is, where the drugs are analogs of these chemicals. These include analogs of intermediates or final products of biosynthetic pathways. Drugs that are analogs of chemicals in biosynthetic pathways include methotrexate, cladribine, and ribavirin.

Still other drugs originated by first identifying a target cell, or target protein, and then by preparing antibodies that bind to that target. Vaccines have a similar origin. Once a target protein is identified, this target protein (or a derivative of it) can be formulated as a vaccine. Typically, vaccines take the form of the target protein derivative, called an "antigen," in combination with a second compound that is an immune adjuvant.

Drugs are also derived using a screening assay and by testing hundreds or thousands of purified candidate compounds using that assay. Where the screening method is automated, the method is called high-throughput screening. The screening assay may consist of tumor cells that are cultured in vitro, where a robot determines if the candidate drug inhibits a particular enzyme in the tumor cell or if the candidate drug kills the tumor cell.

II. STRUCTURES OF DRUGS

A knowledge of the structure of a drug to be used in a clinical trial is needed for the following reasons. First, the issue of whether a drug is hydrophobic or hydrophilic will dictate the nature of the excipient. If a drug is not water-soluble, then the excipient might need to include a solubilizing agent, such as a solvent. Second, the structure can also provide an idea of stability during long-term storage and thus in need of protection from light or in need of cold storage. Third, the structure can dictate the route of administration, and enable a prediction of pharmacokinetics of the drug and pathways of metabolism, transport, and excretion. Fourth, the structure of the drug can help the investigator predict adverse events that might be expected from the drug. For example, if the drug belongs to a class of compounds that activates cytochrome P450, some of the adverse events can be predicted. Fifth, regulatory submissions to the US Food and Drug Administration (FDA), such as the Investigational New Drug (IND), Investigator's Brochure, and the package insert, typically contain a drawing of the drug structure.

a. Origin of Warfarin

Warfarin is a drug that is widely used to prevent blood clotting, for example, in people at risk of heart attacks or strokes (10). A natural product produced during the spoiling of sweet clover inspired warfarin's design. The drug was not named after any kind of warfare, even though it is used in warfare against mice and rats; it was named after the *Wisconsin Alumni Research Foundation*.

Spoiled sweet clover contains coumarin, a compound that inhibits an enzyme in the liver, where the end-result is impaired blood clotting. Blood clotting factors are biosynthesized in the liver, and then released into the bloodstream. Farmers in the mid-West found that cattle bled to death during the process of de-horning, where the cattle had eaten spoiled sweet clover. Eventually, one particular farmer in Wisconsin took a bucket of unclotted blood to researchers at the University of Wisconsin. The researchers examined the blood, as well as samples of spoiled sweet clover, and discovered that the culprit was dicoumarol, a degradative product of coumarin. Researchers synthesized and tested about 50 analogs of this compound. The analogs were

[10] Yeh CH, et al. Evolving use of new oral anticoagulants for treatment of venous thromboembolism. Blood 124:1020–8.