Communications

Activation of Purified Prothrombin in Association with Synthetic Organic Compounds and Platelet Extract[1]

In the clotting of blood, fibrinogen is transformed to fibrin by means of the action of thrombin. The chemical reactions that occur when thrombin arises from prothrombin are not fully understood. Attempts are being made to elucidate the complex problem by isolating and studying purified prothrombin. Efforts are also being made to obtain the substances that participate in the activation of prothrombin in purified form.

When prothrombin preparations that contain Ac-globulin are mixed with calcium, platelet extracts, and a partially purified platelet cofactor, thrombin forms rapidly (*1*). The platelet cofactor, which we obtain from plasma in partially purified form, is considered to be the antihemophilic factor. We have discovered that certain synthetic organic compounds can substitute for it in the activation of purified prothrombin. If there are other known instances where an organic compound can substitute functionally for a protein, they must be rare. We are not aware of any comparable observation. Our finding also has implications related to the hemophilia problem on the basis that the search for therapeutic agents is encouraged. Moreover, technical difficulties are greatly reduced for studying the role of platelet derivatives in the activation of prothrombin.

Our studies have been extensive, but as an illustration of this work Linadryl (4-(2-(benzhydryloxy) ethyl) morpholine) serves as a typical example. A purified prothrombin preparation purposely high in Ac-globulin was made from bovine sources by methods previously described (*2*). The following activation mixture was made in the order stated: 1.0 ml purified prothrombin containing 3000 units/ml plus 0.5 ml of 0.153 *M* $CaCl_2$ dissolved in imidazole buffer (*3*), plus 0.5 ml of 0.1% Linadryl solution plus 0.5 ml platelet extract prepared as previously described (*1*). To this was added purified thrombin to give only 10 units/ml in the reaction mixture. The purified thrombin was obtained from purified prothrombin by activating the latter in 25% sodium citrate solution (*4*). Within 15 to 45 min the prothrombin transforms to thrombin. If thrombin is not added to the activation mixture the transformation of prothrombin to thrombin may not result in a full yield of thrombin. It seems likely here that thrombin is acting by its well-known effect on Ac-globulin. Linadryl is one of the compounds of the antihistamine group. We are continuing our studies with other related compounds. Benadryl (2-benzhydryloxy-N,N-dimethylethylamine HCl), Decapryn succinate (2-(a-(2-dimethylamino-ethoxy)-amethybenzyl) pyridine succinate), and Phenindamine (2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate) are also effective. Histamine itself can also be used.

[1] Supported by research grant H-1467 from the National Heart Institute of the National Institutes of Health, Public Health Service.

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Received December 12, 1953.

An Open Letter to the Assistant Secretary for Research and Development, Department of Defense

I wish to bring to your personal attention a defect in the administration of the rule, based upon existing law, which requires certification, by a designated officer of the armed forces, that individuals working on secret parts of a government research contract are acceptable for access to secret security information in the custody of the contractor. It also suggests a partial remedy for this defect. The intent of the rule is, clearly, to make available to the contractor the services of trustworthy persons. The inordinate delay in such certifications which results under present conditions from even the most trivial facts or rumors turned up in routine investigations is especially crippling to research projects where the people of most value are not nearly interchangeable parts, like machine operators in a factory, and where the time available under a contract may be relatively short.

The situation objected to in the preceding paragraph has been forcibly brought to my attention as director of an urgent defense project supported since January 1951 under Contracts N7onr 288(09) and Nonr 609(02) between Yale University and the Office of Naval Research. This project has been in force for more than three years, but its continuance has had to be negotiated repeatedly, and its life expectancy is not now and never has been as long as a year. The Director of the New York Branch Office of Naval Research is the officer who must, in this case, decide as to secret clearances. He bases his decision upon a Personal Security Questionnaire, filled out by the individual and forwarded by the contractor, here Yale University, and upon such additional information as he can get from the Naval Intelligence Officer of the Third Naval District, also in New York City. Most of any detailed investigation of the individual's history, suggested by

study of his Personal Security Questionnaire and eventually channeled through these officers, is done by agents of the Federal Bureau of Investigation. If, as usually happens in the case of persons on the Yale faculty, or suitable for temporary appointment to render highly specialized services under a research contract, the investigation involves work outside areas administered from New York City, it appears to be the standard practice to make formal requests for such cooperation to officers in other Naval Districts, or overseas, so that in an extreme case there may be questions awaiting from half-a-dozen completely separate and completely uninterested offices, all overloaded with locally imposed tasks. No information as to the progress of any investigation short of completion is allowed to get back to the individual concerned or to the Contractor.

During the life of the project that I am directing, a total of more than 100 persons have, in spite of all this, been cleared for access to secret security information, but delays have tended to increase both in number and in duration, and during such delays the usefulness of the affected individual has been less, the progress of the project as a whole has been slower, and the public interest has been correspondingly damaged. There are now pending three cases more than a year old. For the record, and with the permission of the individuals concerned to make this disclosure, I can report that the individuals thus currently delayed are: Dr. Ray W. Jackson, a Canadian citizen; Professor Carl W. Miller, a member of the physics department of Brown University; and Miss Virginia Withington, an engineer and a Lieutenant in the Naval Reserve (not on active duty). Dr. Jackson's case, as that of an alien, is especially troublesome because the corresponding confidential clearance, within the competence of the Contractor for American citizens, is also currently jammed in this case.

I suggest, in the interest of speed, at least in urgent defense research projects, that, as soon as it appears that inordinate delay in the clearance procedure may occur, the responsible officer in the armed forces be authorized, if this is not already within his discretion, to interview the person under investigation, in order to supplement or clarify the information contained in the Personal Security Questionnaire, to permit open discussion of the delaying circumstances, to provide further guidance for, and more effective pressure upon, supposedly cooperating offices, and to assist generally in reaching a wise and early decision in the case. This would appear especially appropriate in view of President Eisenhower's recent statement on the necessity of allowing anyone accused, however obliquely, of conduct or association impairing his reputation, to know about and reply to the accusation.

During my association with the Navy, both in it and out of it, during the past 50 years, this is the first period in which I have observed it to be dilatory, uncertain, and panicky in handling security questions. I suspect that the same malady affects the Army and the Air Force. I think the reasons for this deplorable situation are sufficiently well known not to need discussion here.

I am sending copies of this letter to a number of people who may be interested, and may also submit it for publication in an appropriate place. I hope any comments that you may wish to make may be equally open to the public.

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Received December 14, 1953.

A Dew Recorder[1]

In the epiphytology of the potato and tomato late blight disease caused by the fungus *Phytophthora infestans,* information was needed on the relation of dew duration to secondary infection. As a result, a search was made for a dew duration recorder. An examination of the literature revealed only the descriptions of several instruments that record quantity of dew. Hence, a dew duration recorder was developed.

The instrument shown in Fig. 1 was constructed to record the onset and duration of dew deposition. The apparatus is simple in construction and operation. The dew detecting element is a strip of lamb gut attached to a pen arm. When dew is deposited on the membrane, it expands and releases the pen arm toward the chart which is attached to a drum driven by a 7-day clock. The pen, filled with common hygroscopic recording ink, traces the period of dew deposition. When the dew evaporates, the element dries and contracts, thereby pulling the pen arm and attached pen away from the chart.

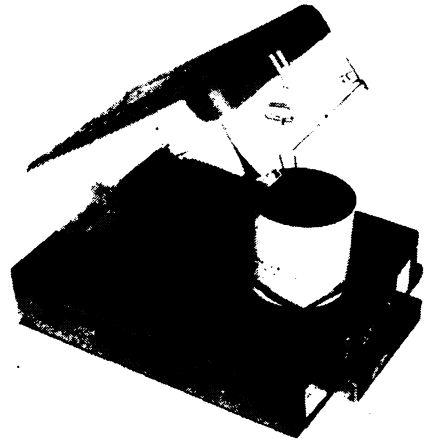

Fig. 1. Wallin-Polhemus dew recorder.

[1] Journal paper no. 2398 of the Iowa Agricultural Experiment Station, Ames, Project 1163. Report of a study conducted under the Research and Marketing Act of 1946. The investigation was cooperative between the Iowa Agricultural Experiment Station and the Division of Mycology & Disease Survey, Bureau of Plant Industry, Soils and Agr. Engineering, U.S. Department of Agriculture.