.5, and 62.5 days, respectively, for the same organs. In contrast, allografts of these organs performed in littermate pairs which had inherited different parental haplotypes had an MST of 19.5, 19.5, 16.5, and 45.5 days, respectively.

TABLE V

*Relationships between Genetically Defined DL-A Haplotypes and the Survival of Allografts of Different Tissues in Cooperstown Colony Littermate Dogs*

| Type of transplant | Total No. of allografts | MST* of allografts under defined donor-recipient genetic conditions | | |
|---|---|---|---|---|
| | | Established or possible DL-A identity | Established or possible DL-A haploidentity | Known or possible presence of different parental haplotypes in donor and recipient |
| | | *days* | *days* | *days* |
| Skin | 34 | 25.1 | 21.8 | 19.5 |
| Kidney | 22 | 28.1 | 24.1 | 19.5 |
| Heart | 14 | 47.1 | 25.5 | 16.5 |
| Liver | 10 | 74.2 | 62.5 | 45.5 |

* MST = mean survival time.

TABLE VI

*Correlation between Genetically and Serologically Defined DL-A Compatibility and the Survival of Allografts of Different Tissues in the Cooperstown Colony*

| Type of allograft | Total No. of transplants | Donor-recipient relationships | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Littermates | | | | Nonlittermates | | | |
| | | DL-A compatible | | DL-A incompatible | | DL-A compatible | | DL-A incompatible | |
| | | No. of allografts | MST* | No. of allografts | MST | No. of allografts | MST | No. of allografts | MST |
| | | | *days* | | *days* | | *days* | | *days* |
| Skin | 42 | 20 | 24.7 | 14 | 16.6 | 5 | 21.8 | 3 | 11.1 |
| Kidney | 48 | 14 | 27.3 | 8 | 14.7 | 9 | 28.3 | 17 | 12.2 |
| Heart | 31 | 10 | 33.9 | 3 | 13 | 8 | 17.8 | 9 | 10.5 |
| Liver | 18 | 8 | 76.7 | 2 | 11 | 5 | 30 | 3 | 5 |

* MST = mean survival time (days).

A correlation between genetically confirmed donor-recipient DL-A incompatibility and the outcome of transplantation of different organs is presented in Table VI. In littermates, the MST of DL-A–compatible allografts was 24.7 days for skin, 27.3 days for kidney, 33.9 days for heart, and 76.7 days for liver transplants. In contrast, the MST of allografts of the same organs transplanted in DL-A–incompatible littermates was 16.6, 14.7, 13, and 11 days, respectively.

In nonlittermate dogs, DL-A–compatible transplants of skin, kidney, heart, and liver had an MST of 21.8, 28.3, 17.8, and 30 days, respectively, while the MST of DL-A–incompatible transplants of the same organs was 11.1, 12.2, 10.5, and 5 days, respectively.

## DISCUSSION

Previous observations have indicated that progress in the application of tissue-typing techniques to the selection of optimally compatible organ transplant donor-recipient pairs in the Cooperstown Colony was dependent upon a further genetic definition of the DL-A system in this colony (20). Such genetic studies were considered to be of particular importance to the assessment of the comparative immunogenicity of the major transplantable organs in the canine species. The present study illustrates the usefulness of genetic analysis in providing a better understanding of serological criteria of histocompatibility. Although absorption studies have shown that most of the presently available DL-A–typing sera are not monospecific, these sera have succeeded in detecting a number of sets of antigenic specificities which are regularly transmitted en bloc from parents to offspring within the Cooperstown Colony. This observation, taken together with the lack of evidence of independent segregation of these antigen(s) in 141 consecutive family studies, supports the contention that the DL-A antigen(s) detected thus far are components of a major immunogenetic system, determined by a single chromosomal region. This interpretation is supported further by the fact that planned immunization programs within the Cooperstown Colony have not produced thus far any antibodies capable of detecting leukocyte antigen(s) segregating separately from the currently known specificities (Table I). It is also in agreement with the observation that none of the matings studied produced more than four different types of DL-A combinations in the offspring. The occurrence of statistically significant positive and negative associations between certain of the DL-A antigen(s) in mongrel dogs is also in keeping with the concept of DL-A as the principal system of leukocyte antigens in the canine species.

The antigenic inclusions observed in the mongrel dog population provide an interesting parallel between the DL-A and HL-A systems. In the latter, such inclusions have been considered by Colombani et al. (30) and by Svejgaard and Kissmeyer-Nielsen (31) to constitute an expression of cross-reactivity between allelic antigens. Similar observations have been reported recently in the H-2 system by Amos et al. (32) and by Shreffler and Klein (33). The inclusions observed in the DL-A system may therefore also be a result of cross-reactions between certain antigenic products of the same locus. Such cross-reactions may provide an explanation for the relatively large number of specificities which has been observed in some of the DL-A haplotypes described in this study (Table II); the actual number of antigens present in such haplotypes may therefore be much smaller.

The genetic analysis of DL-A haplotypes in Cooperstown Colony organ transplant donors and recipients has facilitated a more precise assessment of the role of DL-A compatibility in conditioning allograft survival. The correlations noted between serologically determined and genetically confirmed states of donor-recipient compatibility and the survival of skin, kidney, heart, and liver allografts are in keeping with the concept that the DL-A system is the principal system of histocompatibility in the canine species (19). The longest allograft survivals occurred under conditions of DL-A genetic and serological identify (Table V); transplants performed between littermates bearing different sets of parental haplotypes were accorded the shortest survivals in this category of animals. This result illustrates the potential value of genetically defined states of donor-recipient compatibility in transplantation. It also indicates the possible advantages of analyses of histocompatibility by the haplotype method; in this regard, the DL-A system appears to be similar to the HL-A system (34).

These studies have also provided an opportunity to examine further the comparative in vivo immunogenicity of different major transplantable organs in the canine species. Previous in vitro studies in man (35) and in the mouse (36) indicate that there may be quantitative variations in the concentration of histocompatibility antigens in different tissues. On the basis of such results, it has been suggested, for example, that the heart may be less immunogenic than the kidney. There has also been a number of reports regarding the in vivo behavior of allografts of different tissues under comparable conditions of donor-recipient compatibility. Freeman and associates (37, 38) have noted similar survivals for heart and skin allografts in the rat, while Barker and Billingham (39) have indicated that cardiac allografts may be less vulnerable to rejection than skin, but more susceptible to rejection than renal allografts in the same species. Van Bekkum et al. (40, 41) have noted that cardiac allografts may be more susceptible to rejection than renal transplants in the rat, and White and Hildemann (42), and Sakai (43) have reported that renal allografts may be accorded longer survival times than skin in certain strains of rats. In the canine species, Moseley and associates (44) have provided evidence that skin allografts may be more vulnerable to rejection than renal transplants. Under the conditions of the present study, allografts of skin and kidney have been accorded similar survival times under comparable DL-A–compatibility states. DL-A incompatibilities caused parallel decreases in the survival of skin and renal allografts, while DL-A identity (Table V) was associated with similar prolongations in survival. Cardiac allografts survived for significantly longer periods of time in DL-A identical donor–recipient pairs; they were rejected at a faster rate than skin or kidney in DL-A different pairs. The longest organ transplant survivals were observed with liver transplants performed in DL-A identical donor–recipient pairs (MST = 74.2 days).

It must be noted, however, that the variations in response to different organs

under comparable conditions of DL-A compatibility may be the consequence of a number of variables other than histocompatibility. The early establishment of lymphatic connections with the host by orthotopic skin allografts (45) could, for example, provide an explanation for the greater vulnerability of skin, as compared to whole-organ transplants, whose first connection with the host occurs by a direct surgical anastomosis of major blood vessels. The very short survival of DL-A–incompatible cardiac allografts, when compared with renal allografts, may similarly have been a consequence of physiological differences in the susceptibility of these organs to the events of allograft rejection. Indeed, the pathological lesions of cardiac rejection have been shown to be particularly prominent in the conducting tissues, such as the atrioventricular node, the conducting bundles, and bundle branches (46), making this site a particularly sensitive locus minoris resistentiae during the rejection response.

Liver transplants performed in DL-A identical pairs were accorded longer survival times than any of the other organs studied in the Cooperstown Colony. Calne (47) has reported previously that dogs reject liver allografts at the same rate as kidneys, usually within 7–14 days. The MST of 74.2 days accorded to DL-A identical liver transplants is more in keeping, however, with Calne et al.'s results in pigs (48, 49), which appear to tolerate such allografts for prolonged periods of time. The results presented in this report may, therefore, have provided a further illustration of the possible importance of variables in donor recipient compatibility in studies of the immunological significance of differences in rejection responses.

The behavior of skin and kidney allografts performed under similar conditions of DL-A compatibility constitutes an interesting parallel to the human situation, where a similar correspondence between skin and kidney was first suggested by Ceppellini (50). This consideration, taken together with the similarities documented between the DL-A and the HL-A system, suggests that the Cooperstown Colony may be of value in further transplantation studies which may be eventually applicable to the human situation. In this regard, the availability of genotypically DL-A identical canine donors and recipients may be especially useful in studies of the facilitation of organ transplant survival in the mammalian host.

## SUMMARY

The segregation of the canine DL-A leukocyte group antigen(s) *b*, *c*, *d*, *e*, *f*, *g*, *h*, *k*, *l*, and *m* has been traced in 141 consecutive matings in the Cooperstown Colony of beagles. All of the leukocyte antigen(s) were regularly transmitted en bloc from parent to offspring, with no instance of independent segregation. A total of 23 haplotypes, including six different DL-A antigen patterns (*gl*, *bkhfm*, *bkcd*, *e*, *be*, *fgl*) was observed. 31 different DL-A phenotypes were observed in a population of 100 mongrel dogs. A number of statistically significant positive

and negative associations between individual DL-A antigenic components occurred in this population. The results support the concept of the DL-A system as a complex immunogenetic system governed by a single region (or locus) of an autosomal pair of chromosomes.

Studies of skin, kidney, heart, and liver allografts in the Cooperstown Colony indicated that the longest allograft survivals occur under genetically and serologically defined conditions of donor-recipient DL-A compatibility. Skin and renal allografts generally behaved in parallel fashion, while cardiac allografts survived for longer periods of time (MST = 47.1 days) than kidneys (MST = 28.1 days) or skin (MST = 25.1 days) under conditions of DL-A identity. Heart transplants were rejected at a more rapid rate than kidney, however, in DL-A–incompatible donor-recipient combinations. Liver transplants were accorded the longest survival time (MST = 76.2 days) under conditions of DL-A identity, but were rejected at a rapid rate (MST = 5 days) in DL-A–incompatible nonlittermate donor-recipient pairs.

The results provide further evidence that the DL-A system is the principal system of histocompatibility in the canine species. The differences in survival of different organs under similar conditions of donor-recipient DL-A compatibility suggest, however, the existence of a number of unknown variables which may also be capable of significantly affecting allograft behavior.

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