it is not necessary to refer again to the matter, since the only unity of measurement we need keep in mind is the *wave-length*. The unit commonly used for measurement of the wave-length is the Greek letter for "m" (or micron)—μ. This signifies the millionth part of a metre, or the thousandth part of a millimetre (equals 0.-0393707904 in.); it is also called the micro-millimetre, or, shortly, mm. Thus, using round numbers, the wave-lengths of the visible spectrum extend from 0.400 μ to 0.800 μ. Or, using the milli-micron (or 1/1,000th of a micron), which is written as mμ or $\mu\mu$, the wave-lengths extend from 400 $\mu\mu$ to 800 $\mu\mu$.

To avoid decimals altogether in dealing with these extremely minute fractions, one frequently sees them expressed in Angstrôm Units. The A.U. is one-ten-millionth part of a millimetre, so all that is required is to multiply the micron by 10,000 or the milli-micron by 10; thus, 0.400 μ becomes 4,000 A.U. and 0.800 μ becomes 8,000 A.U. For practical purposes this is most convenient, and in this series of articles, unless otherwise stated, Angstrôm Units will be used to express the wave-lengths.

Before proceeding further it may be advisable in this connection to define briefly a few other units which will crop up later, *viz., ampères, volts, ohms and watts.*

Before giving any scientific definitions, one may translate these terms into popular language by using the analogy of the gas meter. In this way you can speak of the number of ampères as the amount of electricity passing through a meter; the number of volts, as the pressure or strength of the current; and of ohms, as the resistance to be overcome by the current in passing through various substances, such as conductors or wire, etc. In terms of gas, it means the friction of the gas on the pipes and round the many corners and angles through which it must pass. A watt, on the other hand, is really a *unit of energy;* and to continue our analogy of the gas, it may be defined as the amount of energy developed by a certain amount of current expressed in ampères (or cubic feet of gas) at a certain voltage (or pressure), and is therefore the product of these two.

In the next communication these units will be illustrated by reference to numbers.—*The British Journal of Actinotherapy*, January, 1928; Vol. II; 196.

THE IMMORTALITY OF ANIMAL TISSUES AND ITS SIGNIFICANCE*

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The body, as is well known, consists of myriads of cells organized as a harmonious whole. Since these cells are submitted to the rules of a disciplined community, they cannot display all their possible activities. Most of their potentialities remain virtual in normal life. It is during the development of pathological processes that they become actual. They are doubtless responsible for a number of important phenomena, such as inflammation, malignant tumours, wound-healing and others. This train of thought led me, more than sixteen years ago, to study the hidden powers of animal tissues. The surgical methods that I used at the beginning of this investigation soon proved to be inadequate. Fortunately, Harrison published at this time his well-known experiments on the survival *in vitro* of fragments of frog embryos, and demonstrated that tissue cells completely separated from the organism could multiply for a few days. His work was the starting point of the elaborate procedures that I have developed for obtaining pure strains of various cell-types, cultivating them in media of known chemical composition, measuring their rate of growth, etc. Through these methods, it became possible to observe under ideal conditions the fate of animal tissues when they are liberated from the restraint of the body.

The first experiment that gave a decisive result was undertaken on January 17, 1912. Several minute fragments from the heart of a chick embryo were cultivated according to a technique similar to that of Harrison. The bits of tissue went on pulsating and surrounded themselves with connective-tissue cells. But after a few days, pulsations and cell-migration ceased. Degeneration was imminent. An attempt was then made to prevent death by removing the waste products from the cultures. For this purpose, the tissues were thoroughly washed by placing them in a saline solution, and transferred into a fresh medium. Immediately, the heart tissue began pulsating again, and the cells migrated. This treatment was repeated every few days, and the little heart-fragments continued living and beating. However, they did not increase in size. On the contrary, they progressively diminished and faded away, or were killed by bacterial infection. Only one extremely minute fragment of heart remained alive and pulsating. But it was much smaller than a pin head, and could not have failed to disappear within a few days. Then, a drop of embryonic tissue juice was added to the medium. A truly wonderful effect was immediately observed. Fibroblasts began to multiply about the tiny pulsating heart muscle, which was soon surrounded by a large amount of tissue in which it disappeared. The tissues went on growing and could be divided into two parts, which also grew rapidly. Every forty-eight hours, the cultures were washed in Ringer solution by Ebeling or myself, divided into two parts, and cultivated again in embryonic juice. To-day, hundreds of experiments are made every month with the pure strain of fibroblasts descended from the tiny fragment of pulsating tissue that I possessed in 1912. The

* Abstract of an address given at the Third Race Betterment Conference, on Jan. 2-6, 1928, at Battle Creek, Michigan.

colonies are cultivated in flasks with an oblique neck, which protects them from bacterial infection. They grow in a solid medium composed of diluted plasma. This medium is frequently washed in Tyrode solution. On its surface, some embryo juice or other substances used as a nutrient medium, are injected every two or three days. The rate of growth is ascertained by the increase of the area and volume of the colonies. We are entitled to consider the experiment as almost concluded, as it has lasted for a period of nearly sixteen years. Two important facts have been brought to light.

1. The fibroblasts derived from the original heart fragment manufacture large quantities of new tissue from the substances contained in the culture medium. In forty-eight hours, each cell of a colony seems to divide twice, and the colony doubles in volume. Had it been possible to keep all the cells which could have been produced during these sixteen years, their mass would be immense. A colony, originally one cubic millimetre in volume, would produce approximately one cubic centimetre of tissue in about twenty days. After sixty days, the volume of the tissues would be a little more than one cubic metre, and in less than one hundred days, one million cubic metres. It is obvious that tissues growing at this rate for sixteen years would reach a volume greater than that of the solar system.

2. Cell-proliferation is unlimited in time. Today, the rate of growth of the strain of fibroblasts is as great as it was fifteen years ago. The curve representing the variations of the growth velocity during this long period is parallel to the time axis. Time has no action whatever on these tissues. They are immortal.

This property also belongs to other tissues, as was shown by Fischer for iris epithelium, and by Ebeling for thyroid epithelium. Cultures of such tissues have been kept in full activity for several years in my laboratory. Normal and malignant cells of rats, mice, guinea pigs, and human beings were also discovered to be potentially immortal. Although the constituent cells of certain organs, such as the brain, lived *in vitro* only for a short period of time, animal tissues in general must be considered as capable of unlimited proliferation, in time as well as in space.

These facts are of profound significance. They demonstrate not only that tissue cells are endowed with potentialities far greater than they display within the body, but also that these potentialities become actual under definite conditions, *i.e.*, the elimination of certain metabolic products, and the presence of proper nitrogenous food.

It is obvious that the immense capacity for growth possessed by tissue cells must be kept under restraint while these cells live as parts of the organism. If the tissues of an adult animal suddenly were allowed to multiply freely, the body would grow in a rapid and disordered manner, and death would soon occur. Active proliferation of its constituent cells would at once stop the functions of any gland. It is easy to imagine what would become of our memory and personality if the pyramidal cells started to multiply and to disturb the infinite complexity of the association fibres of the cerebral centres. Normal life and anarchical tissue growth are incompatible. The mechanism that causes tissues to be comparatively at rest when they live within the body becomes less obscure after some fundamental properties of these cells were discovered. We found that, if fibroblasts and epithelium are given certain nitrogenous substances, they are compelled to multiply. The substances endowed with the marvelous property of determining cell-proliferation are embryonic proteins, and polypeptids resulting from the digestion of a number of proteins. It is the concentration of such substances in the medium that regulates growth energy. On the contrary, cell multiplication is inhibited by blood-serum. This effect increases gradually with the age of the animal. The substances responsible for this phenomenon are lipoids, as was shown by Baker and myself. In the light of this new knowledge, it becomes entirely probable that the resting condition of adult tissues depends on the composition of the humours in which they are immersed. The cells are like a motor which stops when the fuel is exhausted, and starts again as soon as the combustible is replenished. When inert fibroblasts are extirpated from an old animal and cultivated *in vitro*, they do not display any growth energy. But as soon as they are given embryonic proteins, they multiply again. The factors that prevent tissue cells from manifesting their potentialities during normal life are chiefly a scanty food supply and an inhibiting medium.

The actualization of these potentialities takes place only under the influence of pathological processes, such as skin regeneration, bone-repair, or the growth of a cancer. If tissue cells were not potentially immortal, there would be no cancer. Also surgery would be impossible. Wound-healing and tumour-formation depend entirely on the capacity of adult cells to recuperate their embryonic proliferative activity. In the repair of a wound, leucocytes attracted to the site of injury manufacture directly or indirectly the substances that determine the multiplication of fibroblasts and epithelial cells. If they are prevented from coming, no cicatrization takes place. The growth of cancer is due to the special properties of malignant cells. These cells have the power, through the secretion of proteolytic ferments and acid formation, of producing substances which automatically compel them to multiply in an unlimited manner. In most of the cases, a resumption of cell activity within the adult organism must be attributed to the presence in the tissues of embryonic proteins or of polypeptids.

Although the body is composed of elements that are potentially immortal, it is, and will always be, subject to senility and death. Cells living as part of an organized community do not find in such an environment the conditions required for immortality. The only living forms enjoying eternal youth are the colonies of unicellular organisms which eliminate their metabolic products directly into the outside world. When an animal is composed of a mass of cells organized as a closed system, the process of aging necessarily takes place. Immortality is incompatible with organization. But organization is necessary for the development of a highly differentiated nervous system and for the appearance of mental processes. Death is the price we have to pay for the possession of our brains. This price is not excessive, because the mysterious energy which is created by the cerebral cells, or expresses itself through them, is after all the greatest marvel of this universe.

In spite of the fact that higher animals will never reach immortality, there is some hope that the duration of their life may be artificially increased. The solution of this problem, as well as of the far more important one of improving the quality of living beings, rests on the future progress of cell-physiology and of the chemistry of nutrition. It is for this reason that I have considered it appropriate to lay before the members of this conference the results obtained by one of the most powerful methods created for the investigation of cell-functions. Through these experiments the immortality of animal tissues, and some of their fundamental properties, have been revealed to us. For the present, these findings are only of theoretical interest. But we know, as Claude Bernard has aptly said, that the knowledge of nature always leads to its mastery

THE EARLY DIAGNOSIS OF TUBERCULOSIS

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The title above is not at all synonymous with "The diagnosis of early tuberculosis." When we can make a diagnosis of tuberculosis recently acquired, having a clinical form which renders it obvious and important, the patient is likely to be already past help, as in the acute miliary disease.

One should recognize that latent or occult tuberculosis may form a background in many, if not most, constitutional disorders. For example, there seems to be some relation between tuberculous infection and endocrine disorders, particularly as they affect the thyroid gland. In this and similar fields definite search for evidence of tuberculosis should not be neglected; for the fact that there are no symptoms of clinical tuberculosis does not imply that latent foci of this disease may not be wielding constitutional effects which modify the vital reactions of the body, not to speak of the possibility of their acquiring activity under appropriate conditions.

The writer makes bold to lay down the proposition that the important practical aspect of tuberculous infection is its functional and not its organic relations. We have laboriously learned the same truth in our study of heart-disease, which is wonderfully similar to tuberculosis in its pathological economy; structural defects of the heart interfere but little with efficiency under conditions which do not overstrain compensation.

When tubercles are actively forming, or when a sufficient number of tubercle bacilli are breathing and feeding and disintegrating in the body, the poisoned host manifests the familiar signs and symptoms of active tuberculosis. We know from laboratory studies that different strains of human tubercle bacilli may vary enormously in their virulence or aggressive properties on inoculation. We know also that different species of animals inoculated from the same bacillary culture respond very differently in the extent and intensity of disease produced, or may not respond at all. Clinical evidence leads to the conclusion that both these factors, the virulence (and the quantity) of the bacilli introduced, and the specific resisting power, or immunity, of the host, are the vital factors in every case of human tuberculosis. With these facts in view, a consideration of the numerical factors involved in the problem makes it very probable that in human tuberculosis, by and large, we should be justified in expecting that the distribution of tuberculous infection should be included within the following three groups:

1. Here, the power of the bacillary invader (due to the number, the virulence, or the situation of the germs) is overwhelming as compared with the resistance of the host. This is a very small group with complete and speedy fatality.

2. A group which includes nearly all the cases we commonly recognize as "clinical tuberculosis." Here, the ratio, infection-resistance, is labile and variable, and is distinctly under the control of environment in its broadest sense, including behaviour. Inadequacy of environment has usually allowed extensive propagation of the disease antecedent to its discovery.

3. Our *a priori* classification would relegate to the third group the great majority of the subjects of tuberculous infection. Here the relative vital properties of soil and seed are mutually inhibitory; we may suspect that the struggle between the living bacilli and the equally living tissues results in a truce, wherein, *though there is destruction of neither, there is deterioration in both.*

The foregoing discussion has been elaborated as an interpretation of the writer's actual clinical studies. A huge proportion of our medical clientèle is distinguished by the lack of physical signs leading to specific diagnosis. Symptoms are negatively present, for the patient's lack of power is conspicuous by its absence, and the general practitioner is apt to satisfy himself with the word "neurasthenia." Of course, general nervous stability may be modified or undermined from many directions. Septic absorption from the tonsils or teeth, or elsewhere, may paint a picture duplicating any in our gallery. Hyperthyroidism and, more especially, hypothyroidism,