rising level of economic activity—in the perspective of other objectives of national policy. Assume, for example, that the international situation should necessitate a drastic increase in defense expenditures, such as has been recommended in a number of experts' reports. If, within a short time, the Government were to be embarking on very large additional defense programs for purposes of national security, the responsible adviser would not now recommend special antirecession measures, either public works expenditures or tax reduction. For this reason I hesitated to recommend tax reduction at an earlier time until it became clear what action, if any, the Government would take with respect to national security programs along the lines of the so-called Gaither and Rockefeller reports. Such an appraisal of policies for recovery in the perspective of policies for other national objectives is a function of statesmanship, and the economist, as an adviser, has to make it clear to what extent policies for various national objectives may either support one another or conflict with one another.

Another decisively important aspect of economic statesmanship results from the fact that policies must be decided under conditions of uncertainty. We all know by sad experience that our economic predictions are, to say the least, imperfect.

Using again the current antirecession policy debate as an example, we find two main attitudes. One of these advocates a continued policy of "wait and see," expecting an early upturn of market forces which would make additional government policies unnecessary. The other view is based on the expectation that the market forces will not bring about an early and adequate recovery and therefore recommends additional recovery measures.

The economist advising the statesman will recognize that, whatever view he personally espouses, he may be wrong. Therefore, he must evaluate the harm done in either case if the policy proves to have been based on an erroneous prediction. Assume that the Government does adopt additional recovery measures but that it turns out that the forces of the market bring about recovery independently. Then the total demand—government plus business plus consumer demand—may become excessive, and demand inflation conditions may develop. This would necessitate the adoption of anti-inflation measures at a later time. In the light of all experience we may anticipate that such anti-inflation measures will not be fully effective, and some price rise may result.

Let us now assume that the Government, advised of the probability of an early upturn in market forces, takes no further action but that, contrary to expectations, the upturn does not materialize. As the labor force grows and capacity to produce rises, unemployment and idle capacity increase.

Both types of error are certainly possible. Therefore, it must be evaluated which error will do the greater harm in the light of all aspects of economic, social, and political (in particular, foreign policy) objectives. This is, in my opinion, the crucial consideration in giving advice on final policy formulation.

A renewed rise in prices at a later time would certainly be undesirable, both from an economic and a social point of view. However, it is my opinion that the failure to counteract effectively the recession would be much more harmful and undesirable. We must consider not only the frustration of the unemployed and the irreparable loss of potential production but also the disruptive effect of the recession on the raw-material-producing foreign countries. The latter effect, in turn, might have serious consequences on foreign policy.

For a decade we have stated with pride that we have established the necessary legislative and administrative machinery and that we have the knowledge for dealing with severe economic fluctuations. Failure to use that machinery and that knowledge to prevent a serious or prolonged recession does great harm to the prestige of our political and economic system in the world and supplies ready-made arguments to the critics of that system. The economic adviser has to consider and present the risks involved in either action or inaction. But, in the last analysis, it is the statesman's responsibility to weigh the respective risks and to make the decision.

Specificity of Peptides

New aspects of the specificity of peptides with vitamin and hormone action are described.

D. W. Woolley and R. B. Merrifield

The marked structural specificity required in vitamins and other biologically active substances is a concept so widely held that evidence against such a view excites attention. The purpose of this article (*1*) is to summarize recent work which suggests that several kinds of peptides with recognizable functions in many living things do not conform to the classical picture of rigorous specificity. Rather large changes in chemical structure often do not seriously alter their biological activities. That such a situation should appear among peptides is interesting because the proteins have long been regarded as the prime examples of exquisite structural specificity. This view, too, is undergoing some modification in the light of recent discoveries with certain enzymes and antibodies (*2*).

In the past, the structural specificity exhibited by essential compounds such as the water-soluble vitamins has been striking. Minor variations in chemical constitution, such as the replacement of a $-CH_3$ by $-H$ or $-CH_2 \cdot CH_3$, have led to compounds of much reduced or no potency. Frequently such minor alterations have yielded antimetabolites which antagonize rather than exhibit the biological action. When evidence has been found of lack of specificity, as, for example, in the biotin activity of oleic acid (*3*) or the vitamin B_{12} activity of thy-

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Table 1. Strepogenin activity of various peptides isolated from natural sources. In place of the common abbreviations, the following have been used: A, asparagine; Al, alanine; Ar, arginine; C, half-cystine; G, glutamic acid or glutamine; Gl, glycine or its amide; H, histidine; I, isoleucine; L, leucine; P, proline; Ph, phenylalanine; S, serine; T, tyrosine; V, valine. For discussion of peptides Nos. 1 and 2, see Merrifield and Woolley (*7*); of peptide No. 4, see Tritsch and Woolley (*8*); of peptides Nos. 5 and 6, see Woolley and Merrifield (*10*).

Peptide	Strepogenin activity (unit/mg)
1. SHLVG	85
2. SHLVGAIL	100
3. VHGSL	200
4. LVCGlGAr	200
5. CTIGACPLGl (oxytocin)	300
6. CTPhGACPArGl (vasopressin)	150

midine (*4*), no threat to the basic concept has arisen because the oleic acid, thymidine, and so on have been indicated to be products formed in the organism through the action of the vitamin in question. When the product is supplied in sufficient amounts, the machinery needed for its manufacture may no longer be required. However, this "product explanation" appears unable to account for the lack of specificity to be discussed in this article.

Among the hormones there have been a few striking examples of lack of specificity, but these have not been enough to disturb the general conclusion that, for a given hormonal effect, one needs a single substance or a close relative of it. Some notable exceptions have been the estrogenic action of diethylstilbestrol and of genistine (*5*) and the indoleacetic acid activity of 2,4-dichlorophenoxyacetic acid. Now that similar lack of specificity begins to appear for peptides which are vitamins, hormones, or poisons, the shortcomings of the classical view about specificity must be given more consideration.

Strepogenin Activity of Certain Peptides

A peptide which stimulates the growth of *Lactobacillus casei* and some species of streptococci has been recognized for many years (*6*) and called strepogenin. Recently several pure peptides showing this activity have been isolated and identified (*7–10*). One of these is serylhistidylleucylvalylglutamic acid (SHLVG), isolated from partial hydrolyzates of insulin. A peptide giving rise to these same five amino acids on hydrolysis has very recently been isolated from digests of ribonuclease (*11*) and identified as valylhistidylglutamylserylleucine (VHGSL) by C. H. W. Hirs (*12*).

In the standard strepogenin test with *Lactobacillus casei,* this peptide was 2.3 times as potent as SHLVG. Clearly, then, the amino acid sequence in a pentapeptide containing serine, histidine, leucine, valine, and glutamic acid was not crucial for its growth-factor activity. This sequence could be either SHLVG or VHGSL. Data on the strepogenin potencies of several peptides isolated from natural sources are given in Table 1.

The failure to find a need for a specified sequence of amino acid residues in the peptide chain was not as surprising as was the finding that many of these amino acids could be replaced by others of different chemical structure. The high potency of oxytocin, vasopressin, and leucylvalylcysteinylglycylglutamylarginine would not be anticipated from the fact that SHLVG was active.

A commonly held concept is that peptidic growth factors are active merely because they supply a particular amino acid in an available form. This idea is not adequate to explain all of the strepogenin data. Study of a considerable number of additional peptides has shown that no single peptide-bound amino acid is required for activity. Perhaps there are interchangeable amino acids either of which will confer activity if present in a suitable peptide. Thus, because all known active strepogenins contain either a serine or cysteine residue, one might conclude that what is needed is either a serine- or cysteine-containing peptide and that these are interconvertible by the organism. Nevertheless, several serine or cysteine peptides (for example, seryltriglycylglutamic acid and cysteinylhistidylleucylvalylglutamic acid) were either inactive or of low potency. More is needed than the mere presence of serine or cysteine. What stands out most clearly is that a variety of peptides show high strepogenin activity and that the structural resemblance of those which do is rather remote. Neither the sequence of amino acid residues nor the exact nature of these residues seems to be crucial for this biological activity.

It must not be forgotten, however, that some rather slight structural changes convert an active peptide into a specific antagonist of the growth factor. Thus, threonylhistidylleucylvalylglutamic acid (*13*) is such an antistrepogenin even though it differs by only one —CH_3 from the active SHLVG.

We might console ourselves, as some have done, by saying that strepogenin is a special case with no general biological significance. We might, for example, point out that this factor is not absolutely essential for the growth of the organism. *Lactobacillus casei* will eventually grow maximally in the basal medium if incubation is continued long enough. It is therefore of interest to find other cases of this lack of specificity among other biologically active peptides.

Peptides with Toxic Action

Consider first the case of lycomarasmin. This modified tripeptide of asparagine, glycine, and α-hydroxyalanine is a toxin, formed by the fungus *Fusarium lycopersici,* which causes excised tomato leaves to wilt and curl. A number of closely related peptides were examined for such toxic action in 1948 (*14*), and it was found that the situation was somewhat similar to that now observed with strepogenin. Neither the sequence nor the mode of linkage nor even the exact nature of the amino acid residues was crucial, even though just any peptide would not exhibit the activity. In fact, some were antagonistic.

An analogous situation with respect to the antibiotic peptide gramicidin S was described recently by Katchalski *et al.* (*15*). Random polymerization of the five amino acids found in the natural antibiotic led to antibiotically active peptides. Presumably, several isomeric peptides each contributed antibacterial activity.

We might dismiss these two examples as being concerned with peptides which are poisonous, and consequently of only limited interest for real biological activity. There is much merit in such an objection.

Oxytocic Activity

The same phenomena, however, begin to appear for the hormone oxytocin. The natural hormone isolated from the hypophysis has the structure indicated in Table 1 (*16*). It was not too surprising to learn that another hormone of the hypophysis—namely, vasopressin—exhibited some oxytocic activity (*16*)

because the two hormones differed only in that, in vasopressin, the isoleucine of oxytocin was replaced by phenylalanine and leucine was replaced by arginine or lysine (*9*). Similarly, the potency of a synthetic peptide which was the same as oxytocin except for the fact that isoleucine was replaced by valine (*17*) fitted well with the classical concept of structural specificity. These findings show that the nature of every amino acid residue in the oxytocin molecule is not crucial for activity. Some can be exchanged for related residues. However, the recent demonstration by Schwarz, Bumpus, and Page (*18*) and by Dekanski (*19*) that angiotonin (hypertensin) has high oxytocic activity (when tested on isolated rat uterus) recalls once again the findings with strepogenin and lycomarasmin and gramicidin S. Angiotonin has the structure aspartylarginylvalyltyrosylisoleucylhistidylprolylphenylalanine (*18*) and thus bears little resemblance structurally to oxytocin. If we may extrapolate from the experience with strepogenin, we might not be surprised to find that a peptide composed of the eight amino acids in natural oxytocin, but with their sequence completely changed, would show oxytocic activity (compare SHLVG with VHGSL in the strepogenin test).

Another case of the lack of structural specificity of a peptidic hormone is the vasopressin activity of pepsitensin. Although the structure of pepsitensin has not been established yet, the evidence (*20*) strongly suggests that it will differ considerably from that of vasopressin.

Because the assay systems for biologically active peptides are complex, there is a possibility that simplification of the systems to single chemical reactions might sharpen the specificity. There is, however, no assurance that this will be the case. Some expansion of the classical view about specificity seems to be required.

Summary

The data now at hand show that specificity among biologically active peptides is probably not as exquisite as might have been deduced from experiences with some of the water-soluble vitamins. It is plain that a given biological effect can be evoked by peptides which differ considerably. It is likewise plain that the effect cannot be evoked by a number of other peptides. There is apparently some specificity, but more is involved than that incorporated in the classical view.

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News of Science

Hughes Appointed to Editorial Board

On 1 August Donald J. Hughes, senior physicist at the Brookhaven National Laboratory, was appointed to the Editorial Board of *Science*. Hughes, who was born in Chicago in 1915, took both his undergraduate and graduate work at the University of Chicago. His research for the Ph.D., which he obtained in 1940, was in the field of cosmic rays, in connection with which he was a member of a cosmic ray expedition to South America in 1941. He remained at Chicago as an instructor in the physics department until the U.S. Navy called him to direct a section on underwater ordnance research at the Naval Ordnance Laboratory in Washington, D.C., in 1942. Until 1943, Hughes remained at the Naval Ordnance Laboratory working with mine and torpedo detectors, including a period spent with the British ordnance at Edinburgh, Scotland.

Early in 1943, Hughes joined the Manhattan Project at the University of Chicago at the time the first pile was starting operation. He did classified pile neutron research, including 1 year (1944) spent at Hanford, Washington, when the large chain-reacting piles for production of plutonium were put in operation. In 1945 he returned to Chicago and became director of the Nuclear Physics Division of the postwar Argonne National Laboratory, which was formed by the Atomic Energy Commission. He left Argonne in 1949 to become a senior physicist in charge of a group doing pile neutron research at Brookhaven National Laboratory. In addition, Hughes served as chairman of the Nuclear Cross Sections Advisory Group of the Atomic Energy Commission.

Hughes has worked in practically every branch of neutron physics that can be handled at the pile. With Spatz and Goldstein, at Argonne, he developed a method for measuring fast neutron cross sections, which became the basis of G. Gamow's theory of the origin of the elements and was also applied to the design of fast neutron breeder reactors, such as the experimental breeder reactor now in operation at Arco, Idaho. At Brookhaven, Hughes' group has done significant work in connection with neutron "mirrors," in which the mirror reflection of neutrons was used to measure the neutron-electron interaction, which has a bearing on modern meson theory. His group has also developed the "fast chopper," which has yielded much nuclear information, and techniques of working