Comments and Communications

Ground Substance of the Mesenchyme and Hyaluronidase: A Symposium[1]

The most salient characteristic of this symposium was that of unity underlying a great variety of subjects. For whatever success it achieved was due to the excellent contributions of workers from such diverse fields as chemistry, enzymology, histology, physiology, bacteriology, pharmacology, and clinical medicine. All contributions were fundamentally interested in an enzyme-substrate reaction taking place in the ground substance of the mesenchyme. This was, until recently, an almost abstract conception which now has become a well-defined entity, studied from every angle.

During the last twenty years, catalyzed by the discovery of the spreading factors and important advances in the chemistry of polysaccharides, and through the efforts of many investigators, the newer knowledge of the ground substance has come into prominence. The identification of hyaluronic acid, a component of the ground substance and the substrate upon which some of the spreading factors act, placed a number of these spreading factors in the category of enzymes. In the interim, independent workers studied with excellent results the morphology and physiology of interfibrillar structures. From these contributions, as coordinated in the conference, the ground substance emerged as a coherent unit which, although a part of all organs and tissues, has its own physiognomy and functions; and knowledge thereof appears indispensable for a full understanding of many physiological and pathological phenomena.

The conference was planned and developed along the lines that would seem to be the logical ones to follow in the discussion of a medical subject; that is, it began with chemical and morphological data, passed from this into physiological and pathological subjects, and ended with the clinical applications. Needless to say, this was not the chronological order in which the topics discussed have been studied, since progress in some frequently has been the result of what was already known of the others. As a matter of fact, it was quite revealing in respect to the unity of the symposium that in the great variety of excellent contributions authors rarely kept strictly to specialized fields; cross references were thus numerous and yet discrepancies were minimal.

The first section dealt with fundamental data on the ground substance of the mesenchyme and thoroughly covered the subject. K. Meyer, the chairman, gave a lucid preliminary survey of the mucopolysaccharides of the interfibrillar substance of the mesenchyme. He presented data on the state of hyaluronic and chondroitin sulphuric acids in tissues, and on the physical and chemical properties of these acids. These observations were complemented and extended by the electron microscope studies of Gross, who gave visual representations of the components of the ground substance. Alburn and Williams discussed sources and preparation of hyaluronic acid. A number of histochemical contributions followed. They comprised general studies of the mucopolysaccharides in a great variety of tissues (Bunting, McManus); of the changes in cells and intercellular substances after injection of testicular extract (Bensley); and of comparable changes following inoculation of gonadotropic hormones, and occurring in some pathological conditions such as cancer (Catchpole). It was revealed by these studies that the ground plasm is a dynamic system, changing continuously under the influence of a great variety of factors. In addition, these contributions paved the way for a clearer understanding of the physiological condition existing in the ground substance of the connective tissue. McMaster described it as a viscid medium through which the movement of matter takes place. The section ended with papers dealing with the accumulation of hyaluronic acid in the skin under two extreme conditions of hormone stimulation: in the pretibial edema of Grave's disease (Watson and Pearce); and in the sex skin of monkeys (Duran-Reynals, Bunting, and van Wagenen).

The next section was concerned with the permeability of the ground substance in infection and other conditions. D. H. Sprunt was chairman. The section opened with discussions by Dorfman, Meyer, and Tolksdorf, *et al.* on *in vitro* effects of hyaluronidase. The different modes of action of the enzyme, depending on the linkages of the molecule of the substrate, and the kinetics and specificity of the reactions were reviewed, and the need for establishing a hyaluronidase unit was emphasized. This was followed by a general discussion by Hechter on spreading factors and their mechanism of action, in both the living and the dead animal. The presence of hyaluronidase in inflamed skin was described by Meyer. The importance of bacterial enzymes acting on digestive tract and respiratory mucins (Burnet) was reviewed briefly by Briody. An interesting discussion developed concerning the effect of preparations containing hyaluronidase and other enzymes on the permeability of blood vessels, opposite views being maintained by Zweifach and Chambers on the one side, and by Elster on the other.

With all of these contributions as a background, the conference entered into the important field of the ground substance in infection. A general survey of the subject, covering the effects of mucolytic enzymes, of hydration and dehydration, and of hormones and other agents on the ground substance was given by Sprunt, and Opsahl, White, and Duran-Reynals. This was followed by contributions by Sallman and Birkeland, and by Pike on the production of enzyme and substrate by streptococci, and the meaning of these phenomena in infection. The concept emerged that infection is closely conditioned by a variety of physiological factors which find a direct ex-

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pression in the permeability of the ground substance. Fluctuations in this permeability result in corresponding fluctuations in the severity of the infectious process. Estrogens and gonadotropic and adrenocortical hormones are especially potent in this connection.

The same general topic on the permeability of the ground substance in infection was continued in the following section. M. Lurie, section chairman, gave an excellent general discussion of the mechanisms affecting spreading in infection, particularly in tuberculosis, in which connection he reported his studies on the paramount influence of constitution, sex, hormones, and still other factors on the disease. After this there followed a series of papers on that puzzling phenomenon of the inhibition of hyaluronidase by blood serum (Dorfman, Hadidian), and on the action of antibodies against streptococcal hyaluronidase (Friou, Quinn), which has proved to be an excellent diagnostic aid in streptococcal infections. The newer theories concerning the possible role played by the streptococcal enzyme or substrate in the pathogenesis of rheumatic disease were discussed. The subject was developed by Ragan and Meyer and discussed by Harris. Facts of great interest emerged in the discussion of this controversial subject—e.g., on the condition of the synovial fluid and the variations in the blood inhibitor for hyaluronidase in rheumatic disease.

In the field of cancer, promising results were reported by Simpson on the influence of hyaluronidase in malignant invasion of tissues, and by Fulton, Marcus and Robinson on an inhibitor for the enzyme found in cancer patients. These studies should be correlated with those of Catchpole, in the first section of the conference, concerning the water solubility of components of the ground substance around malignant growths. Another contribution by Anigstein described curious effects on typhus infection by antiorgan sera.

The last section was devoted to pharmacology and the practical applications of hyaluronidase. J. Seifter, chairman, reported results of his extensive studies on the enzyme, which he found to be pharmacologically nontoxic, and considers the perfect adjuvant, since it enhances the diffusion and thus speeds up the action of a variety of therapeutic agents. Warren and Burket and Gyorgy demonstrated the innocuousness of the enzyme in the case of established infection, in animals and humans respectively. Other authors reported the increased therapeutic effects obtained when hyaluronidase was added to local anesthetics (Kirby, Looby and Elkenoff); to penicillin (Sneierson); and to fluids used in hypodermoclysis (Burket and Gyorgy). The latter authors also reported comparable effects when the enzyme was added to dyes injected subcutaneously for diagnostic purposes.

The beneficial effects of hyaluronidase in some cases of human infertility as reported by Kurzrok offer the only instance of a direct therapeutic effect of the enzyme. To this one could perhaps add its dissolving action on renal calculi, as reported by Simon and Sussman. The effects on fertilization in men and cattle appeared to be a rather controversial subject, as discussed by Sallman and Birkeland and by Chang and Werthessen. The conference ended with these papers.

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Correction

My communication "Note on the Chemistry of Dramamine" (*Science*, 1949, **109**, 574) should have made it clear that the name "Dramamine" applies to the *salt* of β-dimethylaminoethyl benzohydryl ether with 8-clorotheophyllin. As it stands, the first sentence in the second paragraph of my note makes it appear that Dramamine is the ether alone, and that is incorrect.

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Book Reviews

Dentistry in public health. (Prepared for the Dental Health Section of the American Public Health Association.) Walter J. Pelton and Jacob M. Wisan. (Eds.) Philadelphia: W. B. Saunders, 1949. Pp. xi + 363. (Illustrated.) $5.50.

This book presents an unusually fine compendium of dentistry's role in public health. The collaborators have presented good summaries on the topics assigned to them. These summaries, although they are brief, contain the fundamental information which the student or the practitioner needs to develop his thinking in terms of public health service.

The extent of the dental health problem is fully outlined. The great number of people who need dental services, the time it takes to perform these services, and the limited dental man power add greatly to the complexity of the situation and cost of service.

The need for reparative as well as preventive and control service is stressed. Reparative service needs to be thought of as an initial service to care for possible accumulated neglect, and a maintenance service—suggesting regular periodic checkup and care after the initial service has been rendered. This makes the dental health problem a different one from others. The book offers a vast amount of information that should be of special interest to those in the field of dental health.

The role of nutrition and diet is discussed, as well as desirability of laboratory tests to evaluate oral conditions and caries activity. The effect of fluorine in water supply is well presented and indications are that this technique may become an effective agent in the control