Studies of the possible effectiveness of #863 in the treatment of human patients infested with the filariae of *Wuchereria bancrofti* have been initiated through the facilities afforded us by the School of Tropical Medicine, San Juan, Puerto Rico.[5] The drug was administered to 27 patients, using various intravenous dosage regimes, without manifestations of systemic toxicity other than transient mild hypotension and tachycardia of no clinical significance. Since the drug usually does not cause an immediate disappearance of microfilariae, in either cotton rats or man, studies of the peripheral blood may be required for many months in order to determine whether sterilization or death of the parent worms has been accomplished.

[5] We are greatly indebted to the director, P. Morales-Otero, for many courtesies; to José Oliver-González, who procured the patients and gave us constant help; and to F. Hernández-Morales, D. Santiago-Stevenson, and Ramón Suárez, Jr., for their clinical aid and excellent cooperation.

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Nomenclature of Parenteral Proteases

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RECENT INTEREST IN CERTAIN PROteases, which participate in blood coagulation (*5*, *21*) and indirectly related proteolytic phenomena, e.g. fibrinolysis (*3*, *16*, *19*), has run into a confusion of nomenclature which should be settled by general agreement. The story of the *parenteral* proteases and fibrinolytic phenomena was fully reviewed in the monumental work of Oppenheimer (*18*), whose classificatory principles have been widely accepted, with some more modern modifications.

PROTEASE, in the broadest sense, refers to all enzymes associated with protein hydrolysis. PROTEINASE is a general term appropriately used when the substrate is the whole protein molecule. Owing to multiplicity of substrates, enzymes acting under this head must be subclassified, empirically, under such generic terms as (1) *peptases*, (2) *cathepsins* (which has largely replaced the older term, ereptases), and (3) *tryptases*, for the three most common types of animal origin; and (4) *papainases*, for an important group of plant proteinases. It is distinctly intended that these terms group together enzymes on the basis of certain similarities, in the case of the first three, to the well-known alimentary prototypes, pepsin, erepsin, and trypsin(s), *disregarding* differences in origin and certain other differences, e.g. in mode of activation, inhibition, substrate specificity, stability, purity, etc. Even pH optima are currently minimized, as chiefly a matter of protein stability and purity. The recent identification of certain proteinases as crystalline proteins (*17*) and the newest means of testing on pure synthetic polypeptide substrates (*1*) are steps toward characterization of a few of these enzymes by their chemical specificity, in terms, for example, of certain linkages in the substrate molecule. The crystalline enzymes thus studied, however, show multiple points of attack on the protein (polypeptide) molecule. Hence, this approach is more successful as a basis for identification of the *individual* enzymes than as a means of classification (cf. *1*).

The Nobel-laureate work of the Rockefeller investigators (*17*), significantly extending the pioneering efforts of Willstätter and others, clearly outlines the general principle that each proteolytic enzyme really constitutes a *complex system*. This is especially well exemplified in the case of pancreatic trypsin: An inactive precursor or zymogen (TRYPSINOGEN, crystalline) is converted into active enzyme (TRYPSIN, crystalline), particularly through the mediation of an "activator," e.g. ENTEROKINASE (*17*), MOLD KINASE (*11*), etc.[1] A crystalline polypeptide (TRYPSIN INHIBITOR, *pancreatic*) inactivates fully-formed trypsin by formation of a crystalline inactive TRYPSIN + INHIBITOR compound (*17*). A recently crystallized protein TRYPSIN INHIBITOR from *soybean* (*12*) probably acts in the same way. Since there is multiplicity both of inhibitors and of the proteases they inhibit (e.g. chymotrypsin and plasma-tryptase, also), the nomenclature, ANTITRYPSIN, should be used with these reservations. The possibility of KINASE inhibitors, directed against the "activators" rather than against the protease proper, is not fully explored in the work on the pancreatic enzymes.

The "thromboplastic-enzyme" theory of blood coagulation (*5*) draws attention to similarities between the experimental actions of pancreatic trypsin and natural TRYPTASE enzymes demonstrable in, but not yet isolated from, plasma (serum), blood corpuscles (including platelets), and tissue source materials. Very recent work (*6*) is completely confirmatory of this idea and suggests adoption of the following nomenclature, in close analogy with the pancreatic tryptase system:

I. TRYPTASE: active protease, prefixed by name of

[1] Crystalline trypsin assists its own formation from crystalline trypsinogen in an autocatalytic manner, and certain factors, e.g. CALCIUM, are important accessories because they prevent loss of enzyme through side reactions of an inactivating nature (*14*).

source material, e.g. *serum*-tryptase, *brain tissue*-tryptase, etc.

II. TRYPTOGEN: inactive precursor on the enzyme, similarly prefixed.

III. TRYPTOKINASE: general term for "activators" of tryptogen, including *streptococcal* TRYPTOKINASE or STREPTOKINASE ("streptococcal fibrinolysin" is criticized below) and suspected *physiological* tryptokinase factor(s) (*9*).

IV. ANTITRYPTASES: tryptase inhibitors (see above), including proved (*6*) actions of the (crystalline) trypsin inhibitors of *pancreatic* (*17*), *soybean* (*12*), and *egg-white* (*6*) origin, *serum*-antitryptase (as yet unidentified), etc. (*10*).

V. ANTITRYPTOKINASES: inhibiting the tryptokinase "activator," including the clearly demonstrated antibody detected in blood after streptococcal infections ("streptococcal antifibrinolysin,"*10*).

TRYPTASE merely means trypsin-*like*, in many experimental situations (*5*). Other suggested terms are criticized as follows: The time-honored term, "FIBRINOLYSIN" (*3, 16, 19*), most recently revived by Loomis, *et al.* (*13*), must be discarded because (1) it suggests a specificity for *fibrin* substrate which is quite unfounded according to data going back to the earliest investigations; and (2) much confusion carries over from the erstwhile failure to distinguish enzyme and its activator(s), e.g. "streptococcal *fibrinolysin*"(*8*) (now recognized as a misnomer, *2*). "FIBRINOLYTIC PROTEASE," as a descriptive noncommittal term, is acceptable (*10*). "PLASMIN" is the latest suggestion (*2*) but is objectionable because (1) it indicates a *plasma* origin and ignores similar protease(s) from tissue (cellular) sources; (2) the plasma presumably gets it from some cellular source in the first place; (3) pending isolation and identification, a specific name is premature; (4) Christensen dismisses, perhaps too lightly, the all-but-forgotten use of the term (Fr. *plasmine*) for a crude salt-precipitated mixture of plasma proteins, by Denis (*4*), which retains historical interest both in connection with coagulation (fibrinogen) and as the first step toward the modern general method of isolation of proteins by fractional precipitation.

TRYPTOGEN (*5*) is preferred to "PLASMINOGEN" for the same reasons. Names like "LYTIC FACTOR" (*15*) are merely preliminary to the establishment of the definite idea. "PROFIBRINOLYSIN" (*13*) must be ruled out because "FIBRINOLYSIN" is inacceptable.

STREPTOKINASE (*2*) is quite acceptable for the streptococcal "activator," especially when it is recognized as one member of a group (hence, *streptococcal*-TRYPTOKINASE) which merits the general term, TRYPTOKINASE.

ANTITRYPTASE(S), again, is a good group name, conveniently used in lieu of TRYPTASE INHIBITOR, and the inclusion of known ANTITRYPSINS (TRYPSIN INHIBITORS) is as interesting as a priori considerations would lead us to anticipate. "ANTIFIBRINOLYSIN" (*13*), following long usage (cf. fibrinolysin), would mean antienzyme, but suffers in light of the criticisms against calling the protease by this term. The use of "ANTIFIBRINOLYSIN" (*10*) for the immunological inhibitor of the *kinase* obviously causes confusion. "ANTIPROFIBRINOLYSIN" is not much better, since it is also involved in the ambiguity of "fibrinolysin." ANTITRYPTOKINASE, therefore, is logically preferred, with ANTISTREPTOKINASE admissible as a special case. Notwithstanding noteworthy differences in origin (*22*), kinase activators (*10*), and exact modes of proteolytic action (*2, 7*), the very striking similarities of natural plasma tryptase to pancreatic trypsin in general proteolytic effects and, particularly, in relation to blood clotting, fully justify the suggested group nomenclature. This classificatory terminology, moreover, has permanent value, even when the individual members of the class become separately characterized on the basis of biochemical character and substrate specificities.

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It is proposed to hold an informal meeting at the Stevens Hotel, Chicago, on the evening of Sunday, May 18, on the occasion of the annual meetings of the Federation of American Biological Sciences, at which this topic may be discussed by interested workers. The author would welcome the names of those who wish to attend and the comments of others, unable to be present, who would like their views to be presented at this meeting.

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