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CONTENTS

AUGUST WEISMANN'S CONTRIBUTION
TO CYTOGERONTOLOGY

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Between 1881 and 1891, August Weismann, Professor of Zoology in Freiburg im Breisgau, wrote a number of essays which were published in a book "Aufsätze über Vererbung und verwandte biologische Fragen" [1]. An English translation of these essays appeared in Oxford in 1891 and 1892 under the title "Essays upon heredity and kindred biological problems" [2, 3].

In these essays, Weismann put forward two important hypotheses concerning natural death in metazoan organisms: 1. Natural death is not a primary necessity, but has been secondarily acquired during the course of Darwinian evolution, and 2. Evolution led to a finite replicative lifespan of somatic tissue cells in animals, but not necessarily in plants.

Since the classic paper of Hayflick and Moorhead in 1961 [4], a limited replicative lifespan has been reasonably established for euploid fibroblasts and several other somatic cell types [5–8]. The possible significance, however, of this phenomenon with regard to the finite lifespan of man and other species is a point of considerable controversy among present day gerontologists. Little if any notice has been taken that Weismann proposed a complete theory of cellular ageing including its evolutionary aspects nearly a hundred years ago. This theory has been presented only in rudimentary form in recent times [9–14]. It is the purpose of this article to present the theory in its full state. Weismann's theory is reconsidered not only for historical reasons, but for the fact that it fulfils the requirements of a modern theory of cellular ageing [15]: it seems theoretically plausible, is supported by present day experimental evidence and makes evolutionary sense. Since Weismann's original essays may be difficult to be obtained by most readers, I shall present his arguments mainly in his own words. In some cases, where I feel that the meaning of the English version deviates from the German one, both versions are cited.

To appreciate Weismann's work in full depth, it would be necessary to contrast his theory with contemporary theories and to present the wealth of examples taken by Weismann from the animal kingdom,

especially from insects, and even from the plant kingdom to illustrate his arguments. This would go beyond the scope of this presentation. Weismann's concept of heredity and Darwinian evolution will be considered so far as necessary for an understanding of his concept of ageing and natural death. The informed reader will note the relevance of Weismann's thoughts to a theoretical foundation of present day experimental work in cytogerontology [4–8], as well as present day theories concerning the evolution of ageing [9–17].

1 WEISMANN'S THEORY OF GERM PLASM

a) Localization of hereditary substance in the nucleus

For reasons extensively discussed in his essays [1, IV; 2, XI], Weismann concluded that "the nuclear loops" (also called nuclear rods, idants, chromosomes in Weismann's essays) "are the material basis of heredity" [2, XI, p. 85].
"Nuclear rods are built up of a series of ancestral plasms (= Ahnenplasmen, Ide), which are not intimately connected together, but as far as mere position is concerned, are arranged next to one another" [2, XII, p. 130] (Fig. 1).
It is important to note that Weismann at the time when he developed his theory of germ plasm, did not know the work of Mendel. His ancestral plasms are supposed to be "hereditary units of higher order, each of which, if it alone dominated the ovum, would be capable of guiding the whole ontogeny and of producing a complete individual of the species" [2, XII, p. 130].
Due to the work of Auerbach, Bütschli and Flemming, Weismann was aware that nuclear loops "are accurately divided in a longitudinal plane, the halves then entering the two daugther nuclei which are being formed" [2, XII, p. 112].

b) Ontogenesis

"As a result of fertilization, the paternal and maternal rods come to lie close to one another in the same nucleus, but undergo no true fusion into a single mass. If we assume that this remains true during the whole ontogeny, we can only suppose that half the nuclear rods of every cell are paternal and half maternal and that both these simultaneously influence the cell" [2, XII, p. 123].

I
Ukz

II
Mkz

III
Tkz

IV
Kz

A
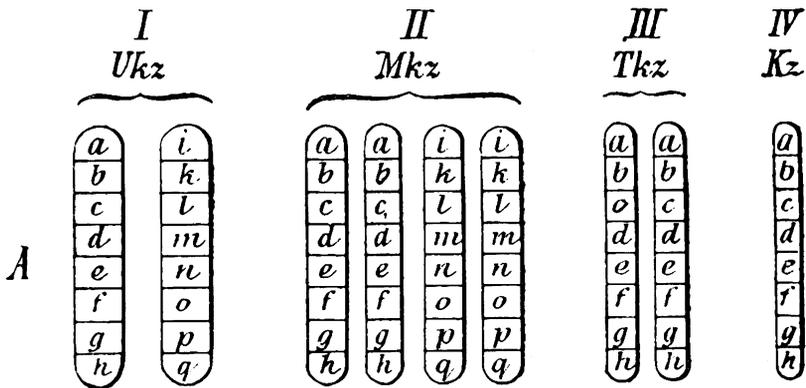
Fig. 1: Diagram showing the behaviour of the idants (= chromosomes) in the various stages of the development of the germ-cells in *Ascaris megalocephala,* var. univalens [from Weismann 3, XII]. Small letters a, b, c ... represent the ids which compose the idants. It is noted that the hereditary units called ids are linearly arranged in the chromosomes and maintain an identical arrangement throughout meiosis. "It is at least possible and perhaps the rule for the order and arrangement of the ids in the idants to remain unchanged from the germ-cells of the parent to those of the offspring" [3, XII, p. 131]. In agreement with the views of van Beneden and Boveri Weismann suggested "that the chromosomes only apparently break up during the nuclear resting stage, but in reality persist" [3, XII, p. 131].

"The theory of germ-plasm may be expressed as follows: The fertilized ovum contains germ-plasm in its nucleus, i. e. idioplasm endowed with the collective hereditary tendencies of the species: at each of the cell divisions by means of which the ovum develops into the organism, this idioplasm splits into quantitatively similar halves in order to form the nuclei of the daugther cells. But these halves are not always qualitatively alike; they are only so when they are to give rise to similar cells: when the cells which arise by division have a different significance in development, their idioplasm also differs in quality. The germ plasm of the ovum is continuously undergoing change during ontogeny, inasmuch as the developmental tendencies are being split up, and become more and more distributed among the members of successive cell generations, until finally each kind of cell in the body contains only that developmental tendency which corresponds with its specific histological

character. Each cell is thus dominated by a specific idioplasm" [2, XII, pp. 114—115].

c) *Continuity of germ plasm*

Weismann supposes that the molecular structure of the nucleoplasm becomes simpler in the course of ontogeny [1, IV, p. 198] and that the changes of germ plasm which take place in a regular and definite manner during ontogenetic development [1, IV, p. 189] are therefore irreversible. To disprove this hypothesis, it had to be shown "that somatic idioplasm is capable of undergoing re-transformation into germ idioplasm" [1, IV, p. 200].

"We can only conclude that continuity is maintained, by assuming (as I do) that a small part of the germ plasm persists unchanged during the division of the segmentation nucleus and remains mixed with the idioplasm of a certain series of cells, and that the formation of true germ cells is brought about at a certain point in the series by the appearance of cells in which the germ plasm becomes predominant" [1, IV, p. 201].

This conclusion was based on the finding that "in the great majority of cases, the germ cells are not separated at the beginning of embryonic development, but only in some of the later stages. A single exception is found in the pole-cells ("Polzellen") of Diptera, as was shown many years ago by Robin and myself. These are the first cells formed in the egg, and according to the later observations of Metschnikoff and Balbiani, they become the sexual glands of the embryo" [1, IV, p. 200] [18].

"In Daphnidae (Moina) separation occurs in the fifth stage of segmentation, and although this is unusually early it does not happen until the idioplasm has changed its molecular structure six times. In Sagitta the separation does not take place until the archenteron is being formed, and this is after several hundred embryonic cells have been produced, and thus after the germplasm has changed its molecular structure ten or more times. But in most cases, separation takes place at a much later stage; thus in Hydroids [19], it does not happen until after hundreds or thousands of cell generations have been passed through; and the same fact holds in the higher plants, where the production of germ cells frequently occurs at the end of ontogeny" [1, IV, p. 202].

d) *Stability and variability of germ-plasm*

"The germ-plasm or idioplasm of the germ cell (if this latter term be preferred) certainly possesses an exceedingly complex minute struc-

ture, but is nevertheless a substance of extreme stability, for it absorbs nourishment and grows enormously without the least change in its complex molecular structure... When we know that many species have persisted unchanged for thousands of years, we have before us the proof that their germ-plasm has preserved exactly the same molecular structure during the whole period" [1, V, p. 278].

On the other hand, Weismann was clearly aware of the fact that a certain variability of the germ-plasm is indispensable for the evolution of species. Weismann expected the source of this variability mainly in sexual reproduction. "The object of this process is to create those individual differences which form the material out of which natural selection produces new species" [1, V, p. 279].

In addition, he considered the possibility that "minute alterations in the molecular structure of the germ-plasm" might occasionally take place due to influences of different kinds and that "such changes would be hereditary" [1, V, p. 277]. In the German edition of his essays upon heredity [1], he added a footnote in 1892, in which he states "Ich glaube heute, daß wir der direkten Einwirkung auf das Keimplasma eine größere Bedeutung zugestehen müssen, als ich es hier getan habe [1, V, p. 330]. (Personal translation: "Today I believe that direct influence on the germ-plasm plays a larger role than I supposed").

Since 1884, Weismann had undertaken a series of experiments "to decide the question of variability in purely parthenogenetic species" [3, XII, p. 161]. For this purpose, Weismann chose a species of Cypris (Ostracoda), which was characterized by a striking and well perceptible marking on the shell (Fig. 2).

"I had at my disposal two very differently marked varieties of the species in question (Cypric reptans) which had been found in the natural state. The species appears to be purely parthenogenetic in this locality... My two subspecies are distinguished as follows: variety A is lighter in colour and there are only a few dark green spots of small size on the clay yellow ground-colour of the shell. Variety B appears dark green because the spots are so much larger that they expose only a little of the clay yellow ground-colour of the shell... The lighter A can be distinguished from the darker B with the naked eye at the first glance. The experiment was conducted in the following way: I placed a solitary individual in a small aquarium, and allowed it to multiply until the whole vessel was full of mature, egg-producing descendants. All the individuals of the colony were then passed in review, and the
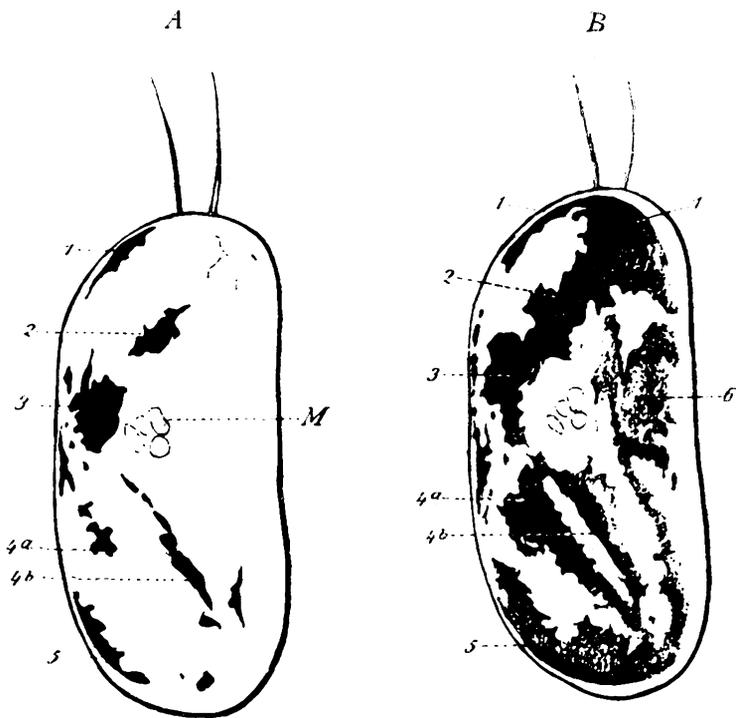
Fig. 2: *Cypris reptans,* Varieties A and B [from Weismann 3, XII].

greater number were killed and preserved, one or more having been selected for breeding, and these were placed separately in fresh aquaria. In this way, in the course of seven years, many thousand individuals have passed through my hands; for the animals breed very rapidly and at all times of the year" [3, XII, p. 161, 162].

"I attempted at first to produce the two forms by artificial selection, breeding from the darkest individual of a colony of the variety A, and from the lightest of a colony of B, in the hope that, perhaps, in the course of generations, one variety might be changed into the other. But I obtained no decisive results" [3, XII, p. 163].

"I now (1891) possess colonies of A, as well as of B, which cannot be distinguished from their ancestors in 1884 and which therefore retained precisely the same markings as those from the original animals" [3, XII, p. 163].

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"I was therefore all the more astonished to find, in 1887, some individuals of the dark green variety B in the same aquarium with the light variety A, and therefore side by side with typical, light, clay-coloured individuals. At first, I thought, although it was most improbable, that these have been accidentally introduced, but the greatest care had always been exercised in all these experiments. Furthermore, after the most painstaking precaution against such accidents, precautions which prevented all possibilities of the eggs being misplaced, there presently appeared another similar case in a different aquarium containing the variety A, and, later on, yet another... Again, in May of the present year, 1891, another case was observed in which a single animal, distinctly belonging to the dark sub-species, suddenly appeared among 540 mature Cyprides of the light variety. Five descendants of this individual closely resemble their mother. For a long time I waited in vain for the converse result, viz. the appearance of light individuals of the variety A among those of the dark sub-species B, and I was coming to the opinion that the latter was the original form of both varieties, when, in the winter of 1890—91, a few typical individuals of A were found in a colony of the subspecies B, which had bred true for many years. This colony had arisen from a single dark individual which, in the course of seven years, had produced many hundreds of descendants all of the typical dark variety" [3, XII, p. 163, 164].

Weismann concludes that "these remarkable phenomena must certainly be ascribed to internal causes, viz. to changes in the composition of the germ-plasm" [3, XII, p. 164].

"We can safely affirm that in parthenogenesis individual variation exists which, as in bisexual reproduction, has its foundation in the composition of the germ plasm itself, and thus depends on heredity, and is itself inheritable" [2, XII, p. 166].

I have cited these experiments in some more detail, because they illuminate Weismann's way of experimentally testing and further developing his theories. We will now consider the part of this theory which is concerned with cellular ageing and its evolution.

2 NATURAL AND ACCIDENTAL DEATH

In an effort to become familiar with Weismann's theory of cellular ageing, it is important to consider his definitions of death and immortality. The somatic cells of metazoa may be the subject of natural or accidental

death [2, III, p. 123]. Accidental death is due to innumerable external conditions, while natural death arises from internal causes [2, III, p. 143]. Both accidental and natural death are characterized by a "definite arrest of life" [2, III, p. 114]. "The real proof of death is that the organized substance which previously gave rise to the phenomena of life, for ever ceases to originate such phenomena" [2, III, p. 115].

"We have hitherto been without a scientific conception of immortality: we must understand by this term — not life without beginning or end — but life which, when it has once originated continues without limit, accompanied or unaccompanied by modification (viz. specific changes in unicellular organisms, or in the germ-plasm of multicellular forms). This immortality is a movement of organic material, which always recurs in a cycle, and is associated with no force that tends to arrest its progress" [3, XI, p. 79].

In this respect unicellular organisms are considered to be potentially immortal.

"The protoplasm of unicellular beings possesses such an arrangement in its chemical and molecular structure, that the cycle of material which makes up life is ever repeating itself, and can always begin afresh so long as the external conditions remain favourable" [3, XI, p. 75].

In metazoans potential immortality has been retained by the cells of the germ line, while natural death evolved in somatic tissue cells. Weismann states "that such wearing out of tissue cells is a secondary adaptation, that the death of the cell, like general death, has arisen with the complex, higher organisms. Waste does not depend on the intrinsic nature of the cells, as the primitive organisms prove to us, but it has appeared as an adaptation of the cells to the new conditions by which they are surrounded when they come into combination, and thus form the cell-republic of the metazoan body" [2, I, p. 61/62].

It is important to note that the word "Anpassung" (adaptation) when used by Weismann does not necessarily mean that evolution of a certain peculiarity of living matter including the loss of a structure or function is brought about by direct selective forces, since panmixia may also take part in bringing about "Anpassung". We shall extensively consider this point later [see 4.b and 4.d].

"Just as it was possible for the specific somatic cells to be differentiated from among the chemico-physical variations which presented themselves in the protoplasm, by means of natural selection, until finally each function of the body was performed by its own special kind of cell; so it

might be possible for only those variations to persist the constitution of which involved a cessation of activity after a certain fixed time. If this became true of the whole mass of somatic cells, we should then meet with natural death for the first time" [2, III, p. 142].

"I trust that it will not be objected that the germ-cells cannot be immortal, because they frequently perish in large numbers, as a result of the natural death of the individual. There are certain definite conditions under which alone a germ-cell can render its potential immortality actual, and these conditions are for the most part fulfilled with difficulty (fertilization, etc.)" [2, III, p. 123].

"The spermatozoon which fails to find an ovum, dies. If anyone finds pleasure in bringing confusion into ideas which have just become to some extent clear, he may speak of this as the normal death of the spermatozoon, I call it an accidental death, although I am well aware that this unhappy accident is far more common than the successful attainment of the normal object of a spermatozoon's life . . .

I believe that spermatozoa want adaptations for the absorption of nutriment, because they do not need them for attainment of the object for which they exist, and that, were it otherwise, they would have been adapted for living longer. Useless adaptations are never met with" [3, XII, p. 203—204].

Weismann performed similar considerations with regard to infusoria which are adapted for conjugation. He knew from the work of Maupas that these unicellular organisms have a limited clonal lifespan [3, XII, p. 176] when they are prevented from conjugation, and considered degeneration of these infusoria as an accidental death, not a natural one, since conjugation is one of the conditions which must be fulfilled in these organisms to retain their potential immortality [3, XII, p. 204].

3 WEISMANN'S CONCEPT OF CELLULAR AGEING

In the eighties of the 19th century, it became evident "that the vital processes of the higher (i. e. multicellular) animals are accompanied by a renewal of the morphological elements in most tissues" [2, I, p. 21; see also 2, III, p. 146].

"Millions of blood corpuscles are continually dying and being replaced by new ones. On both the internal and external surfaces of the body countless epithelial cells are being incessantly removed, while new ones arise in their place: the activity of many and probably of all glands

is accompanied by a change in their cells, for their secretions consist partly of detached and partly of dissolved cells; it is stated that even the cells of bone, connective tissue, and muscle undergo the same changes, and nervous tissue alone remains, in which it is doubtful whether such an renewal of cells takes place" [2, I, p. 21].

"This statement leads us to seek the origin of death, not in the waste of single cells, but in the limitation of their powers of reproduction. Death takes place because . . . a capacity for increase by means of cell-division is not everlasting, but finite. This does not however imply that the immediate cause of death lies in the imperfect renewal of cells, for death would in all cases occur long before the reproductive power of the cells had been completely exhausted. Functional disturbances will appear as soon as the rate at which the worn-out cells are renewed becomes slow and insufficient" [2, I, p. 21—22].

Weismann proposes further "it follows that the number of cell-generations which can proceed from the egg-cell is fixed for every species, at least within certain limits; and this number of cell-generations, if attained, corresponds to the maximum duration of life in the individuals of the species concerned.

Shortening of life in any species must depend upon a decrease in the number of successive cell-generations, while conversely, the lengthening of life depends upon an increase in the number of cell-generations over those which were previously possible" [2, I, p. 22].

The maximum number of somatic cell generations possibly does not only vary in different species "but even in the various kinds of cells in one and the same species of animal" [2, III, p. 147].

To test the validity of this hypothesis "the question must be answered as to whether the kind and degree of reproductive power resides in the nature of the cell itself, or in any way depends upon the quality of its nutriment" [2, I, p. 29].

"Sie können von mir allerdings den Nachweis verlangen, daß überhaupt der Modus und die Quantität der Fortpflanzung in der spezifischen Natur der Zelle selbst begründet ist und keineswegs bloß von ihrer Ernährung abhängt" [1, p. 34].

4 EVOLUTION OF AGEING

As an introduction of Weismann's thoughts concerning the evolution of ageing, we shall first consider some general points.

1. Weismann strictly rejected that acquired characters could become hereditary, while many of Weismann's contemporaries, including Darwin himself, felt that this idea could not be dismissed if one was to explain the course of evolution (a).
2. Weismann considered the reasons for retrogressive development in nature in great detail and introduced the important term "panmixia", which will be defined in (b). These ideas will provide us with the logical structure essential for an accurate understanding of Weismann's concept of the evolution of ageing.

a) Molecular reasons to reject the transmission of acquired characters

In an appendix entitled "On the supposed transmission of acquired characters" [1, V, p. 319—322], Weisman clearly points out the molecular reasons which speak against the possibility of any transmission of aquired characters. As an example, Weismann considered the proposed transmission of epilepsy artificially induced in guinea pigs.

"We can form no conception as to the means by which an acquired morphological change in certain nerve cells ... can be possibly transferred to the germ cells: for this ought to take place in such a manner as to produce in their minute molecular structure a change which, after fertilization and development into a new individual, would lead to the reproduction of the same epileptogenic molecular structure of the nervous elements ... as was acquired by the parent. How is it possible for all this to happen? What substance could cause such a change in the resulting offspring after having been transferred to the egg or sperm cell? Perhaps Darwin's gemmules may be suggested; but each gemmule represents a cell, while here we have to do with molecules or groups of molecules. We must therefore assume the existence of a special gemmule for each group of molecules, and thus the innumerable gemmules of Darwin's theory must be imagined as increased by many millions. But if we suppose that the theory of pangenesis is right, and that the gemmules really circulate in the body, accompanied by other gemmules from the diseased parts of the brain, and that some of these latter pass into the germ-cells of the individual, — to what strange results would the further pursuit of this idea lead? What an incomprehensible number of gemmules must meet in a single sperm- or germ-cell, if each of them is to contain a representative of every molecule or group of molecules which has formed part of the body at each period of ontogeny. And yet such is the unavoidable consequence of the supposition that acquired

molecular states of certain groups of cells can be transmitted to the offspring" [2, V, p. 324 f.].

"We suppose that characters acquired (in the true sense of term) by the parent cannot appear in the course of the development of the offspring, but all the characters exhibited by the latter are due to primary changes in the germ" [2, II, p. 78].

"It is only by supposing that these changes arose from molecular alterations in the reproductive cell that we can understand how the reproductive cells of the next generation can originate the same changes in the cells which are developed from them; and it is impossible to imagine any way in which the transmission of changes, produced by the direct action of external forces upon the somatic cells, can be brought about" [2, II, p. 80].

b) Retrogressive development in nature

"As soon as an organ becomes useless, the continued selection of individuals in which it is best developed must cease, and a process which I have termed panmixia takes place. When this process is in operation, not only those individuals with the best developed organs have the chance of reproducing themselves, but also those individuals in which the organs are less well developed. Hence follows a mixture of all possible degrees of perfection, which must in the course of time result in the deterioration of the average development of the organ. Thus a species which has retired into dark caverns must necessarily come to gradually possess less developed powers of vision; for defects in the structure of the eyes, which occur in consequence of individual variability, are not eliminated by natural selection, but may be transmitted and fixed in the descendants. This result is all the more likely to happen, inasmuch as other organs which are of importance for the life of the species will gain what the functionless organ looses in size and nutrition" [2, V, p. 299].

"Blind animals always possess very strongly developed organs of touch, hearing, and smell, and the degeneration of the wingmuscles of the ostrich is accompanied by a great increase in the strength of the muscles of the leg. If the average amount of food which an animal can assimilate every day remains constant for a considerable time, it follows that a strong influx towards one organ must be accompanied by a drain upon others, and this tendency will increase, from generation to generation, in proportion to the development of the growing organ, which is

favoured by natural selection in its increased blood-supply, etc.; while the operation of natural selection has also determined the organ which can bear a corresponding loss without detriment to the organism as a whole" [2, II, p. 88].

"The complete disappearance of a rudimentary organ can only take place by the operation of natural selection; this principle will lead to its elimination, in as much as the disappearing structure takes the place and the nutriment of other useful and important organs" [2, II, p. 89].

"New possessions are not invariably added to the old, but the latter are often rendered superfluous in the course of time and taken away. Nor does this happen in an ideally perfect way, suddenly, as if by magic, but slowly, in accordance with existing laws, so that the process remains uncompleted through long ages. But ultimately the organ which is no longer essential to life is done away with altogether, and the balance between the structure of the body and its functions is restored so that, in this sense also, retrogression may in truth be said to be a part of progress" [3, IX, p. 30].

c) *Weismann's concept of the evolution of multicellular organisms from unicellular organisms*

"In the course of the phyletic development of the organized world, it must have happened that certain unicellular individuals did not separate from one another after division, but lived together, at first as equivalent elements, each of which retained all the animal functions, including that of reproduction" [2, II, p. 75—76].

"The Homoplastides, that is cell-colonies built up of equal cells, have not yet gained any natural death, because each of their cells is, at the same time, a somatic as well as a reproductive cell: and they cannot be subject to natural death, or the species would become extinct" [2, III, p. 127] (Fig. 3).

"The germ plasm (nucleoplasm) of some homoplastid organism . . . must have become modified in molecular structure during the course of phylogeny, so that the colony of cells produced by its division was no longer made up of identical units, but of two different kinds. After this separation, the germ cells alone retained the power of reproduction possessed by all the parent cells, while the rest only retained the power of producing similar cells by division" [2, IV, p. 208] (Fig. 4).

The formation of homoplastids and heteroplastids from monoplastids can easily be understood as an adaptation which favoured the survival
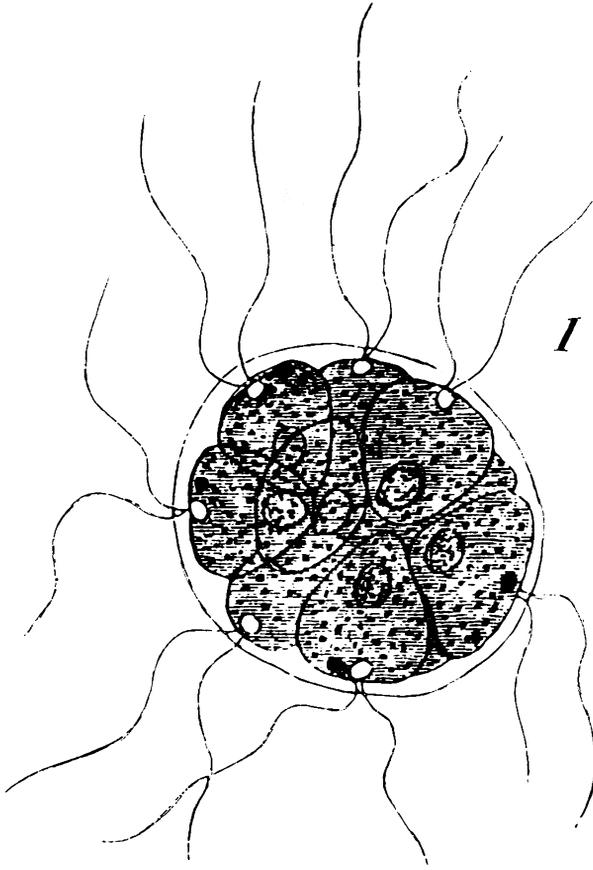
Fig. 3: *Pandorina morum* (after Pringsheim), a swarming colony [from Weismann 2, IV]. Each cell is, at the same time, a somatic as well as a reproductive cell and potentially immortal.

of a species. The advantage of a germ-cell surrounded by somatic cells adapted to create an optimum environment for survival and propagation of these germ cells may easily have outweighed the disadvantage that not all cells of such a heteroplastid could act as germ cells.

"Division of labour would produce a differentiation of the single cells in such a colony: thus certain cells would be set apart for obtaining food and for locomotion, while certain other cells would be exclusively

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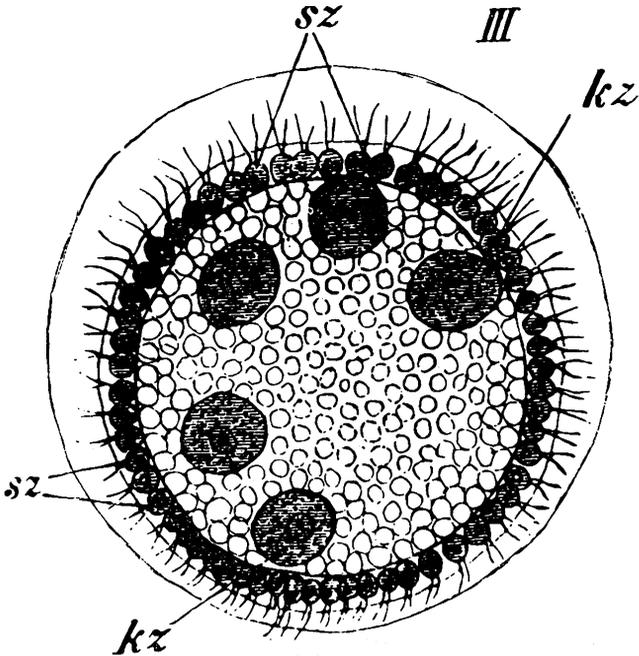
Fig. 4: A young individual of *Volvox minor* still enclosed in the wall of the cell from which it has parthenogenetically produced. The constituent cells are divided into somatic cells (sz) and germ-cells (kz) [from Weismann 2, IV]. Potential immortality has been retained by the germ-cells, while the somatic cells have a finite lifespan.

reproductive. In this way colonies consisting of somatic and of repro-ductive cells must have arisen, and among these for the first time death appeared. For in each case the somatic cells must have perished after a certain time, while the reproductive cells alone retained the immortality inherited from the Protozoa" [2, II, p. 76].

"Es entstanden so Kolonien, die aus Körperzellen und aus Keimzellen zusammengesetzt waren und bei denen wohl zuerst die Erscheinung des individuellen Todes sich einbürgerte, indem die Körperzellen nach ge-wisser Zeit zugrunde gingen, während die Keimzellen allein die von den Protozoen ererbte Unsterblichkeit beibehielten" [1, p. 84].

"We can easily imagine that all the succeeding stages in the develop-ment of the Metazoa have been due to the same causes which were ef-

ficient at the earliest period. Variations in the molecular structure of the reproductive cells would continue to appear, and these would be increased and rendered permanent by means of natural selection, when their results, in the alteration of certain cells in the body, were advantageous to the species. The only condition necessary for the transmission of such changes is that a part of the reproductive substance (the germ-plasm) should always remain unchanged during segmentation and the subsequent building up of the body, or in other words, that such unchanged substance should pass into the organism, and after the lapse of a variable period should reappear as the reproductive cells. Only in this way we can render to some extent intelligible the transmission of those changes which have arisen in the phylogeny of the species; only thus can we imagine the manner in which the first somatic cells gradually developed in numbers and in complexity" [2, II, p. 80].

d) *The evolution of natural death as a result of "panmixia" plus selective processes*

If one accepts that "division of labour" [3, XI, p. 74] among cells increases the probability of viable offspring in a certain species the evolution of metazoan organisms can be understood in principle. We arrive now at the critical point of Weismann's evolutionary theory of natural death of the metazoan organism. Why did evolution not work in favour of somatic cells which retained their potential immortality?

Weismann was well aware of this difficulty. Considering glandular secretions and blood corpuscles he stated that "we must admit that the histological elements do, as a matter of fact, wear out in multicellular animals" [2, I, p. 61].

"The glandular secretions which are composed of cell-detritus, prove that the cells of a complex organism may acquire functions which result in the loosening of their connexion with the living cell-community of the body, and their final separation from it. And the same facts hold with the blood corpuscles, for the exercise of their function results in ultimate dissolution. Hence it is not only conceivable, but in every way probable, that many other functions in the higher organisms involve the death of the cells which perform them, not because the living cell is necessarily worn out and finally killed by the exercise of any ordinary vital process, but because the specific functions in the economy of the cell-community which such cells undertake to perform, involve the death of the cells themselves" [2, I, p. 62].

"But it does not therefore follow that the somatic cells were compellled to loose the power of unlimited cell-production, although in accordance with the law of heredity, they could only give rise to cells which resembled themselves, and belonged to the same differentiated histological system" [2, I, p. 28].

"Daraus folgt aber durchaus nicht, daß den somatischen Zellen die Fähigkeit unbegrenzter Zellfortpflanzung hätte verlorengehen müssen, sie hätte sich nur nach den Gesetzen der Erblichkeit auf die Hervorbringung ihresgleichen, d. h. derselben spezifisch differenzierten Gewebszellen beschränkt halten müssen" [1, p. 33]. "The replacement of cells is certain in many tissues (in glands, blood etc.), so that we can never seek a satisfactory explanation in the train of reasoning indicated above, but we must assume the existence of limits to the replacement of cells" [2, I, p. 63].

These sentences show that Weismann was clearly aware of the problem that stem cell populations in somatic tissues can preserve the structural integrity of the tissues. Blood cells are the most obvious example for this capability.

"It is certainly true that the question as to the necessity of death in general does not seem much clearer from this point of view... It must be admitted that we can see no reason why the power of cell-multiplication would not be unlimited, and why the organism should not therefore be endowed with everlasting life" [2, I, p. 23].

So far "the existence of immortal Metazoan organisms is conceivable" [2, III, p. 148].

"If it was advantageous to the somatic cells to preserve the unending life of their ancestors — the unicellular organisms, this end might have been achieved, just as it was possible at a later period, in the higher Metazoa, to prolong both the duration of life and of reproduction a hundred- or a thousand-fold. At any rate, no reason can be given which would demonstrate the impossibility of such an achievement" [2, III, p. 142].

"It might well be imagined that in some organisms it would be a great advantage if every part possessed the power of growing up into the whole organism and of producing sexual cells under appropriate circumstances. Such cases might exist if it were possible for all somatic nuclei to contain a minute fraction of unchanged germ plasm" [2, IV, p. 215].

For example "certain plants can be propagated by pieces of rhizomes, roots or even by means of leaves" [2, IV, p. 215] [20]. Weismann cites

Sach's lectures on the physiology of plants "In the true mosses almost any cell of the roots, leaves and shootaxes and even the immature sporogonium, may grow out under favourable conditions, become rooted, form new shoots, and give rise to an independent living plant", and continues "Since such plants produce germ-cells at a later period, we have here a case which requires the assumption that all or nearly all cells must contain germ-plasm" [2, IV, p. 216].

To make evolutionary sense Weismann's theory has now to answer the question why did evolution not — at least not in general — succeed, figuratively speaking in constructing Metazoan bodies in which worn out cells in somatic tissues could be replaced by new ones without any limit so that the structural integrity of the tissue as a whole would be preserved in spite of the continuous death of cells in a certain stage of differentiation.

Weismann points out that any individual even if it would be endowed with the possibility of unending life "would sooner or later fall victims to some accidental death so that there would be no possibility of real immortality" [2, III, p. 155].

In many species "an accidental end is the rule and is therefore strictly speaking normal" [2, I, p. 22].

"There is no species of animal which is not exposed to destruction through various accidental agencies — by hunger or cold, by drought or flood, by epidemics, or by enemies, whether beasts of prey or parasites. We also know that these causes of death are only apparently accidental, or at least that they can only be called accidental as far as a single individual is concerned. As a matter of fact a far greater number of invividuals perish through the operation of these agencies than by natural death. There are thousands of species of which the existence depends upon the destruction of other species" [2, I, p. 11].

"The dependance of the duration of life upon the external conditions of existence is alike common to plants and animals" [2, I, p. 33].

"The duration of life in plants also is by no means completely fixed and ... may be very considerably altered through the agency of the external conditions of life ... In course of time, and under changed conditions of life, an annual plant may become perannual, or vice versa. The external factors which influence the duration of life are here, however, essentially different, as indeed we expect them to be, when we remember the very different conditions under which the animal and vegetable kingdoms exist" [2, I, p. 33]. It is a common-place that "the

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longest period of reproduction possible, when accompanied by very great fertility, is, as a rule, advantageous for the maintenance of the species" [2, I, p. 19].

"As soon as the long-lived individuals in a species obtain some advantage in the struggle for existence, they will gradually become dominant, and those with the shortest lives will be exterminated" [2, I, p. 20].

Whether an increase or even a decrease of the lifespan is favourable for a species depends on a number of factors which all affect the only currency of evolutionary success, the number of viable offspring. Weismann points out these factors: "We might accurately calculate the amount of increase which would be produced in any given case if the necessary data were available, viz. the physiological strength of the body, and its relations to the external world, such as, for instance, the power of obtaining food at various periods of life, the expenditure of energy necessary for this end, and the statistics of destruction, that is, the probabilities in favour of the accidental death of a single individual at any given time ... But we are still far from being able to apply mathematics to the phenomena of life; the factors are too numerous, and no attempt has been made as yet to determine them with accuracy" [2, III, p. 158].

These considerations show that "with every change in the structure of a species, and with the acquisition of new habits, the length of its life may, and in most cases must, be altered" [2, I, p. 20].

Weismann gives a great many examples to exemplify that the duration of life can increase or decrease during evolution [2, I, III]. While Weismann does not propose any common "death mechanism", he points out in a very general outline the possible course of a Darwinian evolution in producing Metazoans with a limited replicative lifespan of somatic cells. In his opinion, the same mechanisms are principally at work which he has described to explain a retrogressive development of organs, i. e., the action of panmixia plus natural selection. It is interesting to note that Weismann's considerations cited below contain the germs of an error theory [21].

"If then this real immortality is simply a cyclical movement conditional on certain physical properties of protoplasm, why should it be inconceivable that this property, under certain circumstances, should alter to some extent, so that the phases of metabolic activity should not exactly repeat themselves, but after a certain number of cycles should come to an end, resulting in death? All living matter varies, and why is it

inconceivable that variations of protoplasm should arise which, while fulfilling better certain functions advantageous to the individual, should be associated with a metabolism that does not exactly repeat itself a metabolism that sooner or later comes to a stand-still? To my mind the descent of the immortal to the condition of mortality, is less to be marvelled at than the fact that monoplastids and germ-cells have remained immortal. The slightest change in the properties of living matter might involve such a descent, and certain essential peculiarities in the composition of this substance must be most rigidly maintained, in order that the metabolic cycle may sweep on with perfect smoothness, and raise no obstacle against its own persistence. Even if we know nothing further of these essential peculiarities of structure, we may at least maintain that the rigorous and unceasing operation of natural selection is necessary to maintain them. Any deviation from this standard ends in death. I believe that I have shown that organs which have ceased to be useful become rudimentary, and ultimately disappear owing to the principle of panmixia alone, — not because of the direct effect of disuse, but because natural selection no longer maintains them at their former level. What is true of organs is also true of their functions; for function is but the expression of certain peculiarities of structure, whether we can directly perceive the connection or not. If then the immortality of unicellular beings rests on the fact that the structural arrangement of their substance is so accurately adjusted that the metabolic cycle always comes back to the same point, — why should, or rather, how could this property of the protoplasm, which is the cause of immortality, be retained when it ceased to be necessary? And clearly it is no longer of use in the somatic cells of heteroplastids. From the moment that natural selection relaxed its hold upon this property of the protoplasm, the power of panmixia began to be felt, and ultimately led to its disappearance ... Let us suppose that certain individuals appeared among the monoplastids with such variation of the chemical or molecular characters, that the continuous recurrence of their metabolic cycle came to an end, so that natural death became a necessity. These individuals could never give rise to a persistent variety. But if individuals with a similar variation in their somatic cells arose among the heteroplastids, no detriment would be felt by the species: the body-cells would indeed die, but the undying germ-cells would secure the continuance of the species. By means of the distinction between somatic and germ-cells, natural selection was enabled to direct its attention, to speak metapho-

rically, to the immortality of the germ-cells, and to an entirely different range of properties among the somatic cells, such as the capacity for movement, irritability, increased powers of assimilation, &c. &c. We do not yet know whether an increase in these properties is directly connected with a change of constitution involving the loss of immortality, but it is not impossible that this may be the case; and, if so, the somatic cells would have ceased to be immortal more quickly than if panmixia were the only agency at work" [3, XI, p. 75—77].

"With our inadequate knowledge it is difficult to surmise the immediate causes of such a selective process. Who can point out with any feeling of confidence the direct advantages in which somatic cells, capable of limited duration, excelled those capable of eternal duration? Perhaps it was in a better performance of their special physiological tasks, perhaps in additional material and energy available for the reproductive cells as a result of this renunciation of the somatic cells; or perhaps such additional power conferred upon the whole organism a greater power of resistance in the struggle for existence, than it would have had, if it had been necessary to regulate all the cells to a corresponding duration" [2, III, p. 142].

"I have adduced in my fourth essay the cases of the Volvocinean genera, *Volvox* and *Pandorina,* as examples of the differentiation of the lowest heteroplastids from the homoplastids. All the cells of *Pandorina* are similar and perform similar functions. *Volvox,* on the other hand, consists of somatic and germ-cells, and it is here that we should expect the introduction of natural death. Dr. Klein's recent observations [22] show that this, as a matter of fact, takes place: as soon as the germ-cells are matured, and have left the body of the Alga, the flagellate somatic cells begin to shrink, and in one or two days are all dead. This is all the more interesting because the somatic cells fulfil nutritive functions for the aggregate. It is true that they are not alone in performing the office of assimilation, for the germ-cells also contain chlorophyll; but the immense size which the latter attain in *Volvox* can only be explained on the supposition that they receive nutriment from the somatic cells. These cells are so constituted that they assimilate, but when once the spherical colony has attained its definite size they have ceased to grow. By means of a fine protoplasmic network the body-cells pass on to the germ-cells all the nutriment they acquire from the decomposition of carbon dioxide and water, and when the reproductive cells are mature they die. In this case adaptation for supplying nutriment to the germ-

cells may have hastened the introduction of death among the somatic cells, inasmuch as some structure may have arisen in the latter which rendered possible more energetic assimilation, but which was accompanied by an expenditure of nutriment, and which, after the lapse of a certain time, involved the complete cessation of assimilation, and consequently the death of the organism.

The conception of a change in the protoplasm which involves the loss of immortality is to my mind no more improbable or more difficult than the commonly received view of the differentiation of somatic cells which gradually takes place in their phylogeny, by which they are enabled to assume various natures, i. e. absorption, secretory, muscular, nervous, etc. An unchangeable immortal protoplasm does not exist, only an immortal 'form or activity' in organic matter" [3, XI, p. 78].

5 CONCLUSION

According to Weismann natural death has evolved as an interplay between panmixia and natural selection. He has founded the hypothesis that unequal divisions of cells appear in multicellular organisms resulting in one daughter cell which retains an infinite replicative lifespan, while the replicative lifespan of the other daughter cell becomes finite. The separation of the immortal germ line and mortal somatic cell lines should be brought about by such unequal divisions. Weismann's theory does not exclude, however, the possibility that somatic stem cells with an infinite replicative lifespan exist for example in plants and possibly also in certain tissues of animals. Since germ cells are produced at the end of ontogeny in higher plants, each cell of the adult plant organism still contains a minute fraction of germ plasm according to Weismann's terminology and is potentially immortal. The maximum replicative lifespan of somatic cells is open to the influence of natural selection plus panmixia and can be increased or decreased by this influence. It is evident that this influence differs with the position of cell types in the cell-republic of the Metazoan body. As long as the conditions necessary for a potentially infinite replicative lifespan of certain cells are of selective value for a species, these conditions are maintained by natural selection, otherwise they are lost by panmixia.

Medawar has noted that "evolutionary advancement is a compromise between what is desirable in the abstract and what can in fact be done; that the lesser evil must be put up with if it makes possible the greater

good" [9]. Since the interplay between panmixia and natural selection is open to countless variations the compromise by which evolution of natural death was brought about may differ and a variety of cellular and molecular mechanisms which lead to natural death may be expected in the animal and plant kingdom.

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