Longevity in Mice with a genetically determined Muscular Dystrophy

The recent communications by Dowben[1] and Tubis *et al.*[2] regarding possible therapeutic procedures for mice with a genetically determined form of myopathy[3] have prompted this preliminary communication commenting on some problems relating to longevity in animals with this defect.

The value of such therapeutic work is three-fold. First, by prolonging the life-span of these animals it becomes possible to obtain critical details on the mechanism of the disease as it progresses. Secondly, effective therapeutic agents may give valuable leads regarding the primary metabolic nature of the defect. Thirdly, agents which prolong the life of animals with muscular dystrophy or alleviate the disease process would seem to be logical agents to employ in a clinical testing programme involving human beings with muscular dystrophy.

The last point is important because at present the rationale for employing certain therapeutic measures in patients suffering from various forms of muscular dystrophy is based largely on the results of tests in which experimental animals have been used[4]. If the results of these tests are accepted uncritically or their limitations not fully realized, it is likely that large amounts of time and money will be expended on clinical trials which unfortunately do not have the slightest probability of success.

Approximately two years ago we designed and initiated an experiment to test the efficacy of several agents in extending the life-span, and arresting the disease process, in mice suffering from a genetically determined muscular dystrophy. The agents used were felt to have potential value, by virtue of previous work either in our laboratories or in those of other investigators. It was our impression that in some reported work not enough attention had been paid to simple problems of animal management that might significantly influence the outcome of the experiments. Therefore, the method of handling the control animals in our experiment was determined by two observations made in routine mouse-colony maintenance. First, the transition period (between 2 and 2½ weeks of age), during which a suckling mouse changes to a diet of solid food, can be facilitated by the temporary use of a powdered form of the food pellet regularly used in the colony. Secondly, mice with muscular dystrophy often experience considerable difficulty in managing pelleted food and water when they are presented in the usual way through small glass tubes attached to inverted bottles. Regardless of whether these difficulties result from a generalized muscular weakness or from a particular involvement of the muscles of mastication, it was apparent that we had to entertain the hypothesis that these animals succumb to inanition resulting from their inability to consume sufficient pelleted feed or to a self-imposed inanition arising from an inadequate intake of water. It was decided, therefore, to maintain each of the animals in separate pens supplying them each day with fresh powdered food (U.B.C. mouse ration No. 6) and fresh water in small open vessels placed directly on the floor of the pen. The therapeutic substances being tested were added in appropriate levels to the powdered food.

While a number of the mice in various 'treatment' groups have lived for periods exceeding nine months, several of the untreated dystrophic animals in the control series have lived equally as long. One animal in the control group died at the age of eleven months and another still alive promises to exceed this record. So far as we are aware these are the oldest dystrophic mice yet reported.

Although the experiment is not yet complete, we believe that the results so far are significant in two principal respects: First, any claims regarding the ability of a particular agent to prolong the life-span of mice suffering from this form of muscular dystrophy must be examined with extreme caution and viewed against the background of adequately nourished control dystrophic survivors. Secondly, the progressive pathological changes previously described in this disease in the house-mouse should be re-examined in order to differentiate between those attributable to concomitant dietary deficiencies and those truly resulting from primary muscle disease.

Three additional points should be emphasized: First, not all the animals in this experiment have lived to the ages mentioned above. Secondly, there is no evidence that the disease process of the muscle is modified in any way since the affected animals still die prematurely and post-mortem examination demonstrates that muscle wasting is still extreme. Thirdly, our management procedure is begun some time after the first signs of the disease are observed[2].

On the basis of these three points we do not believe that the 'therapy' used in our experiments has any effect on the fundamental metabolic error underlying the disease, and we must stress emphatically that we are making no claims whatever about the life-prolonging ability of our diet. It seems more reasonable to believe that this ability, and perhaps that of the diet reported by Coleman[5], results from the provision of more of the essential nutrients per unit mass of feed and hence assures what is essentially an adequate intake of protein, energy and micronutrients.

A full report on this experiment together with pathological findings arising from it will be presented at a later date.

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Agglutination of Sensitized Alligator Erythrocytes by Rheumatoid Factor(s)

Recently, it was found that alligator erythrocytes can be effectively used as carriers for reactant globulin in tests for rheumatoid factor(s)[1-3]. The cells are remarkable because most human sera do not contain heterophile antibodies to them, and the cells show extraordinary durability under osmotic and mechanical stress[1,2].

The present investigation was carried out to determine the effects of euglobulins from healthy individuals