GENETICAL SOCIETY OF GREAT BRITAIN

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ATTEMPTS TO TEST THE INACTIVE-X THEORY OF DOSAGE COMPENSATION IN MAMMALS

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This theory postulates that in the somatic cells of female mammals one of the two X-chromosomes is genetically inactivated and, since either one may be inactive in different cells of the same animal, that this gives rise to the mosaic phenotype of female mammals heterozygous for sex-linked genes. It follows that if a female carries two non-allelic sex-linked mutant genes affecting the same character, one on each X-chromosome, then one or other mutant should act in all her cells, and she should have no normal patches. Attempts are being made to confirm this for three pairs of mouse mutants affecting coat colour and coat structure. Female mice homozygous for *pp* and carrying Cattanach's translocation (including the allele $+^{p}$) on one X-chromosome are variegated wild-type/pink eye. Similar mice with the gene Mo^{dp} on the other X-chromosome show no *pp* patches and are indistinguishable from ordinary $Mo^{dp}+$, *i.e.* either the gene Mo^{dp} or the translocation, and hence the $+^{p}$ allele, is active in all cells. Similarly, in mice carrying the gene *tabby*, *Ta*, on one X, and a second gene affecting hair structure on the other, *Ta* appears to act only in the patches where the other gene is not acting.

IS SEX-LINKED *TABBY* REALLY RECESSIVE IN THE MOUSE ?

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Lyon's theory of sex-chromosomal gene inactivation implies that in the mouse and other mammals one cannot tell whether a sex-linked gene is dominant or recessive just by looking at the heterozygous female phenotype, since only one X-chromosome is supposed to be genetically active in each individual cell from an early stage in development. However, as a converse to the apparent random inactivation of certain autosomal colour genes when they are translocated on to an X-chromosome (producing a variegated effect) one might expect that genes on part of an X-chromosome translocated on to an autosome would then remain active in all the cells. Such a situation should allow one to test whether particular sex-linked genes are dominant or recessive.

During an experiment on the induction of XO mice by the method of L. B. Russell (post-fertilisation irradiation) an apparently wild type female was produced, which in fact turned out to be heterozygous for sex-linked *Tabby* (*Ta*) although completely lacking the black transverse banding of the coat which is characteristic of the *Ta*+genotype. Its breeding behaviour suggests that this suppression of the *Tabby* effect is indeed the result of a segment including $+^{ta}$ being translocated on to an autosome and remaining active in all cells. If so, this would indicate that *Tabby* is really a fully recessive gene like its mimic, *crinkled.*

A SEX-LINKED BLOOD GROUP AND SOME OF ITS APPLICATIONS

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A blood group antigen called Xg^a has recently been described (Mann, Cahan, Gelb, Fisher, Hamper, Tippett, Sanger and Race, 1962). It differs from other red cell antigens because the gene responsible is X-borne: this is shown by a different distribution of Xg^a in the sexes (about 62 per cent. in males compared with about 89 per cent. in females) and by the manner of its inheritance.

In collaboration with many experts we are testing families which segregate for other X-borne characters in the hope that the Xg groups will contribute to the linkage map of the X chromosome.

The antigen has so far contributed disappointingly little information for or against the theory of Lyon concerning the inactivation of one X in female cells.

CYTOLOGICAL AND BIOCHEMICAL STUDIES ON GARGOYLISM

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and

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Blood films have been examined from 34 patients, in whom a diagnosis of gargoylism suggested itself on clinical grounds with varying degrees of probability. The lymphocytes from 19 patients contained specific inclusions, in 14 patients no abnormal inclusions were found and in one case the result was ambiguous. Urine from nine patients was analysed for the presence of mucopolysaccharides. In five patients large quantities of acid mucopolysaccharides, which were resistant to hyaluronidase, were present; these patients also had abnormal lymphocytic inclusions. The urine of four patients contained normal amounts of acid mucopolysaccharides, which was hyaluronidase sensitive, and in these patients the lymphocytes were normal. No corneal opacities were found in any of the patients with normal lymphocytes. It is suggested that patients showing clinical features of gargoylism, but whose lymphocytes and mucopolysaccharide excretion are normal, may represent a different group which is biochemically, and probably genetically, distinct from gargoylism.

The possibility of distinguishing the heterozygous carriers of gargoylism will be discussed.

THE CONSEQUENCES OF AUTOSOMAL IMBALANCE IN MAN

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Three varieties of autosomal trisomy, and various rearrangements, both balanced and unbalanced, have been described in man. Balanced aberrations are quite compatible with a normal phenotype, and the cases which have been described as abnormal are possibly fortuitous associations. A series of cases of trisomy, mosaic trisomy, and duplication will be presented. These are quite consistent with the expectation that the phenotypic disturbance of an excessive amount of autosomal material is proportional to this excess. One case of presumptive deficiency (absence of short arm of the 18th chromosome) was more severely affected than would be expected from an excess of similar magnitude. The pattern of phenotypic disturbance is far less specific than in *Drosophila* or *Datura*: this is probably a consequence

of the paucity of patterned structures in man. In none of the three trisomic syndromes repeatedly described in man can the chromosome involved be regarded as uniquely identified, and neither clinical nor cytological discrimination is adequate, at present, to allow the inference of complete specificity. The similarity in phenotype of a mosaic trisomic for a large acrocentric and a trisomic for a smaller chromosome (17 or 18), and of this syndrome with the XO phenotype, suggest strongly that the effects of chromosomal imbalance may be, in part, non-specific and unrelated to genic imbalance.

A HUMAN PEDIGREE SHOWING TRANSMISSION OF A TRANSLOCATION IN THE 13-15 CHROMOSOME GROUP

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The transmission of a translocation of the 13-15/21 or 21-22/21 type is well known as being responsible for the occurrence of " mongolism " in several families. Other translocations have been recorded, but no information regarding their transmission is available.

A translocation between two chromosomes of the 13-15 group has been discovered in a female patient suspected as a sex anomaly. Both male and female carriers have been found among the members of the family and transmission is known through at least three generations. The translocation probably corresponds to that reported by Lejeune in 1959 in a case with Klinefelter's syndrome. Since in the pedigree sex anomalies are not associated with all carriers, it is probable that the two phenomena are independent of one another.

Linkage of the translocation with blood group loci is being investigated to try locate any one of them.

THE SPECIFIC CHROMOSOME ABNORMALITY IN CHRONIC MYELOID LEUKÆMIA

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It now seems most likely that the abnormal chromosome found in chronic myeloid leukæmia—the Philadelphia or *Ph*[1] chromosome—is related to the inception of the disease, and is not an epiphenomenon occurring during the evolution of the disease. The morphological features of the chromosome will be described together with its frequency in cells from blood cultures and in both direct and cultured marrow preparations in the untreated patient.

Consideration will also be given to the effect of both X-ray therapy and chemotherapy, and to cytogenetic developments that occur during and after the terminal transformation of the disease into one of acute leukæmia.

CHROMOSOME REARRANGEMENTS IN APPARENTLY NORMAL INDIVIDUALS

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Chromosome rearrangements of several types have now been found to be associated with various forms of congenital malformation in man. A number have also been described in apparently normal individuals. In the course of our cytogenetic investigations of patients with leukæmia or with another malignant disease, of therapeutically irradiated patients and of the relatives of patients known to have a chromosome abnormality, we have found several instances of chromosome abnormality which are apparently coincidental. A chromosome rearrangement has been found in the brother of a woman with an abnormality of the sex

chromosomes. One patient with breast cancer has been found to have a constitutional chromosome abnormality; three patients with chronic myeloid leukæmia, and possibly a fourth such case, were found to have a chromosome abnormality in addition to the Philadelphia chromosome. Also a very large Y chromosome has been found in a number of cases. The possible significance of these observations is briefly discussed.

CHROMOSOME ABNORMALITIES IN AN IRRADIATED HUMAN POPULATION

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Using the blood culture technique, studies have been made on a number of patients treated with medium kilovoltage X-rays to the spinal axis for ankylosing spondylitis. Observations, apart from those on unirradiated patients, have only been made on individuals irradiated in a standardised way and given only one course of treatment. The majority of patients have been given a total skin dose of 1500 rads over the spinal axis in 10 daily exposures, but a few have had greater doses over the same time interval. In all, the studies on the irradiated patients cover a period of time from the completion of treatment to nearly 20 years later.

The results will be discussed in regard to the different types of abnormality produced, their frequency and persistence, and their possible relation to other radiation-induced effects in this group of subjects, particularly the induction of leukæmia and other forms of cancer.

CLONAL PROLIFERATION IN IRRADIATED AND NEOPLASTIC MAMMALIAN TISSUES

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A near-lethal, wholy-body dose of radiation delivered to a mouse causes the destruction of the greater part of the reticular tissues. Morphologically identifiable structural changes are common in the chromosomes of the few cells that survive and from which tissue regeneration takes place. Clones of cells, each defined by a distinctive set of marker chromosomes, are frequently identified in the bone marrow, spleen, thymus, and lymph nodes of the mice after regeneration is complete. Evidence obtained so far indicates that regeneration may sometimes proceed from as few as two or three surviving cells; that there is considerable cellular migration from one anatomical site to another; and that different clones proliferate at different rates.

Clones of cells, similarly defined, are commonly found in reticular neoplasms of the mouse, Chinese hamster, and man. In many instances the cells taken from a single neoplasm are all members of the same clone. This permits the inference that the neoplasm, or at least that part of it which was sampled, arose through the proliferation of a single abnormal cell.

A case of acute human leukæmia revealed a complex of interrelated clones. The observations were consistent with a step-wise origin of the variant types and ultimate derivation from a single cell.

MUTATION AND REPLICATION IN *USTILAGO MAYDIS*

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After ultraviolet irradiation of heterozygous diploid cells of *Ustilago*, individual markers may become homozygous in a few per cent. of the survivors as a result of induced mitotic crossing-over. This is known since the reciprocal products of an

exchange can often be recovered. Diploid cells which are homozygous for a particular biochemical marker can revert to prototrophy as a result of rare back mutation in one of the mutant alleles. Amongst reversions induced by ultraviolet light, a small proportion are homozygous for loci which were originally heterozygous, as a consequence of mitotic crossing-over. By using appropriate selective media and the replica plating technique, it is possible to show that sometimes the revertant colony is mosaic and consists of the reciprocal products of the exchange. This demonstrates that the mutation is present in both daughter cells of the first division after irradiation; and therefore that it was transmitted from the chromosome not to just one, but to both chromatids. The data so far collected are not compatible with some current ideas of ultraviolet induced mutagenesis, since these postulate that mutation does not occur in the pre-existing gene but only as an error in replication.

ASCOSPORE COLOUR MUTANTS IN *ASPERGILLUS NIDULANS*

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Ascospore colour mutants of two kinds were obtained from *Aspergillus nidulans* after U.V. or $NaNO_2$ treatment of conidia: (1) Blue ascospores; (2) Colourless ascospores. The wild type has red ascospores.

Four blue mutants map in linkage group II within 0·5 unit, symbol of locus bl_1. Four out of five colourless mutants map in linkage group I within 1 unit, symbol of locus cl_6, and one in linkage group IV, symbol of locus cl_4.

In crosses these characters are non-autonomous in either the ascus or the perithecium (containing about 10,000 asci). The ascospores of a whole perithecium have the phenotype of either one or the other parent irrespective of the crossed or selfed origin of the asci, *i.e.* all the ascospores in a selfed perithecium have usually a phenotype corresponding to its genotype while in a crossed perithecium they have usually the phenotype of either parent. However, in a small proportion of perithecia of these crosses the ascospores have the wild type phenotype.

The relevance of these results to maternal effects on gametes will be discussed.

MAPPING OF THE CORRELATED CHARACTERS FIMBRIATION AND RHAMNOSE-FERMENTATION IN *SALMONELLA TYPHIMURIUM*, USING COLICINE AGENTS AS FERTILITY FACTORS

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Most strains of *Salmonella typhimurium* ferment rhamnose (*rha*$^+$) and produce the filamentous appendages called fimbriæ (*fim*$^+$). Amongst strains isolated from natural sources the two characters are almost completely correlated (J. P. Duguid, personal communication), which suggested that they might be controlled at a single locus, or at very closely linked loci. Recombination between a *rha*$^-$*fim*$^-$ strain and multiply marked stocks of strain LT2, which is *rha*$^+$*fim*$^+$, was obtained by the use of the colicine agents *colI* and *colEl* as fertility factors. The frequency of various recombinant classes shows that *rha* lies between *metA* and *str*, and that *fim* is not closely linked to *rha*, in the single "circular" linkage group.

TRANSDUCTION OF FIMBRIATION AND RHAMNOSE-FERMENTATION CHARACTERS IN *SALMONELLA TYPHIMURIUM*

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Of 346 strains of *Salmonella typhimurium*, 254 were genetically "fimbriate" (capable of forming fimbriæ) and fermented rhamnose promptly, *i.e.* within 24 hr.; 90 were genetically non-fimbriate and rhamnose-negative (though giving "late"

fermentation by the emergence, after several days, of rhamnose-fermenting mutants that were still non-fimbriate) ; and 2 exceptional non-fimbriate strains were rhamnose-positive.

On culture for 48 hr. in static tubes of broth containing *c.* 10^{10} particles of PLT22 phage prepared from a fimbriate rhamnose-positive donor culture, 83 out of 85 of the rhamnose-negative non-fimbriate strains yielded fimbriate transductant organisms, in all cases rhamnose-negative. None of these 85 stains gave fimbriate variants when tested with phage prepared from non-fimbriate donor strains, though the two exceptional rhamnose-positive non-fimbriate strains did so. When rhamnose-negative non-fimbriate cultures were treated with phage from a rhamnose-positive fimbriate donor and were plated on rhamnose medium, rhamnose-positive transductants were obtained, in all cases non-fimbriate. Fimbriation and rhamnose fermentation characters are thus closely correlated in their occurrence in wild-type strains, but the controlling genes are apparently independent.

NON-CHROMOSOMAL INHERITANCE OF STRAWBERRY JUNE YELLOWS

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Strawberry seedling families raised from June Yellows affected and non-affected varieties have been observed in the field for four years. Families raised by selfing separate inflorescences of the same plant, and from selfing different plants of an affected clonal variety have each given significant differences in proportions of affected seedlings ; as have crosses between affected and non-affected varieties. Observations confirm that the inheritance of June Yellows is non-chromosomal. Parallels in gametic transmission are now seen to exist between June Yellows and some soil borne ringspot viruses, despite failure to transmit June Yellows artificially by any standard method. The experiments will be reviewed in the light of this recent knowledge.

RNA AND PROTEIN SYNTHESIS BY LAMPBRUSH CHROMOSOMES

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H^3-uridine has been used for following RNA synthesis, and H^3-phenylalanine for following protein. Most lateral loops incorporate H^3-uridine throughout their lengths, but an easily recognised structure, the giant granular loop characteristic of chromosome XII of *Triturus cristatus cristatus*, incorporates H^3-uridine in a restricted zone neighbouring the thinner of the two loop insertions in the chromosome axis. After incorporation, the labelled RNA moves around the loop and reaches the thicker insertion about 10 days later. The movement can be speeded up by injecting the newt with gonadotrophin. If, as we think, this movement is a movement of loop axis as well as gene product, the total length of DNA fibre at the giant granular loop locus can be calculated, and by extrapolation the total length of DNA fibre per haploid chromosome complement can be derived. The calculation suggests that newt chromosomes are not multistranded.

THE CHROMOSOMES OF ALGÆ

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In different Sub-Groups of this assemblage of extremely dissimilar organisms, atypical chromosome organisations and nuclear division may be found, as well as the conventional type.

The main chromosome types so far as they are known will be briefly reviewed.

THE TIMING OF SPERMATOGENESIS IN *DROSOPHILA MELANOGASTER* USING TRITIATED THYMIDINE

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The spermatogenic cycle in the adult testis of *Drosophila melanogaster* has been timed using tritiated thymidine to label the germ cells.

Newly emerged males were injected with tritiated thymidine into the abdomen and then mated at the rate of two females per male per day.

The labelling was followed by sectioning daily samples of testes, and in addition smears of sperm from the ventral tube of inseminated females were examined for the first appearance of labelled sperm in the ejaculate.

Within 24 hr. following the injection both spermatogonia and cysts of young spermatocytes at the proximal end of the testis were labelled.

It was found that the period from DNA synthesis in the very early spermatocyte to insemination in continuously mated males was 10 days. Of this period, spermatocyte maturation took four days and spermiogenesis five days.

GENETIC CORRELATION AND ENVIRONMENT

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The genetic correlation between body size and development time of *Drosophila melanogaster* may be zero or close to unity, according to the composition of the larval diet during selection for larger size. On live yeast, and various suboptimal synthetic media, there is little or no evidence of correlation; also selection for fast or slow development time involves little change in size. But on media with a low RNA/protein ratio increase in size is regularly accompanied by more or less proportional lengthening of the larval period, while effective selection for faster development reduces size as well. These characteristic differences are maintained under the usual culture conditions, although development time of the "fast" lines generally does not differ from or exceed that of the unselected. The correlated changes and other tests suggest that selection has influenced the hormonally controlled relations between larval growth and differentiation. Body size may be altered by purely environmental means, with or without similar correlated changes in development time, by adjusting the composition of the diet and this indicates an approach to more systematic changes in development, using genetic variation which is generally concealed or inaccessible to selection.