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Afternoon Session

Chairman: PROFESSOR R. E. TUNBRIDGE, O.B.E., M.D., M.Sc., F.R.C.P., *Department of Medicine, The General Infirmary, Leeds* 1

Nutrition and longevity in animals

By A. COMFORT, *Nuffield Research Fellow in Gerontology, Department of Zoology, University College, London, W.C.*1

The rate at which the mortality of animals increases with age, and consequently their life span, can be altered nutritionally in two main ways—by a large number of factors, including specific deficiencies and poisons, general malnutrition, and surfeit, which will kill them prematurely; and by a few dietary manoeuvres which affect the rate of development, and consequently the duration of the life cycle as a whole.

These effects are not always separable; most often they co-exist. For practical purposes the survival curve of an animal that undergoes actuarial ageing can usually be considered as a plateau of 'adult vigour' followed by a more or less steep decline centred about the 'specific age', or modal age of adult death: factors which alter the slope of the initial plateau or cause it to crumble away are those that produce 'premature death', though factors that alter its length and displace the specific age relative to the origin alter the 'life-span' or rate of ageing—though the distinction is difficult to make in real instances and breaks down in extremes, e.g. total deprivation of food, severe poisoning. A more practical distinction is that though it is extremely easy to kill animals prematurely by dietetic means there are relatively few ways of making them live unusually long, and it is these that are of special interest to experimental gerontology.

Invertebrates

The life cycle of many invertebrates can be lengthened in some or all of its stages by the giving of an amount of food less than that which produces maximal growth and development. The exceptions are chiefly animals or stages which draw heavily on stored reserves. In general, larvae and adults which show continued cell multiplication respond to moderate dietary restriction by lengthening the life cycle, but imagoes and adults of fixed cell number can more often be kept alive by replacement of reserves, or by reduction of activity or egg-laying which tend to exhaust them.

A few invertebrates respond to dietary restriction by reduction in size (Planarians, Child, 1915) or, when starved completely, by active de-differentation (*Lineus lacteus* Dawidoff, 1924); these can apparently be grown and de-grown indefinitely. Forms which undergo numerous adult moults (*Daphnia magna*, Ingle, Wood & Banta, 1937) respond by increasing the duration of each instar, and consequently the total life; the longest lives are obtained by restriction of growth for three-quarters or more of the normal lifetime number of instars, followed by full feeding.

In insects in which metamorphosis is incomplete, the optimal intake of food, and particularly of protein, for rapid growth produces a shorter total life-span than a poorer diet; in *Blatta orientalis* and *Periplaneta americana* the optimal protein intake for longevity of all the stages is about half that which gives the fastest development (Haydak, 1953). In holometabolous insects, dietary slowing is confined to the larval stages, which can be extended by intermittent fasting (*Lymantria*, Kopeć, 1924)—with beetle larvae to many years: the life of imagoes, on the contrary, usually seems to be increased by food supplements (butterflies, Frohawk, 1935) especially in females (*Musca domestica*, Rockstein, 1959), and still more by the prevention of egg-laying (*Musca domestica*, Rockstein, 1959; *Ephestia*, Norris, 1934; Köhler, 1940), since in both feeding and non-feeding adults the longevity is determined by stored reserves, particularly of protein. Bees present a special problem; here feeding controls development and the choice between two life cycles, that of a queen, lasting up to 5 years (Pflugfelder, 1948) and that of a worker, which depends directly on how much pollen protein is kept back for individual use, rather than used for rearing brood. Broodless or 'winter' workers have a life-span of 300–400 days compared with 30–70 days when brood is present (Maurizio, 1959). Attempts have been made to increase the life-span of insects with vitamin supplements on the model of royal jelly, but with small effect (Gardner, 1948).

Vertebrates

The relation of speed of development to mortality pattern is of particular interest in fish, reptiles and amphibia whose growth is 'indeterminate', because of the suggestion of Bidder (1932) that their longevity might be equally indeterminate compared with that of mammals. Unfortunately, little work has so far been done on their nutrition. By far the largest body of data on vertebrates has been obtained from experiments on rodents: in applying the conclusions from them to man it must be remembered that the growth pattern of rats in particular is in some respects more like that of fish than of primates, since growth can be re-started after maturity. This work on rodents has been fully reviewed by Silberberg & Silberberg (1951). In a series of long-term experiments McCay and his co-workers (McCay & Crowell, 1934; McCay, Maynard, Sperling & Barnes, 1939; McCay, Pope & Lunsford, 1956; Saxton, 1945) first showed that the life-span of rats could be prolonged by restriction of growth and development by dietary means. Rats receiving a diet adequate in everything but calories were found to remain immature and at the same time relatively free from the diseases which affected fully fed litter-mates. After restriction in this way for periods up to 1000 days survivors were capable of resuming growth

and reproduction, living in all substantially longer than the normally grown controls. The gain in further expectation of life was not equal to the period of underfeeding, and was greater in males than females. The retarded rats remained active but, initially at least, sexually immature (Asdell & Crowell, 1935): in early experiments the chief finding was that members of each retarded group were still alive after the death of all the controls, and the gain in life-span was limited to the minority of retarded survivors from a sizeable early mortality, but the aggregate curves based on later experiments (McCay, Sperling & Barnes, 1943) show definite lengthening of the adult 'plateau' and displacement of the modal age of death.

Less severe or intermittent restriction also prolongs life, but chiefly by cutting early mortality, with less effect on the specific age. Riesen, Herbst, Walliker & Elvehjem (1947) found that in Wistar rats the gain was rougly proportional to the severity of restriction: starvation for 1 day in 3 or 4 produced a significant increase in mean life. The benefit from retardation is greater in rats on an omnivorous than on a vegetarian diet (Carlson & Hoelzel, 1947, 1948). By fasting 1 day in 3, increases in mean expectation of 20% in males and of 15% in females are obtainable without arrest of growth (Carlson & Hoelzel, 1946). Thomasson (1955) found that the survival curve of rats receiving 27% fat in the diet in the form of butter was oblique, with little initial plateau. If rape-seed oil was substituted the plateau was prolonged by about 25 weeks, and the curve became more rectangular: growth was slower, chiefly because appetite was decreased, and there was a marked reduction in renal disease.

Experiments of the same type have been made upon mice, with very similar results. Both total and reproductive life-span can be increased by calorie restriction. On a diet containing half the calories (as lard and dextrose) in the standard mouse diet, C_3H females which are normally sterile at 11–12 months were still rearing litters at 21 months, the longest records being in mice restricted for 11–15 months and then fully fed (Carr, King & Visscher, 1949); fasting on 2 days out of 7, with or without addition of nucleic acid to the diet, produced an increase of 50–60% in the life-span of albinos (Robertson, Marston & Walters, 1934).

Mice have the advantage of being available as inbred lines, which vary in life-span and predominant cause of death. They are also free of the enzootic lung infections which complicate rat-longevity studies. Several investigators have studied special effects of calorie restriction or of limiting intake of particular foodstuffs. Tannenbaum (1947) found that female DBA mice restricted to a weight of 19–20 g showed a striking absence of spontaneous tumours, which were the chief cause of death in 30 g controls. In YBR/Wi 'yellow' mice, a high-fat diet reduced the incidence of amyloidosis but greatly shortened life (Silberberg & Silberberg, 1955, 1957*b*) but a high-carbohydrate diet, though it produced obesity, did not affect life-span; C57 mice responded to a high-fat diet by developing a high incidence of arthritis (Silberberg & Silberberg, 1957*a*). King, Lee & Visscher (1955) found that in C_3H mice given a diet containing the normal trace-element additives, there was a high incidence of sudden heart failure after about a year, and of foetal resorption, which could be prevented either by added tocopherol or by omission of trace elements. 'Obese'

(*ob*, *ob*) mice whose weight was restricted by a diet low in calories have proved remarkably long-lived, reaching 1027 days (Lane & Dickie, 1958): the gain from restriction was greater than in the non-obese hemizygotes (*ob*, +). In a few instances vitamin supplements have been found to improve performance: vitamin A (Sherman & Trupp, 1940), pantothenic acid (Anonymous, 1949; Pelton & Williams, 1958) but the examples probably represent the remedying of deficiencies.

The evidence of studies with rodents is unanimous chiefly in showing that calorie intakes below the optimal for rapid growth increase the life-span. At least two effects seem to be present — a reduction in the pathological processes induced by overfeeding, and an actual postponement of development, and consequently of senescence. The results of mild restriction probably represent the first, and of severe restriction which actually checks growth or retards reproduction, the second. Basal metabolism in restricted rats is intermediate between that of normal young and normal adult rats (Will & McCay, 1943). Their size restriction is a restriction in cell number, retarded animals having the cellular population appropriate to size group, not age group (Fukuda & Sibatani, 1953). The operative effect seems to be mediated by the pituitary—it is a dietary hypophysectomy (Samuels, 1946) and is antagonized by extraneous growth hormone (Hruza & Fábry, 1957). Tissues from retarded animals have a shorter latent period in tissue culture (Holečkova, Fábry & Poupa, 1959) and some workers have found that the tail collagen in such animals is 'young' in its response to heat shrinkage (Chvapil & Hruza, 1959). Evidence regarding food restriction in normally grown adult animals is less spectacular—gains in general seem to reflect the avoidance of overweight (McCay *et al.* 1956).

Studies with mice require to be read in the light of the large differences in pathology between strains; in many of these, the removal of one age-dependent cause of death such as amyloidosis might produce a large step-wise gain in the 'specific age'.

The findings concerning life prolongation in rats and mice, and the evidence that in almost all the forms examined, from suctorians (Rudzinska, 1951) up, overnutrition accelerates increase in mortality or generates pathological processes as much as does undernutrition, have lead some workers to inquire whether the acceleration of puberty observed over the last century in the children of privileged countries may not involve an eventual reduction of life-span (McCance & Widdowson, 1955; Sinclair, 1955). The analogy must be treated with reserve, but excessive nutrition may well contribute substantially to the incidence of pre-senile diseases in prosperous people today, and hence to an effective acceleration of statistical ageing.

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Osteoporosis and calcium deficiency

By B. E. C. Nordin, *University Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, W.1*

It is generally assumed that there is little or no calcium deficiency in the western world. This assumption rests on two considerations. The first is that the average