SOMATIC VARIABILITY IN MAMMALIAN PIGMENTATION PARTICULARLY HUMAN, WITH AN ATTEMPT TO RELATE THE PHENOMENA OBSERVED TO CERTAIN INHERITED CONDITIONS IN MAN

by

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Presented as a thesis for the Degree of M.D. in the University of Adelaide.

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PREFACE

The existence of mutation in the genes of germinal cells has been agreed upon and we have gone a long way towards an understanding of this process in chemical terms.

We believe that the genes of somatic cells are not fundamentally different from the genes of germinal cells, and that mutations must occur in these genes. If frequencies of gene mutation in somatic cells are in any way comparable with those which have been studied in germinal cells, then millions of somatic mutations must occur every day in any individual.

If this is so then there are two possibilities. The first possibility is that despite the frequency of this phenomenon there is no part of our physiology which is upset by it, and in fact biologically it is unimportant. The second possibility is that in the multicellular diploid organism there are potentially serious consequences of frequent somatic mutation, that the body may develop mechanisms to combat these serious consequences, and that occasionally the organism as a whole suffers from a failure of these mechanisms.

Geneticists as a class are very wary of discussing somatic mutation because it does not lend itself to the mathematical rigors which were foreshadowed by the work of Mendel. This seems to be a somewhat negative approach - if it is there it should be studied; a phenomenon which can be inferred to occur in every living person must be as worthy of attention as for instance the acquiring of photographs of the reverse side of the moon. If eventually somatic mutation can be proved not to occur then a major

biological discontinuity has been proved - between germinal and somatic cells. If technological advance makes it more and more convincing that somatic mutation occurs and is a fundamental biological phenomenon, then the techniques of conventional genetics will undoubtedly be enriched by a greater understanding of the mechanisms involved.

Introduction to the Subject Matter of the Thesis

"Somatic variability in mammalian pigmentation" in the title of this thesis means several things - it means the patterns of skin and coat colour of animals, it means pigmentary mosaicism with which an individual is born, and it means changes in skin colour or hair colour of a discontinuous nature which may develop during extrauterine life. The particular cell system under study is the melanocyte system, although only to a very limited extent at the microscopic level. The production of a pigmentary change is assumed to have a basis in altered biochemical activity of a melanocyte or a group of melanocytes. A limited number of sections of pigmented tissue were studied microscopically, but in the main reliance was placed on the very well documented light microscopic and electron microscopic studies which have been and are still being made in various parts of the world.

Somatic variability of pigmentation in many animals obviously has adaptive significance (e.g. giraffe, zebra) and one can infer that evolution has brought this about by mechanisms of gene activation or gene inactivation of a sort which at the present time are only just beginning to be understood.

Setting aside this group of phenomena the thesis here recorded considers that some mosaicism is not adaptive. A model system has been built on the hypothesis that somatic and germinal mutations occur at about equivalent frequencies, and are probably subject to much the same laws e.g. in relation to ionizing radiation. The model has been applied to certain of the mosaic phenomena in humans, and has been extended to include the malignant cell which is a cell of aberrant behaviour arising from one

or another normal tissue.

The particular phenomena studied are freckles, birthmarks and moles, and significant relations between the occurrence of these on individuals have been shown. Red hair has been implicated by the hypothesis that the red haired individual is in general a homozygote, and the brown haired and freckled individual a heterozygote of genes at one particular locus. The occurrence of red hairs on a brown haired person and brown hairs on a red haired person has similarly been related to individual gene action. The biochemistry of marsupial, higher mammalian, and human hair pigments have been studied in order to provide a biochemical basis for the genetic model. Work has been done on the free pigments which are found on the skin and amongst the hair of marsupials, and efforts to synthesize some of these pigments from 3-aminotyrosine are recorded.

Finally a number of inherited human disorders involving multiple tumour formation are recorded and a discussion of how these might fit the model is made. A broader implication of the problems of malignancy is made.

I N D E X