and bones only as the square of the length; so that, if an animal doubles its length without alteration of proportions, "its ability to overcome forces has quadrupled, the forces it has to overcome have grown eight times as great." "But," writes D'Arcy Thompson, "as Galileo also saw, if an animal be wholly immersed in water, . . . then the weight is counterpoised to the extent of an equivalent volume of water. . . . Under these circumstances there is no longer a physical barrier to the indefinite growth in magnitude of the animal."

Giant trees, cultures of chick cells and of paramecium, measurements of plaice and of sponges, all indicate that indefinite growth is natural. Galileo proved it fatal to swiftly moving land animals, therefore swiftly moving mammals and birds were impossible until their ancestors had evolved a mechanism for maintaining specific size within an error not impairing adequate efficiency. Even without evidence of ever-growing organisms, we could not suppose that the close correspondence to specific size, which we see in all swiftly moving creatures of earth or air, results from mere "senescent" fading-out of the zygotic impulse to cell division and cell increase. Specific size is probably most important to birds, with their aeroplane mechanics strictly enjoining conformity of scale to plan; but to men it is most noticeable in man. Only familiarity prevents marvel at the rarity of meeting a man more than 20 per cent. taller or shorter than 5½ ft., or of discovering his remains in any place, of any race, of any epoch. Probably our erect posture enforces accurate proportions of length to weight, for running.

Adequate efficiency could only be obtained by the evolution of some mechanism to stop natural growth so soon as specific size is reached. This mechanism may be called the regulator, avoiding the word "inhibitor" so as not to connote a physiological assumption. However ignorant we are of its nature, its action is traced in anthropometric statistics: a steady diminution in growth rate from a maximum at puberty to vanishing-point in the twenties. That the regulator works through change in the constitution of the blood is shown by the perpetual division of Carrel's chick cells in embryonic plasma, whereas cell division is ended in the heart of a hen.

I have suggested that senescence is the result of the continued action of the regulator after growth is stopped. The regulator does efficiently all that concerns the welfare of the species. Man is within 2 cm. of the same height between 18 and 60, he gently rises 2 cm. between 20 and 27, and still more gently loses 1 cm. by 40 or thereabouts. If primitive man at 18 begat a son, the species had no more need of him by 37, when his son could hunt food for the grandchildren. Therefore the dwindling of cartilage, muscle, and nerve cell, which we call senescence, did not affect the survival of the species; the checking of growth had secured that by ensuring a perfect physique between 20 and 40. Effects of continued negative growth after 37 were of indifference to the race; probably no man ever reached 60 years old until language attained such importance in the equipment of the species that long experience became valuable in a man who could neither fight nor hunt. This negative growth is not the manifestation of a weakness inherent in protoplasm or characteristic of nucleated cells; it is the unimportant by-product of a regulating mechanism necessary to the survival of any race of swiftly moving land animals, a mechanism evolved by selection and survival as have been evolved the jointing of mammalian limbs, and with similar perfection.

(NOTE.—Though Galileo's law is the usual cause of the evolution of specific size, with consequent senescence, there are other causes. Mrs. Sexton, of the Marine Biological Association, told me that in her sand-hopper cultures both females and males eventually stop breeding and growing, and

die of old age. Probably many animals which move in shoals have specific size, because the largest are selected for death by the animals which prey on them. An animal which preyed exclusively on Gammarus, one by one, would also have specific size; Lankester (loc. cit., p. 41) points out the advantage of small size to a species which feeds on small things singly. Whales have specific size (*Proc. Linn. Soc.*, 1925, p. 18), possibly related to their feeding, possibly inherited from their active flesh-eating land ancestors.)

THE EXPERIMENTAL STUDY OF SENESCENCE*

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Conclusive evidence regarding problems of senescence is very scarce. This is mainly due to the fact that most of the numerous experiments which have been performed deal with isolated cases, few workers having had the opportunity of carrying out observations and experiments on a group of animals sufficiently large and sufficiently homogeneous to permit the collection of decisive data.

ANIMAL STOCK USED

At present such an opportunity exists, and is used to some extent, in this laboratory. The present writer imported, three years ago, some pairs of Wistar rats from which a "standard" stock was bred. Most of the stock, which is maintained at a strength of approximately 3,000 animals, has been derived from one ancestral pair by continuous litter-brother by litter-sister mating. The rest of the stock is as highly inbred as the sex ratio of the litters of the early generations permitted. The environmental conditions are kept as constant as possible, the animals being housed in standard cages in a special building fitted with thermostatic central heating and a cooling device. No artificial selection has been applied to the stock. The control half of the stock is permitted to die off without interference save in certain cases such as mammary tumours, which are very frequent in our colony, bites, skin and hair parasites. Individual records are kept of all stock animals, the cages being examined daily.

The stock was used during the last two years for a number of endocrinological, nutritional, and behaviour experiments. The Edinburgh stock has in common with the original Philadelphia stock certain advantages and shortcomings. Early growth is rapid, mortality during the first eighteen months of life is low, and resistance to infection high; on the other hand, emaciation after the eighteenth month of life is frequent, when many animals die without showing consistently specific pathological changes. Also, the duration of life, both average and maximum, appears to be rather short.

It will not be possible to publish adequate vital statistics or conclusive experimental data before the end of 1933; at present only a few preliminary notes can be given, and it will have to be remembered that these notes refer to animals of the first generation. It will have to be taken into account that the animals of successive generations are not absolutely comparable with each other since the degree of inbreeding obviously increases with each generation, and it remains to be determined to what extent this factor influences the mortality rate and other important characteristics. The oldest age observed in the male was 1,004 days, in the female 982 days. This is considerably below the maximum ages recorded by previous breeders.

* Read in opening a discussion in the Section of Comparative Medicine at the Centenary Meeting of the British Medical Association, London, 1932.

WHAT IS SENESCENCE?

When speaking of observations and experiments on senile rats, or for that matter on any other animal, it would seem necessary to define clearly what is meant by the term "senile." The literature does not contain any satisfactory definition. In most cases unsatisfactory external appearance combined with comparatively old age, dysfunction of the sex organs, and similar characteristics were used as an indication of senility. But observations on our stock show that these characteristics are not strongly correlated with each other, and the problem of what constitutes senescence is as complex in the rat as it is in man. It is found, for instance, that about half of the aged animals (which have already lived beyond the age of 24 months and have only a small expectation of life) did not show external signs of senescence such as were described by previous authors as typical for the aged rat. In many of these aged animals the external appearance continued to be satisfactory—the fur was in good condition, posture reflexes were apparently normal, though no quantitative analysis has as yet been carried out. Such animals die quite suddenly without having undergone any apparent phase of senescence. No consistent cause of death was found.

In other animals senescence was manifest and changes similar to those described by Steinach were observed. The animals were sluggish, uncertain in their movements, their posture reflexes were very slow, their general activity was greatly reduced, respiration was irregular, the eyes were pale, and the fur was thin and not cleaned. These changes constitute a gradual biatropy and may develop at any time between the twenty-second and thirtieth month of life, and continue sometimes for two or three months. Several days to a fortnight before death some animals refuse food but drink readily. No consistent cause of death was found.

These two "types" of ageing involving presence or absence of manifest senescence respectively are not sharply defined, and are, of course, distinguishable only by subjective observation. It is found, however, that the weight curves of the animals endorse the subjective impression. The more manifest senescence is, the more definite is the downward trend of the weight curve. In animals without manifest senescence the weight curve remains more or less "plateaued" until very shortly before death, when either a sudden steep fall or else, surprisingly enough, a sudden and rather steep rise occurs.

The two types which may be roughly distinguished include both males and females. Yet preliminary observation indicates that senescence becomes manifest more readily in the female than in the male.

INFLUENCE OF THE GONAD

Most of the authors concerned with the problem of "reactivation" of the senile organism seem to imply that atrophy or dysfunction of the gonad is necessarily involved in the syndrome of senescence. Some regard the generation of gonadic function as a criterion of senility. This assumption certainly cannot be maintained with respect to our stock.

(a) *Testicular Function in "Non-Senile" Aged Males.*—To refer to males first, it is found that aged males which do not exhibit manifest senescence may continue to show spermatogenesis and functional seminal vesicles. (The condition of the seminal vesicles can safely be regarded as an indicator of testicular secretion.) On the other hand, several cases of aged but not manifestly senile males were recorded in which the testicles had ceased to produce spermatozoa and were apparently greatly reduced in size and in endocrine function.

(b) *Testicular Function in "Senile" Aged Males.*—Similar conditions were found in aged males showing very manifest signs of senescence. Thus spermatogenesis and internal secretion can continue or else be absent (or practically absent) in obviously senile males. Moreover, three cases were recorded in which the testicles of animals obviously and manifestly senile seemed almost atrophic (small, flaccid, and of purplish colour), while the seminal vesicles of these males were the largest the present writer has ever observed in any rat of any age. Microscopically the testes were found to consist of interstitial tissue, containing Leydig cells and unspecified elements, and of empty tubuli.

(c) *Ovarian Function in Aged Females.*—As to the female, conditions resemble those found in the male. Fertility ceases in the females of the Edinburgh stock about the eighteenth month of life. The maximum age of fertility was 26 months (one case). Sexual periodicity (oestrous cycle) continues for varying periods after fertility has ceased; thus many animals will mate without becoming pregnant or pseudo-pregnant. The presence or absence of oestrous periodicity is certainly not absolutely correlated with the manifest appearance of the animal. Females of the senescent type may come in oestrus regularly; aged females of the non-senescent type may not come in oestrus at all. In some cases the signs of oestrus were found shortly before death in rats which died after a period of manifest senescence at ages varying from 27 to 28 months. In most cases necropsy or biopsy revealed a state of the ovary and uterus corresponding to the observations on the oestrous periodicity. Animals which showed oestrous periodicity had, as a rule, well-developed ovaries and uteri—this applies to an animal which died at the age of 29 months and was manifestly senile. On the other hand, the findings in animals which did not come into oestrus differed. In some of them the ovary was of senile appearance, consisting mainly of a stroma of small unspecified cells and of small follicles (mostly of distorted shape) lying peripherally. Kariolysis of the ova was observed. In other cases, however, a phenomenon was observed which cannot yet be explained. The ovaries in these cases were of normal gross and histological appearance, while the uterus appeared to be very thin and showed glandular atrophy histologically, low cubic to columnar epithelium, and general signs of degeneration, such as were described previously. In a number of aged females of senile appearance which showed no oestrous periodicity the ovary was found to be of normal appearance, but the uterus was distended by blood or a fluid of low viscosity, stained dark by blood pigments. This is the only pathological finding made in comparatively numerous cases.

CONCLUSIONS

The observations briefly summarized in the preceding paragraphs show quite clearly that senescence is not absolutely correlated with absence of ovarian or testicular function, and that it can develop even in males in which excessive testicular secretion may be assumed to exist in view of the very prominent development of the accessory genital glands. Conversely, aged animals may preserve a satisfactory general condition although gonadic function is reduced. Whether any correlation between ovarian and testicular function on the one hand, and the general condition of the organism and duration of life on the other, does exist will be determined when the complete data are available.

In a number of aged males and females (all more than 24 months of age) in which ovary and testicle were found to show senile changes at biopsy and where the absence of oestrus or the condition of the accessory glands indicated reduction of endocrine gonadic function, one gonad

was removed for histological purposes, and the state of the genital organs was ascertained as far as possible. In six animals which were examined at a later date again it was found that no compensatory hypertrophy had occurred. Fourteen of the animals were subjected to experiments with gonadotropic hormones (*p*-factors, prolans) prepared in most cases from pregnancy urine by a method published previously, and in three cases anterior lobe grafts were given. It was found that within eleven to twenty-one days restitution of gonadic function occurred. Corpora lutea were found in the ovaries, and the uteri of these animals were found to be of functional appearance.

As to the testicle, the findings varied. Slight or pronounced enlargement of the testicle was found in six cases. All animals save one, which died during the treatment, showed a definite enlargement of the seminal vesicles. The histological findings differed considerably. In four animals spermatogenesis, which was found to be absent in the control testicle removed before the injections started, had recurred in the remaining testicle. This result cannot be easily reconciled with our general knowledge regarding the influence of gonadotropic hormones upon the testicle, since experiments carried out in this laboratory and elsewhere have failed to establish spermatogenesis as an effect of gonadotropic hormones. In the remaining cases the histogenetic influence of the injections upon the testicle was slight and apparently restricted to the interstitial tissue; this is in accordance with findings on prepuberal or pubescent animals. The influence of the injections upon the general condition of the animals was not marked, although it seems that in a few cases an improvement in the general condition occurred; in the remaining animals no distinct influence was manifest.

The experiments so far conducted show, in accordance with previous findings, that the senile gonad can be reactivated, at least in some cases. The senescence of the gonad seems to be due to the lack of the specific stimulating factor represented by the gonadotropic hormones of the anterior lobe, and not to any general condition of the organism or to the absolute age of the gonad itself. It is difficult to reconcile with these conclusions observations which claim that interference with the testicle itself led to a reactivation of testicular secretion, since the deficiency is one of extra-gonadic factors. However, further experiments with vaso-ligature and similar methods are in progress. The experiments with injections of gonadotropic extracts are also repeated on a larger scale so that any existing influence on duration of life should be detected.

GROWTH AND SENILITY

In view of the fact that no absolute correlation between gonadic function and the senescence of the organism as a whole was manifest, it seemed desirable to examine the relation between general functions and senescence. The investigation of growth in relation to senescence suggests itself. Growth may be regarded not as an incidental attribute of the early phases of life, but as an essential condition of what, for the present, one might call "youth," whether the latter be defined statistically (expectation of life) or biologically (by reference to the intensity of functions, efficiency of the organism as a whole, etc.).¹

Experiments with the injection of growth-promoting extracts from the anterior lobe into aged animals were therefore arranged. The extracts used were either pre-

pared by the ammonia method (Wiesner and Sheard) and contained gonadotropic hormones or else were free of the latter, the method of van Dyke and his colleagues being used. So far the experiments have shown that many senile animals can react with considerable growth to the administration of growth-promoting extracts. In the meantime the increase in weight is taken as the sole indicator of growth. This is permissible in the absence of pathological conditions such as anasarca or obesity; any error introduced by the use of the weight curve as an indicator of general growth will, it is hoped, be corrected by *x*-ray records to be taken in future experiments.

It appears that in some cases the administration of growth extracts had a beneficial influence upon the general condition of the rat. At present the mortality rate of the experimental male group is only half that of the uninjected special control group, while no significant differences between respective mortality rates of the experimental and control females have occurred. Yet it will remain impossible to draw any definite and reliable conclusion before the groups will have died off.

It need hardly be emphasized that the observations briefly related above represent only a few preliminary notes. Our observations, however, may serve as indicating lines of further research. It is hoped that by the end of the coming year the number of experiments on aged animals will be sufficiently large to permit more definite conclusions. Also, experiments undertaken by the writer's colleagues will probably yield some more objective data as to changes occurring in old age and the reaction of the senile organism to the administration of gonadotropic and growth-promoting extracts.

The writer would like to express his gratitude to Miss N. M. Sheard, who is superintending the rat colony, and to Mr. T. B. Macaulay, LL.D., whose generosity made it possible to build up and maintain the colony.

ANEURYSM OF ABDOMINAL AORTA AND THROMBOSIS OF SUPERIOR MESENTERIC ARTERY ASSOCIATED WITH A BULLET WOUND OF THE LUNG

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The case recorded below has considerable medico-legal interest in respect to the establishment of a causal relation between the passage of the bullet and the formation of the aneurysm. There is no evidence of syphilis as an aetiological factor, neither does the site of the aneurysm nor its form correspond with those of an atheromatous lesion. In any case the abdominal aorta is a rare site for spontaneous aneurysms, and since the lesion present corresponds in type to a traumatic aneurysm, one is forced to the conclusion that the latter diagnosis is correct.

CASE RECORD

The patient, an ex-soldier aged 45, was admitted to the Royal Victoria Infirmary, Newcastle-on-Tyne, at 1.30 p.m. on July 24th, 1931, suffering from an "acute abdominal crisis" of thirty-six hours' duration, with a diagnosis of intussusception. He had been taken ill thirty-six hours previously with pain in the epigastrium, nausea, and vomiting, and had been treated medically for gastro-enteritis. The bowels had been opened several times during the attack and

¹ To regard growth as more than a mere epiphenomenon of youth seems justifiable from a general biological point of view; the classical experiments of Hartmann on the immortalization of *Planaria* may be mentioned in this context, and particular reference may also be made to the point of view developed by Ehrenberg, according to whom the term "growth" may be taken in a wider sense than the usual one which implies actual increase in size.