In the same issue of SCIENCE, Kirtley F. Mather, who discusses "The Problem of Antiscientific Trends Today," says,

> Scientists, by the very nature of their mental habits, are internationalistic rather than chauvinistic in their outlook. [He adds that] Scientists, moreover, are naturally devoted to the principles of democratic freedom that shine so clearly in our constitutional Bill of Rights, based as they are upon the one most important freedom of all, the freedom to think one's own thoughts and to express them so that they may be appraised in the court of public opinion.

Assuming that one's own country is worth while, one cannot be soundly "internationalistic" without being truly patriotic in the effort to protect and preserve our own country. The international situation has so deteriorated that the first thing on the agenda is to do one's best to appraise it correctly and act wisely. The danger is a real and present one.

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β-Glucuronidase and Glucuronide Synthesis

IN a recent review of the relationship between estrogens and enzymes, Fishman (*1*) discusses his hypothesis that the enzyme β-glucuronidase acts synthetically in the animal body. It therefore seems appropriate at the present time to recount briefly the principal evidence for the existence in the animal body of a glucuronide-synthesizing system, distinct from β-glucuronidase.

Fishman's hypothesis was originally put forward to explain his discovery (*2–4*) that the β-glucuronidase activity in nonsex organs, such as liver, rises in response to the administration of menthol or borneol, whereas the activity of the enzyme in uterus and vagina is increased by administration of esteriol or other estrogens. The complete explanation rests on three distinct postulates: (*a*) that the enzyme acts synthetically *in vivo*, (*b*) that the tissue activity responds adaptively to the presence of excess substrate, and (*c*) that the enzyme differs in specificity or function according to its location in the body. Without accepting the others, we shall limit ourselves here to considering the first and key postulate.

β-Glucuronidase is present in nearly all animal tissues that have been studied (*5*), and its activity is measured *in vitro* by following the hydrolysis of biosynthetic glucuronides (*6–8*); its activity in certain organs can be made to rise or fall *in vivo* by administering a variety of both glucuronidogenic and nonglucuronidogenic agents (*2–4, 9–11*); certain glucuronides cause a rise in activity (*4, 9*); *in vitro* this enzyme is powerfully inhibited by saccharate (*12–15*), an effect that has recently been shown to be due to saccharo-1:4-lactone present as impurity in the saccharate solution (*16, 17*); it is not inhibited by fluoride, iodoacetate, dinitrophenol, or sulfate (*12, 18*).

The activity of the glucuronide-synthesizing system can be measured in tissue slices and appears to require oxidation and phosphorylation; this enzyme system has been found only in liver and, to a minor extent, in the kidney (*19–21*); its activity in liver is unaltered by treating animals with agents that cause changes in liver β-glucuronidase activity (*20*); *in vitro*, glucuronide synthesis is not inhibited by saccharo-1:4-lactone (*14, 17*), but it is inhibited by anaerobiosis, cyanide, iodoacetate, fluoride, azide, dinitrophenol, and sulfate (*19, 21*); glucuronic acid in low concentration does not stimulate glucuronide synthesis by liver slices, nor does it overcome depression due to various causes (*19, 21*); in high concentration, glucuronic acid itself inhibits glucuronide synthesis *in vitro* (*21*), as it does β-glucuronidase (*12, 15*).

From their study of phenol conjugation by tissue slices (*22*), De Meio and Arnolt arrived at certain conclusions regarding glucuronide synthesis that are contrary to some of the points mentioned above. It was later shown, however, that their method did not measure conjugation of phenol with glucuronic acid (*23*), a finding that has been accepted by De Meio (*24*).

Florkin, Crismer, Duchateau, and Houet (*25*) obtained evidence for every slight condensation of glucuronic acid with borneol after prolonged incubation of the two compounds together in high concentration in presence of β-glucuronidase, but they considered that it did not follow that glucuronides are synthesized by this mechanism *in vivo*. Using a very sensitive color reaction for *o*-aminophenylglucuronide (*23*), Karunairatnam and Levvy (*12*) could find no condensation of *o*-aminophenol with glucuronic acid in presence of β-glucuronidase or crude liver homogenates. Under suitable conditions, any hydrolytic enzyme should theoretically be able to catalyze the reverse reaction, but several instances are known where resynthesis in the body proceeds by quite a different mechanism.

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SINCE the important contributions of Levvy and Kerr have been repeatedly discussed (*1–3*), this comment is merely intended to restate our attitude toward the concept of β-glucuronidase as a catalyst of the synthesis of glucuronides and to clarify—if it is possible—the prevailing viewpoints on glucuronide synthesis.

With regard to the first consideration, although direct proof that the enzyme catalyzes the conjugation of glucuronic acid *in vivo* is lacking, this mechanism is at least theoretically possible and there are good reasons for its existence (*1–3*). This concept became the basis of a working hypothesis proposed in 1940 (*4*) in an attempt to explain certain glucuronidase phenomena in animals, and it has been helpful in suggesting new experiments and has led to the discovery of new information. It will remain a useful *ad hoc* hypothesis until it has outlived its value for our purposes, or until future work suggests a better explanation of the role of the enzyme.

It is Levvy's implied contention that certain of his *in vitro* data negate the validity of the working hypothesis which we favor. It should be pointed out, however, that the translation of *in vitro* data into valid deductions *in vivo* is always hazardous even with the use of surviving tissues, unless the *in vitro* findings do coincide with observations in the whole animal. In our view, the findings in the whole animal are more readily explained on the basis of a predominately synthetic action of β-glucuronidase. The weight that one wishes to attach to negative *in vitro* results is a matter of personal opinion.

With respect to the second consideration, two mechanisms for glucuronide synthesis have received attention. The first entails the synthesis of glucuronides from three carbon precursors without the participation of glucuronic acid itself. A requirement of oxidation and phosphorylation is stated by Lipschitz and Bueding (*5*), Karunairatnam *et al.* (*6*), and Storey (*7*). One suspects that the processes of oxidation and phosphorylation concern the synthesis of glucuronic acid only and not its conjugation. The other concept holds that glucuronic acid itself is the immediate conjugating compound and that the enzyme β-glucuronidase participates in the conjugation (*4*).

This second mechanism is supported in part by direct experimental evidence in the intact animal. Thus, King (*8*) and Packham and Butler (*9*), using radioactive carbon, have shown that the synthesis of borneol glucuronide in the guinea pig and of naphthyl glucuronide in the rat takes place with the preformed molecule of glucuronic acid. Glucuronic acid, administered intraperitoneally, was incorporated into biosynthetic naphthyl glucuronide (*9*) at twenty times the rate of any three carbon precursors.

This observation does not rule out the possibility that there may be other mechanisms of glucuronide synthesis not requiring preformed glucuronic acid, nor does it necessarily prove that β-glucuronidase catalyzes the conjugation. It does lend added support to the working hypothesis discussed here.

It is hoped that the exposition of these varying viewpoints concerning a biologically important phenomenon may benefit other investigators who may undertake work in this field.

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Book Reviews

Probit Analysis: A Statistical Treatment of the Sigmoid Response Curve. 2nd ed. D. J. Finney. New York–London: Cambridge Univ. Press, 1952. 318 pp. $7.00.

The first edition (reviewed in SCIENCE, **107**, 76, [1948]) has proved very useful and was sold out some time ago. The second edition is nearly the same in content, but somewhat extended, with better paper and printing. The jacket and preface list the new material and the sections that have been changed.

The section on alternative distributions has been broadened, and discusses use of the angle transformation. The sections on maximum likelihood estimates, on the Parker-Rhodes equations, and on probits for quantitative response are revised to use a simplification of equations recently obtained by the author himself.

A new chapter has been added. It is not unified as