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THERAPEUTIC USES OF YEAST
NUCLEINIC ACID, WITH SPECIAL
REFERENCE TO ITS EMPLOYMENT IN
TUBERCULOSIS. REPRINTED FROM THE
MEDICAL NEWS, FEB. 27, 1897**

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THE PHYSIOLOGICAL ACTION AND THERAPEUTIC USES OF YEAST NUCLEINIC ACID, WITH SPECIAL REFERENCE TO ITS EMPLOYMENT IN TUBERCULOSIS.¹

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Nucleins and Nucleinic Acids.—I have elsewhere spoken of nucleins as follows: "Physiologically, nucleins may be said to form the chief chemical constituents of the living parts of cells. Speaking broadly, we may say that the nuclein is that constituent of the cell by virtue of which the histological unit grows, develops, and reproduces itself. It is the function of the nuclein of the cell to utilize the pabulum within its reach. It must be evident that those tissues most abounding in cellular elements contain relatively the largest amount of nuclein. It must also be seen that it is by virtue of their nuclein that the cells of various organs and organisms possess and manifest their individual peculiarities. We should, therefore, expect to find that the nuclein of the yeast cell is not identical with that of the bacillus tuberculosis, and that the nuclein of the spleen differs from that of the thymus gland. The number of kinds of nuclein is limited only by the variety of cells. Nuclein is the chemical basis of that part of the cell

¹ This paper contains the material used in special lectures delivered to the students of the Department of Medicine and Surgery of Michigan University, November, 1896.

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designated by the histologist as the nucleus, sometimes called chromatin on account of the readiness with which it absorbs and holds coloring agents. It is the nuclein of the bacterium which takes up and retains stains, and it is on account of the fact that the nuclein of the bacillus tuberculosis differs from that of other bacilli that we are able to distinguish the former from the latter by its tinctorial properties. Differences in reaction with staining agents so plainly seen under the microscope are only outward manifestations of less apparent and more important differences in chemical composition.¹

Chemically, the nucleins are complex, proteid bodies, especially characterized by the large amount of phosphorus which they contain. Nucleins can be split up by the action of dilute mineral acids into albuminous bases and nucleinic acids. The nature of the base and the acid obtained in this way will vary with the nuclein in which they originate. Yeast nuclein differs in both its basic and its acid constituents from leuco-nuclein as obtained from the thymus gland. The nucleinic acids on being further broken up by the action of dilute mineral acids yield the so-called xanthin bodies, and here again it is true that the products obtained will depend upon the kind of nucleinic acid acted upon. One nucleinic acid may yield only adenin, and for this reason it may be designated as adenylic nucleinic acid, while another may furnish xanthin abundantly, possibly to the exclusion of other bases, and this may be termed xanthylic nucleinic acid. Kossel has demonstrated some

¹The Nucleins and Nuclein Therapy; Annual Address on Medicine. Transactions of the Michigan State Medical Society, 1894.

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of the chemical differences between nucleic acids from diverse sources. Yeast nucleic acid yields, on being broken up by the action of dilute mineral acids and heat, guanin and adenin; while testicular nucleic acid furnishes adenin, hypoxanthin, and xanthin; and thymus nucleic acid gives adenin only. These are what might be called gross differences. It is probable that finer distinctions exist between members of the same group. I have frequently observed that different samples of yeast vary not only in the amount of nucleic acid yielded, but that the products differ in the intensity of their germicidal action. Of course this may be due to differences in other constituents of the yeast cells, and the greater or less difficulty of obtaining the nucleic acid in an approximately pure condition. In the first year of my work on this subject I used baker's compressed yeast, and sometimes I wholly failed to obtain a nucleic acid with distinct germicidal properties, while at other times the result was quite satisfactory, although at no time did I secure a product equal in germicidal strength to that subsequently prepared from pure cultures of brewer's yeast. It is within the range of possibility that by an investigation of the different varieties of yeast cells and with due attention to the conditions under which the cells are grown, we may secure not only a richer yield of nucleic acid, but an acid of greater germicidal strength.

The difference in chemical composition and in germicidal action between nucleic acids from different kinds of cells is, in some instances at least, accompanied by differences in physiological action.

Thus, while Lillienfeld¹ has found that thymus nucleic acid coagulates the blood when injected intravenously in certain quantities, it will be shown in this paper that a much larger per cent. of yeast nucleic acid may be injected intravenously without any such effects.

Certain substances which are histologically and functionally nucleins do not yield any xanthin base as a decomposition product. These are called par-nucleins. Some of these are antecedents of true nucleins. Thus, the yolk of the egg contains a par-nuclein, which may be isolated by removing the accompanying proteids by peptic digestion. This substance does not yield a xanthin base, but during the process of incubation it develops into a true nuclein.

Generally speaking, nucleins and nucleic acids are insoluble in dilute acids and soluble in dilute alkalies. They are insoluble in alcohol. The last mentioned fact has not, however, prevented the quite extensive employment by the profession of alcohol said to contain nuclein. It is needless to say that any beneficial effects obtained by the use of this preparation should be attributed to alcohol and not to nuclein. The terms "nuclein" and "nucleic acid" are frequently used interchangeably. In fact, it is by no means always easy to determine whether in a given kind of cell the nucleic acid exists free or combined with some basic substance; and it is extremely difficult to obtain the nucleic acid in any quantity wholly free from albuminous substances, and as nucleic acid combines with any albuminous sub-

¹ *Ueber Blutgerinnung Zeitschrift f. physiologische Chemie*, B. 20, S. 89.

stances present, the chemist is by no means always certain which of the terms "nuclein" or "nucleinic acid" will the more honestly fit a given product.

Pure yeast nucleinic acid contains about nine per cent. of phosphorus. While a small quantity can be prepared in a sufficiently pure state to yield this amount I have so far found the preparation of such a pure article in quantities large enough for any extensive physiological experimentation or therapeutical use impracticable. The purest nucleinic acid which has been used in the work detailed in this paper contains a fraction less than seven per cent. of phosphorus.

The Theory upon which these Studies of Nucleinic Acid have been Based.—The working hypothesis which I developed in beginning my researches on the nucleins, and which may be found in my address before the Medical Section of the first Pan-American Medical Congress,¹ may be condensed to the following propositions:

1. The phagocytic theory of Metschnikoff, in so far as it teaches that the polynuclear white blood-corpuscles are active agents in preventing or retarding the multiplication of pathogenic germs in the body, is true.

As Metschnikoff has stated, there is no claim that there are not other agents which may also combat the progress of disease.

2. The polynuclear corpuscles do not eat the bacilli, but they destroy the germ by virtue of the chemical action of some constituent or secretion.

¹ "The Principles of Immunity and Cure in the Infectious Diseases." Transactions of the first Pan-American Medical Congress. Vol. 1, p. 152.

3. The germicidal properties of blood-serum, demonstrated by the researches of Fodor, Nutall, Buchner and others, are due to a substance, or to substances, that originate in the polynuclear white blood-corpuses.

4. The natural resistance of the body to bacterial disease will be strengthened by a physiological increase in the production of polynuclear white blood-corpuses.

5. This increase in the polynuclear corpuses may be induced by introducing into the animal the most distinctive constituent of these cells, which is nuclein.

The foregoing statements were formulated in 1891 and I then began my studies on nuclein from yeast and from certain animal glands. In 1892 the first experiments were made on healthy and tuberculous guinea-pigs, and in May, 1893, tuberculous patients were treated for the first time with this agent.

The Germicidal Action of Nucleinic Acid.—In May, 1893, a paper by Novy, McClintock, and the writer,¹ detailed experiments by which we demonstrated the germicidal action of testicular, thyroid, and yeast nucleins upon bacillus venenosus, staphylococcus pyogenes aureus, and albus, and bacillus anthracis. Additional details of similar experiments were given in the address read before the Medical Section of the first Pan-American Medical Congress, already referred to. The paper by McClintock and myself² read before the same congress, demonstrated

¹ The Germicidal Properties of Nucleins. MEDICAL NEWS, May 30, 1893.

² The Nature of the Germicidal Constituent of Blood-serum." Transactions of the first Pan-American Medical Congress. Vol. 1, p. 238.

that the germicidal properties of blood-serum are due to the presence of nuclein. In February, 1894, Kossel¹ published a paper which confirmed our results.

It is unnecessary to go into any detailed statement concerning the germicidal action of yeast nucleinic acid at this time, as any one desirous of doing so can consult the publications referred to. There is, however, one point which seems to me to be of special importance, in view of certain recent German investigations. While yeast nucleinic acid is a powerful germicide, it is not equally potent with all kinds of bacteria. Indeed, there are some germs on which this acid can scarcely be said to manifest a germicidal effect. This is true of certain putrefactive germs. This is of interest, in view of the discovery of Pfeiffer,² that the blood-serum of an animal, immunized against a specific bacterium, becomes decidedly more germicidal to that germ than to any other. This discovery is now being utilized in attempts to distinguish the typhoid and cholera bacilli from others which closely resemble them morphologically and tinctorially. It would seem from this that the germicidal constituent of the blood-serum can be trained to act more energetically upon a given bacillus. Pfeiffer states that the germicidal constituent of the blood-serum of his immunized animals is not a nuclein, and this makes the fact that yeast nu-

¹ "Weitere Beiträge zur Kenntniss der Nucleinsäuren," *Archiv. f. Anatomie und Physiologie, Physiologische Abtheilung*, 1894, S. 194.

² "Ein Neues Grundgesetz der Immunität." *Deutsche med. Wochenschrift*, 1896, S. 97. Also, *Zeitschrift f. Hygiene und Infectiouskrankheiten*, B. 20.