Genet. Res. Camb. (1986), **47**, *pp.* 217–223 *Printed in Great Britain*

Abstracts of papers presented at the Mammalian Genetics Group meeting held in the Linnean Society Rooms, Piccadilly, London, on 28 and 29 November 1985

Adenosine deaminase deficiency in wasted mice

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Wasted (*wst*) is a spontaneous mutation in the mouse which is associated with neurological abnormalities and immunodeficiency, and results in death at about 30 days. We have found low levels of erythrocyte adenosine deaminase (ADA, E.C. 3.5.4.4) in *wst/wst* homozygotes. The enzyme, which catalyses the breakdown of purines, is reduced to 38 and 67% of normal in *wst/wst* and +/*wst* mice respectively. In addition, erythrocyte ADA in *wst/wst* mice has an increased K_m for deoxyadenosine and a decreased K_m for adenosine. Tissue ADA from wasted mice shows no alteration in electrophoretic mobility or in thermal stability. However, the alteration in kinetic parameters suggests the presence of a mutation in the structural gene for ADA in these mice. ADA deficiency in man causes severe combined immunodeficiency (SCID), a disease which is fatal in early childhood. As the phenotype of wasted mice has several features in common with SCID, we suggest that the mice provide a possible model for the human disease, and could be potentially of use in gene therapy studies.

Linkage Studies on Chromosome 19 in Man

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We have studied the segregation of Myotonic Dystrophy (DM) and DNA-polymorphisms for C3 and ApoCII in a number of informative families. In addition we have employed a highly informative centromere C-banding polymorphism (19cen) in 5 of these families. Current results are:

Locus vs. Locus	$\Theta = 0{\cdot}00$	0·05	0·10	0·20	0·30	0·40
DM-ApoCII	7·184	6·422	5·634	4·004	2·371	0·898
DM-19Cen	$-\infty$	1·693	2·352	2·340	1·638	0·618
DM-C3	$-\infty$	−2·309	−1·197	−0·318	−0·054	−0·020
ApoCII-19Cen	$-\infty$	−1·698	−0·637	−0·050	−0·057	−0·038
ApoCII-C3	$-\infty$	−4·908	−2·998	−1·353	−0·616	−0·226
19Cen-C3	$-\infty$	1·641	1·882	1·665	1·083	0·413

Thus no cross-over between DM and ApoCII has been observed. A cross-over between ApoCII and DM on one side and 19Cen and C3 on the other has been observed in two instances. Localization of C3 to the 19pter-19p13.2 region and of ApoCII the proximal portion of the long arm of chromosome 19 has been accomplished using in situ hybridization and is compatible with results obtained using somatic cell hybrids. We believe these data are most consistent with the order 19pter-C3-19Cen-DM/ApoCII-19qter. Further linkage studies using a number of polymorphic probes are in progress.

H-Y Antigen and Spermatogenesis

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From a meiotic and histological analysis of *XO/XY* mosaic mouse testes we conclude that the mouse *Y* chromosome carries a gene which is expressed in the germ line during spermatogenesis. The *XO* germ cells,

although they can form spermatogonia, very rarely enter the meiotic pathway, and no *XO* cells are seen at the first meiotic metaphase. *XO* germ cells carrying the *Y*-derived *Sxr* factor are not subject to this early spermatogenic block, so *Sxr* must include the spermatogenesis gene. *Sxr* also includes the genetic information for testis-determination and for the expression of the transplantation antigen *H-Y*. Recently a variant *Sxr* (designated *Sxr'*) was described which still carried the testis-determining information but did not confer *H-Y* antigenicity. *XO Sxr'* germ cells behave like *XO* germ cells and unlike *XO Sxr* germ cells, in arresting early in spermatogenesis. This suggests that the product of the spermatogenesis gene may be *H-Y* antigen.

Lack of *Xce* effect upon preferential maternal *X* expression in mouse yolk sac endoderm

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Genetic and cytogenetic studies have shown that heterozygosity at the *X* chromosome controlling element (*Xce*) locus causes unequal *X* chromosome expression in female mice which is attributable to primary non-random *X* inactivation (Johnston & Cattanach, *Genetical Research* **37**, 151, 1981; Rastan, *Genetical Research* **40**, 139, 1982). Cytogenetic studies have also indicated that *Xce* heterozygosity can modify the preferential maternal *X* expression seen in yolk sac endoderm of 13½ day foetuses (Rastan & Cattanach, *Nature* **303**, 635, 1983).

Quantitative electrophoresis has now been used to assay the expression of the *X*-linked phosphoglycerate kinase (*Pgk-1*) locus at 13½ days in yolk sac endoderm, yolk sac mesoderm and foetuses carrying different *Xce* alleles. Non-random *Pgk-1* expression attributable to *Xce* heterozygosity was observed in foetus and yolk sac mesoderm, but only maternal *Pgk-1* was expressed in yolk sac endoderm. No evidence that *Xce* genotype can moderate preferential maternal *X* expression in yolk sac endoderm was therefore obtained. The discrepancy between the present genetic and earlier cytogenetic results might be explained by cell or enzyme contaminations but could mean the *Pgk-1* expression does not reflect *X* chromosome expression.

Variation in response of C3H/He and C57BL/6 mice to a range of doses of phenobarbitone

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The presence of nodules in the liver of mice after chronic exposure to chemicals is a controversial topic in the assessment of potential environmental hazards. Phenobarbitone is a potent inducer of nodules in some strains in longer term toxicity tests. A factorial design was used to investigate the biochemical responses of C3H/He and C57BL/6 to a range of doses of phenobarbitone (0–100 mg/kg) administered over 3–14 days. Phenobarbitone induced a range of drug metabolising enzymes, cytochrome P-450 and microsomal protein in both strains. The effect increased steeply up to doses of about 70 mg/kg and then levelled off at high doses. The response decreased with increasing lengths of dosing. A dose of 85 mg/kg was chosen as maximally stimulating dose for a series of long term studies. There were highly significant differences in the profiles of the responses of the two strains. Liver weight increased much more quickly in C3H/He as did the amount of cytochrome P-450. Mixed function oxidase activities were higher in C57BL/6 mice and the pattern of response over different lengths of dosing differed between the two strains.

(Supported by the UK Ministry of Agriculture, Fisheries and Food)

Chromosome association at MI, and MII segregation in trisomic 16 and 19 heterotopically matured mouse oocytes

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Trisomy (Ts) 16 and 19 mouse fetuses were produced by mating Rb9Rma/Rb2H (for Ts16) or Rb1Wh/Rb163H (for Ts19) monobrachially homologous heterozygous males with all acrocentric A/Strong females. Ovaries were dissected from trisomic fetuses on d14-16 gestation (plug = d1), grown *in vitro* for 1 week, transplanted heterotopically into spayed adult female recipients, and three weeks later, mature oocytes from the successful grafts were cultured *in vitro* for 4 h. (to study MI) or 16–40 h. (MII). Association between the monobrachially homologous Rb-chromosomes and the trisomic 16 or 19 acrocentric was studied in 98 Ts16 and 249 Ts19 MIs. Pentavalent configurations occurred in 74·5% of Ts16 and 44·2% of Ts19 MIs; quadrivalents (with the trisomic acrocentric as a univalent) in 9·2% (Ts16) and 10·8% (Ts19) respectively. In 1% Ts16 and 4% Ts19, the absence of chiasma formation between the two Rbs and/or the trisomic acrocentric, resulted in two Rb-bivalents and a univalent (i.e. the trisomic acrocentric) in the same cell. Rb-trivalents and Rb-bivalents occurred together in 14·3% of Ts16 and 39·4% of Ts19 MIs. Segregation at MI anaphase, studied by counting MII chromosomes, was distorted by secondary non-disjunction of the monobrachially homologous Rbs. Disomic 16 and 19 (i.e. with both Rbs) MIIs were observed with 18·75 and 19·6% frequencies (expected = 6·25%) respectively. The ratio of balanced to unbalanced MIIs was 1:4 in both trisomies.

Why do toxicologists use outbred animals?

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Although inbred strains of laboratory animals are widely used in most disciplines, outbred stocks continue to be used for virtually all toxicological screening. This is justified on the grounds that the aim is to model man, who is outbred, and also that the aim is to screen on a wide range of phenotypes. However, it violates the principles of experimental design as it leaves a major variable, genotype, uncontrolled. Moreover, the arguments do not withstand critical examination. We do not insist on using animals weighing 70 kg on the grounds that we wish to model man who weighs 70 kg. A model does not have to resemble man in every respect, and in toxicological screening there is no reason why the genetic structure of the test population must be the same as the genetic structure of a human population. Nor is it true that by screening with an outbred stock we are testing a wide range of phenotypes. Outbred animals are phenotypically rather uniform, though marginally more variable than an inbred strain. If we wish to test on a wide range of phenotypes, then the best strategy is to use several isogenic stocks. This need not increase the total size of the experiment.

The proximal region of the *t* complex is inverted in *t*-haplotypes

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We have analysed the genetic structure of the proximal part of the mouse *t* complex in its wild type and *t*-haplotype form using cloned probes derived by microdissection (Röhme *et al.*, *Cell* **36**, 783, 1984). For genetic mapping of DNA markers on the wild-type chromosome we have used 26 BXD recombinant inbred lines as well as information derived from the analysis of partial *t*-haplotypes. In addition we have extended the mapping of markers in *t*-haplotyes reported previously (Fox *et al.*, *Cell*, **40**, 63, 1985). The comparison of the genetic structure of wild type and *t* chromosomes reveals another large inversion in the proximal part of *t*-haplotypes extending from proximal of *T* to distal of Tcp1. The inversion described here and the distal inversion described previously (Artzt *et al.*, *Cell*, **28**, 471, 1982) may account for the recombination suppression in +/*t* heterozygotes in the

t complex region. We have observed partial *t*-haplotypes which arose by rare crossing over events between wild type and *t* chromosomes within the proximal inversion (t^{wLub2}, Tt^{Orl}, t^{h45}, t^{ae5}) resulting in the duplication and deletion of genetic material. In addition we observed other partial haplotypes which presumably also have arisen by unequal crossing over in $+/t$ heterozygotes.

Small eye (Sey) is a homozygous lethal mutation affecting the development of both lens and nasal placodes

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Small eye (Sey) is a semidominant, homozygous lethal mutation. We have established a colony at Mill Hill, by mating and backcrossing onto C57BL/10 two heterozygous males obtained from Dr Ruth Clayton, Department of Genetics, University of Edinburgh. Heterozygotes are distinguished by the abnormal size and shape of their eyes, and by the presence of cataracts. Preliminary reports suggested that these abnormalities were associated with the accumulation of extracellular matrix glycoproteins (references in Green, 1981) we therefore investigated the distribution of laminin and fibronectin in eyes from $(+/-)$ adults and in embryos of different ages. During this we found that homozygous mutant (Sey/Sey) embryos can be distinguished as early as 9·5 days post coitum by the complete absence of both lens and nasal placodes. They continue to develop, but die shortly after birth. Of 406 embryos examined between 9·5 and 18·5 days after mating heterozygotes, 23 were very retarded and abnormal, 110 were of normal size but had neither lens nor nasal placodes (or eyes and noses), and 273 had both eyes and noses. Histological examination of homozygous mutants failed to show any abnormal distribution of laminin or fibronectin, and the cranial ganglia V and otic vesicles appeared normal. Unlike the lens, the nasal placodes do not depend upon interaction with the embryonic brain for their growth and differentiation. We therefore suggest that the Sey mutation affects the cephalic ectoderm at an early stage, possibly during the induction of nasal and lens placodes by the chordamesoderm.

Reference

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Expression of *X*-linked phosphoglycerate kinase in early mouse embryos homozygous at the *Xce* Locus

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Expression of maternally derived *X*-chromosomal *Pgk-1* alleles was investigated in oocytes and early embryos of the mouse, dependent on two alleles of the *Xce* locus (Xce^a, Xce^c). Our results on Xce^c homozygous females show that maternal *Pgk-1* is expressed on day 4 of embryogenesis, confirming data obtained with Xce^a/Xce^c heterozygous females. Timing of reactivation of maternal *Pgk-1* seems therefore not to be influenced by the *Xce* locus. It is shown, that oocytes from Xce^c homozygous females have a balanced PGK allozyme ratio, whereas in oocytes from Xce^a/Xce^c females the ratio is 60:40. In adult tissues of Xce^c homozygotes the PGK-1 ratios are balanced too. Besides the relative activities of the PGK-1 allozymes, absolute activities were determined in oocytes from three types of *Xce* homozygous females. Oocytes from Xce^c homozygous females were shown to have only half the PGK-1 activity of Xce^a derived oocytes, independent of the PGK allele linked to Xce^c. In contrast, the activities of G6PD, another *X*-linked enzyme, are not influenced by the *Xce* locus.

Differential expression of genes on the inactive *X* chromosome in transgenic mice

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During development of the female mouse embryo one of the two *X* chromosomes is inactivated in a random manner in most cell lineages. However, in the extraembryonic trophectoderm and primary endoderm lineages there is preferential inactivation of the paternally derived *X* chromosome. At the level of the expression of *X*-linked genes, the inactivated *X* chromosomes of the extra-embryonic and somatic tissues appear equally inactive. However, there are differences in the timing of their replication and the level of DNA modification as determined by gene transfer. The identification of transgenic animals carrying *X*-linked modified α-fetoprotein (AFP) genes allowed us to examine whether the inactivation process extends to an autosomal gene which is normally expressed at high levels in selective extraembryonic and somatic cells, and if so, whether the inactivation process is different in these two tissues. Our results demonstrate that the *X*-linked AFP genes were expressed on the inactive *X*-chromosome in the visceral endoderm of the yolk sac but could not escape inactivation in liver. Thus the transcriptional activity of the AFP minigene on the inactive *X*-chromosome is dependent upon the tissue in which it residues, and most probably reflects differences in the nature of the maintenance of the extraembryonic and embryonic inactive *X*.

DNA polymorphism in the highly mutable Peru mouse strain

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Structural and restriction enzyme site polymorphisms detected by DNA probes provide the means of following the inheritance of altered gene and linkage groups. Such polymorphisms may also provide information on evolutionary relationships between different species and races and on patterns of geographical migration. In molecular studies structural polymorphisms and mutations associated with the integration of viral or transposable elements are invaluable in the isolation and cloning of both the mutant and wild type genes; for example murine leukaemia virus (MLV) integration is known to cause mutations in the mouse, and has been used to clone a locus affecting coat colour (Jenkins *et al.*, *Nature* **293**, 370, 1981). Since Peru mice are highly mutable a number of these mice were screened for MLV integration site polymorphisms as a possible basis of genetic instability. None were detected. In another approach a Peru mutation for a new LDH enzyme variant was found to be associated with polymorphism detected by an LDH probe. The structural basis of this LDH polymorphism is under investigation. During these studies a structural polymorphism was also found in a standard laboratory strain in the *X*-linked phosphoglycerate kinase gene (*Pgk-1*). This polymorphism provides another marker for inheritance of the *X*-chromosome.

Fertility recovery of sterile male carriers of *t*-loci after injections of organ extracts

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New *t* haplotypes (called *Lg* for Liège) were obtained from the tailless strain T/t^{12}. New homozygous lethal t^{Lg} haplotypes were selected for testing male sterility. Heterozygous females t^{Lgx}/t^{12} were used to obtain a colony of presumably sterile t^{Lgx}/t^{12} males. After pretesting males to eliminate sterility of non-specific origin, they were injected with extracts of genital tracts from fertile males and mated with the same females. The following genotypes were tested t^{6}/t^{12}, t^{Lg7}/t^{12}, t^{Lg8}/t^{12}, t^{Lg9}/t^{12}, t^{Lg12}/t^{12}. A slight proportion of males injected with crude extracts recovered some fertility. In the same conditions, males injected with liver extracts as control did not yield positive effects. To investigate the nature of substances responsible for the recovery, the extract was purified and fractionated. The testicular fraction (F6) induced a higher recovery than the crude extract whereas a fraction from

the rest of the genital tract (F7) did not yield positive results. So far, there was a stage specificity for the recovery. The induction process was limited to the last segments of spermatogenesis, i.e. sperm from ductus deferens and epididymis. We attempted to correlate the present results with abnormal RNA metabolism occurring in genital tracts of sterile males. No correlation could be established.

X-chromosome deletions in embryo-derived (EK) cell lines associated with lack of *X*-chromosome inactivation

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The predictions of a model for the initiation of *X*-chromosome inactivation based on a single inactivation centre were tested in a cytogenetic study using six different embryo-derived (EK) stem cell lines, each with a different sized deletion of the distal part of the second *X*-chromosome. Metaphase chromosomes were prepared by the Kanda method from each cell line in the undifferentiated state and after induction of differentiation, and cytogenetic evidence sought for a dark-staining inactive *X*-chromosome. The results confirm the predictions of the model, in that when the inactivation centre is deleted from one of the *X*-chromosomes neither *X* present in a diploid cell can be inactivated, and in addition considerably further localize the position of the inactivation centre on the *X*-chromosome.

Association of H-2 with variation in testicular development in *CXB* mice

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The testes of C57BL/6By mice are smaller than those of BALB/cBy mice at 30, 60 and 120 days. The CXB recombinant inbred lines differ in mean absolute testis weights at all three ages. The mean weights at 60 and 120 days are highly correlated ($r = 0{\cdot}98$) and the range found similar, with no line having as small testes as C57. In contrast the phenotypic pattern before puberty is quite different, with the majority of lines having testes as small as C57, and only two resembling BALB. The correlation between 30-day weight and growth from 30 to 60 days is insignificant ($r = 0{\cdot}12$). The SDP for 30-day weight is identical to that for *H-2* and for other chromosome 17 markers. Reciprocal F1 males, heterozygous for *H-2*, have intermediate testis weights at 30 days. Pathological effects of the *H-2* region on testicular development include inhibition of differentiation (Eicher *et al.* (1982) *Science* **217**, 535), testicular hypoplasia and sterility (*Hst*, Forejt & Ivanyi (1975) *Genetical Research* **24**, 189) and T-region effects on testicular size. The prepubertal difference described here is not associated with infertility. It will be further investigated, both developmentally and genetically, using congenic and congenic-recombinant strains.

Genetical aspect of the semi-specific interaction between *Mus musculus domesticus* and *Mus musculus musculus* in eastern Europe

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The analysis of allozymic variation in Bulgarian populations of *Mus musculus domesticus* and *Mus musculus musculus* has revealed the existence of eight diagnostic loci and the occurence of gene flow between them. So despite a genetic isolation, there is no reproductive isolation between these two parapatric semi species which interact in a narrow zone of hybridization. This zone is asymmetrical south to north with more extensive introgression, in terms of distance, of *domesticus* alleles across the boundary line. On the other hand the

mitochondrial introgression seems to occur only in the direction *musculus* towards *domesticus*. The width of the zone can be estimated considering that 80% of genetic change (as measured by a hybrid index) occurs over a distance of 20 km. The extent of introgression varies markedly among loci and in the same time between the two semi species. The asymmetry of introgression, the extreme steepness of the transition of genetic character and the inversion of mitochondrial and nuclear introgressions could be related to a difference of allelic propagation which could be explained by a population structure model. The differential character of introgression among loci would argue in favour of a selective control, involving reduced fitness in backcross generations, caused by disruption of co-adapted parental gene complexes. Laboratory interbreeding experiments were carried out to find the level where differential sorting of genotypic combinations occurs (genic conversion, meiotic drive, gametic selection, individual selection...).

Unusual ratios of glucose phosphate isomerase allozymes in mice

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Heterozygous *Gpi-1s*^{a}/*Gpi-1s*^{c} mice produce three electrophoretically distinct allozymes of the dimeric enzyme glucose phosphate isomerase, GPI-1A, GPI-1AC and GPI-1C. The GPI-1C allozyme (CC homodimer) is unstable and usually of reduced activity. An unusually high ratio of GPI-1AC: GPI-1A was found in $6\frac{1}{2}$ day *Gpi-1s*^{a}/*Gpi-1s*^{c} embryos but not in adult brain or kidney. The ratios in other tissues indicate that the effect is not embryo-specific. GPI-1AC was found to be less stable than GPI-1A and this difference probably accounts for the variation in GPI-1AC:GPI-1A ratios, seen between tissues. A preliminary analysis of allozyme ratios in *Gpi-1s*^{b}/*Gpi-1s*^{a} and *Gpi-1s*^{c}/*Gpi-1s*^{a} $6\frac{1}{2}$ day embryos produced by *Gpi-1s*^{b}/*Gpi-1s*^{c}♀ × *Gpi-1s*^{a}/*Gpi-1s*^{a}♂ matings suggests that the elevated AC:A ratio is caused by a *cis* acting genetic determinant that maps close to or within the *Gpi-1s* structural gene. This could reflect (1) elevated specific activity of the GPI-1AC heterodimer (2) duplication of the *Gpi-1s*^{c} structural gene or (3) the effect of a variant of a *cis*-acting regulatory gene that is associated with the *Gpi-1s*^{c} structural gene and causes enhanced synthesis of GPI-1C monomers.