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POTENTIATORS OF MUSCULAR CONTRACTION – SUGGESTIONS FOR PHYSIOLOGY DEMONSTRATIONS

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Student laboratory exercises in physiology courses frequently illustrate features of skeletal muscle contractility using muscles of the frog. In recent years a variety of simple and readily available chemicals has been found to enhance the mechanical response of a skeletal muscle to a single brief electrical stimulus of sufficient strength to produce a maximal twitch response in the untreated muscle (Sandow, 1964). In appropriate concentrations these drugs do not alter the muscle's response to tetanic stimulation evoked by a train of suitable series of single shocks. These drugs are therefore said to be potentiators of twitch contractions.

Potentiators may be in the form of cations, anions or neutral molecules. Examples of each of these categories can be used to demonstrate the lability of the twitch to modification by drug action and thus to qualify the frequently cited all or none law as applied to skeletal muscle twitch contraction. The degree of twitch potentiation has been shown to vary inversely with the initial twitch to tetanus tension ratio (Isaacson, 1962).

Anionic potentiation by nitrate may be shown by preparing amphibian Ringer's solution in which sodium nitrate is substituted for sodium chloride. Potentiation by nitrate is readily reversible upon return of the muscles to normal chloride Ringer's solution.

Potentiation by a cation can be illustrated by adding 0.05 mM zinc chloride to the normal Ringer's solution (Isaacson and Sandow, 1963). As cited in the previous reference, it may be desirable to avoid phosphate buffer and instead use a tris (hydroxymethyl) amino-methane chloride buffer [2mM] when using cationic potentiators such as zinc that may complex with phosphate. To speed up the reversal from zinc potentiation 0.1 mM EDTA (ethylene diamine tetra acetic acid) may be added from a stock solution that should be titrated to pH7 (Sandow and Isaacson, 1966). (Fig. 1)

The alkaloid caffeine may serve as an example of a neutral potentiator, (Sandow and Brust, 1966). For caffeine effects, simply add caffeine (1mM) to amphibian Ringer's solution. Reversal from caffeine effects may be achieved by returning a muscle to normal Ringer's solution. (Fig. 2)

To avoid the possible complication of interpretation that the nerve endings in the whole muscle could present, one can simply add d-tubocurarine chloride (curare) to reach a concentration of 2×10^{-5} g/ml in each of the Ringer's solutions. A half-hour presoak in curarized Ringers should block the nerve endings. By determining the maximal shock strength needed to evoke a maximal twitch response at the start of the experiment, and using slightly supermaximal shocks one can also rule out the possibility of recruitment of previously unexcited muscle fibers as explaining the twitch enhancement (Kahn and Sandow, 1950 and 1955).

REVIEW SUPPLEMENT

With this issue of the Physiology Teacher, we continue our efforts to meet the needs of physiology teachers by publishing the enclosed "Review Supplement" in addition to the usual suggestions for laboratory experiments and teaching methods. The idea for this collection of abstracts of review articles originated with Dr. Arthur Guyton (Past-President of APS) and was presented to the Education Committee for consideration as an activity of the committee.

To give our readers some insight into the background of the implementation of the idea and into other functions of the Education Committee of the American Physiological Society, we are publishing (page 8) the more pertinent correspondence with regard to the review supplement.

We sincerely hope that this supplement lives up to our expectations: that it serves as a valuable aid to teachers planning courses for the coming year. Please send us your comments.

Editor

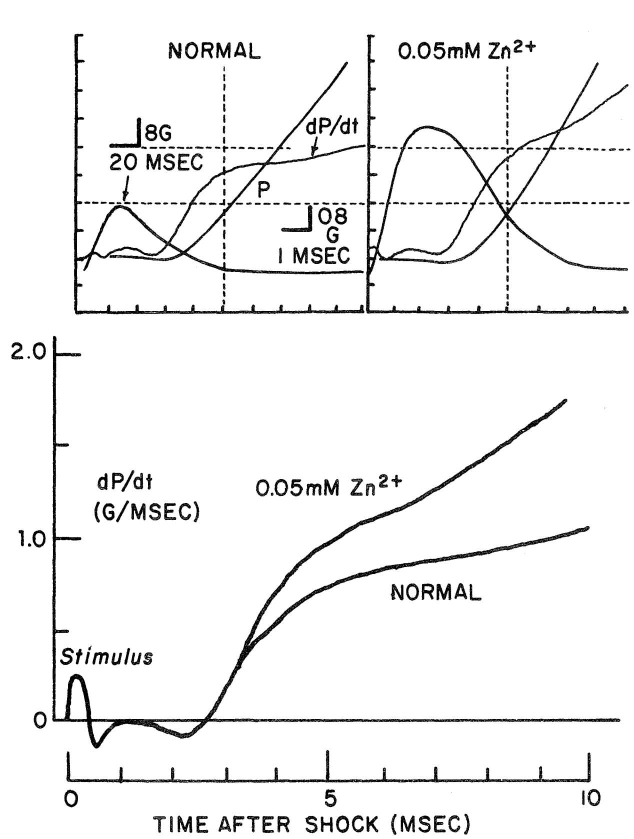

Fig. 1. The effects of 0.05 mM Zn^{2+} acting after 30 minutes on the isometric twitch of frog sartorius muscle.

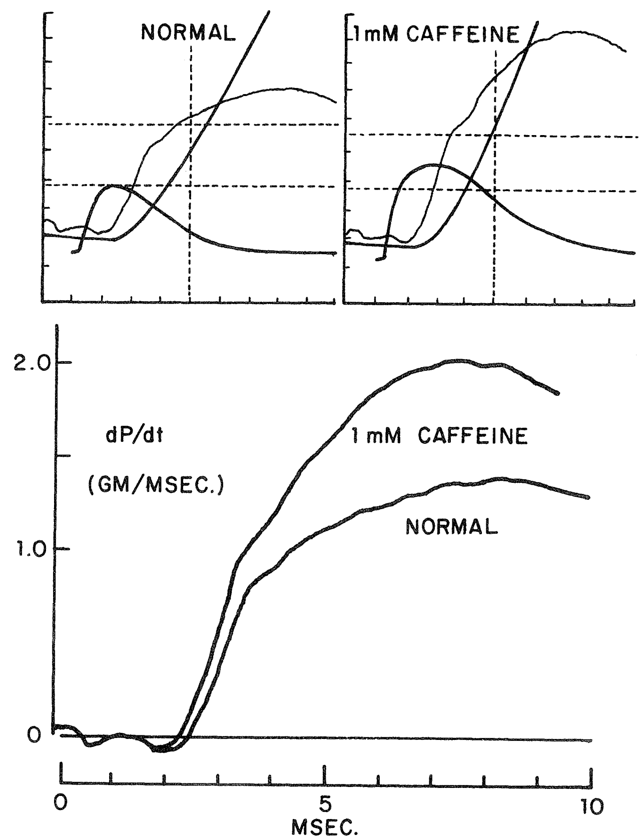

Fig. 2. The effects of exposure to 1mM caffeine for 20 minutes on the isometric twitch of frog sartorius muscle at 24°C.

As for the interpretation of how these drugs can enhance twitch contractions there are a variety of studies that deal with what is referred to as excitation – contraction coupling (Fig. 3) (Sandow, 1964 and 1965; Sandow et al, 1965; Taylor et al 1969 and 1972; Brust, 1965, 1969; Bianchi, 1961; Isaacson and Sandow, 1967). The general process that leads to activation of the contractile tension within skeletal muscle involves an internal release of calcium from its storage sites bound to the sarcoplasmic reticulum of muscle (for a review readily applicable to teaching purposes see Hoyle 1970). Each of the drugs that are cited herein as twitch potentiators has been found able to cause the release or impede the binding of some fraction of the calcium normally bound to *in vitro* preparations of sarcoplasmic reticulum isolated from skeletal muscle (Weber and Herz, 1968; Carvalho, 1968).

For caffeine, its relatively rapid rate of permeation through the surface membrane of skeletal muscle (Bianchi, 1962) provides a basis for kinetics of potentiation which are cited as requiring about 3 and 6 minutes respectively for the half-times of development and reversal of potentiation by 1mM caffeine (Sandow and Brust, 1966) in the sartorius muscle of the frog.

From studies of the kinetics of development and reversal of potentiation by nitrate (Kahn and Sandow, 1955; Hill and MacPherson, 1954) and zinc (Isaacson, 1969; Isaacson and Sandow, 1963; Isaacson et al, 1970a, b; Sandow and Isaacson, 1966; Edman and Grieve, 1966; Stanfield, 1973, 1975) it appears that the sarcolemma may be a site at which these drugs initiate the process that leads to the enhancement of twitch contractions.

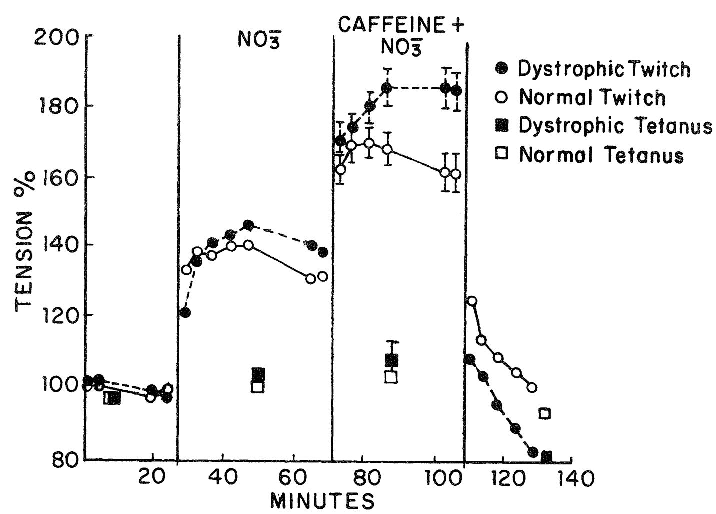

Fig. 3. Effect of NO_3^- alone, followed by effects of combination of nitrate (121mM) and caffeine (1mM) on the peak twitch tension output of normal and dystrophic soleus muscles of the mouse.

Nitrate has been found to lower the mechanical threshold to contractures evoked by depolarization of the sarcolemma by elevated concentrations of potassium (Hodgkin and Horowicz, 1960). A similar effect is also produced by caffeine, (Sandow et al 1962). Zinc in the concentration recommended (0.05 mM) does not change mechanical threshold, although it causes a sizable prolongation of the action potential duration of the skeletal muscle's electrical response to a single shock stimulus (Isaacson and Sandow, 1963; Taylor et al 1972).

In summary, the use of these drugs in laboratory exercises may provide opportunities to illustrate a number of the features emerging in the concept of how the mechanical responses of muscle are modulated by events occurring both at the surface membranes as well as at the membranes of the sarcoplasmic reticulum.

ACKNOWLEDGEMENT:

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I am also grateful to my many colleagues at William Paterson College whose frequent awards of release time for research rendered this work possible.

Figures 1, 2 and 3 have been redrawn from FEDERATION PROCEEDINGS *24*:1116-1123, 1965 and *28*: 1649-1656, 1969."

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CURRICULUM CONTENT SELECTION FOR MEDICAL STUDENTS

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Medical schools must train students to base their clinical decisions on scientific knowledge and give them the necessary scientific background for these decisions. However, though there is a distinct need for an adequate basic science preparation, many schools are curtailing their teaching efforts in this area. Visscher (19) reported that in the last ten years the average number of hours devoted to basic science teaching in medical schools has decreased by 31%. Instructors in all disciplines are being compelled to contend with a press for time when they select curriculum content. The curricula were already crowded with information and more is being reported every year. To make matters worse, medical schools suffer from departmental autonomy so that the efficiency that could be gained by interdisciplinary communication is seldom achieved.

In the 18th century Dr. John Morgan, the colonies' first professor of medicine, complained about "private" lectures because they presented information to the students in an inconsistent manner (14). We have, with few good exceptions, made little progress since Morgan's time. Faculty members still act independently as private lecturers and they often have little knowledge of what other instructors will present in the future, are teaching presently, or have presented in the past. Such lack of communication makes it impossible to select, organize, and present pertinent scientific information meaningfully and effectively. Given these problems a solution must be sought in which instructors will:

1. define in minute detail the "core" content needed in the medical curriculum.
2. jointly plan sequences of instruction.
3. change the medical curriculum as new scientific information is accumulated.

This paper deals with an orderly plan for selecting curriculum content. The methods of this plan are demonstrated by an example in which a portion of the core cardiovascular physiology needed by a medical student is defined.

CORE CONTENT DEFINITION:

Since the physician is the last member of the health care team to which responsibility can be passed, it is imperative that he be trained to the upper limit of his ability and this can only be accomplished by a considered selection of curriculum content. Curriculum content selection is begun by asking the question: What do you keep and what do you discard? Leading medical educators (Welch 20, and Osler 15) maintained that only information which is essential for the understanding of contemporary methods of diagnosis and treatment should be retained for the teaching of medical students. This circumscription of essential information will serve as the definition of the "core" of knowledge in this paper. We are not limiting "core" to an outline or a series of headings; rather it is a precisely defined and complete unit of information.

IDENTIFICATION MECHANICS:

Robert Gagné (6,7,8,9) has developed a series of procedures for identifying core scientific information. These procedures can be adapted for medical curriculum use. The scheme is listed below with the medical school adaptations for cardiovascular physiology in parentheses.

1. Define the terminal level of training. (A medical student taking National Board Examination, Part II)
2. Define the expected terminal capabilities of the student. (Patient care by a physician)
3. Identify the scientific principles used in the terminal capabilities. (Core of cardiovascular principles used in the problem-solving situations within a medical clinic)
4. Ask, "What a student must comprehend or know how to do, to be instructed in these principles" (6). (Subordinate principles and concepts that support the core cardiovascular principles identified in procedure number 3. Together, these principles and concepts constitute a portion of the core of the curricular content)
5. Ask, "What a student must comprehend or know how to do, to be instructed in the subordinate principles and concepts" (6).
6. Repeat the above procedure until the defined core of curricular content reaches a specific lower level of training. (Presumed level is that of an entering medical student)

CORE ORGANIZATION:

The learning objective of the medical curriculum is to aid the student in developing the ability to solve clinical problems (item No. 2 above). To do this a knowledge of scientific principles and subordinate learning objectives are needed. When an instructor attempts to identify core information by working backwards from the clinical problem solving level, a map of core curriculum content begins to unfold. This type of map is called a "content hierarchy" (6), it outlines what the student should have at his command before he takes the next learning step. When such a hierarchy is used as an instructional guide it assures that the core material is presented in a logical sequence and it guards against the omission of essential material from the curriculum. In this paper a portion of the core of cardiovascular physiology is identified and presented in the form of a hierarchy of knowledge.

RELEVANT KNOWLEDGE IDENTIFICATION:

The cardiovascular principles used in the problem solving situations within a hypertension clinic are presented to demonstrate the mechanics of selecting core information. This was done in consultation with Dr. Andrew Zweifler a member of the internal medicine staff at the University of Michigan Medical School. Dr. Zweifler made available a "Hypertensive Review" pamphlet previously prepared by members of the hypertension unit at the University of Michigan hospital. This pamphlet contained:

1. A check list of observations required in the physical examination of a possibly hypertensive patient.
2. A list of mandatory and elective diagnostic laboratory procedures.
3. The patient's past history.
4. The patient's family history.
5. A summary of etiology, complications, diagnoses, and recommendations.

From these sources and others we have compiled a list of major clinical observations involved in the making of clinical decisions related to cardiovascular function.

This list includes:

1. Systolic and diastolic pressure.
2. Pulse pressure.
3. Heart rate.
4. Murmurs.
5. Evidence of congestive heart failure.
6. EKG.
7. Heart size.
8. Endocrine effects on the cardiovascular system.

From these focal points of information the series of procedures leading to the completion of a content hierarchy was begun.

HIERARCHY ORGANIZATION:

Figure 1 is a hierarchy of headings relating to blood pressure, EKG, and congestive heart failure. The more complex topics to be learned are located at or near the top of the hierarchy, and the subordinate topics are arrayed beneath them. The hierarchy content is arranged so that an instructor or student can select a topic and then trace backwards to the subordinate information. This hierarchy is designed to be followed from left to right and from the bottom up. For instance, let us assume that an individual selects Heart Rate as the topic he wishes to study. He would trace down and to the left until he reaches Action Potentials (Myocardial). He would then proceed to Intrinsic Rhythmicity of the Heart, Neural Control of Heart Rate (Chronotropic Control), Heart Rate Parasympathetic Control, Heart Rate Sympathetic Control and finally Cardiac Impulse Conduction. This procedure leads the individual from the prerequisite knowledge of the basic science to the clinical observation.

A second section of the hierarchy contains the major topic headings listed in alphabetical order. In this section of the hierarchy the complete core of information would be included and would be presented in a very concise manner. Each bit of information found under a major topic heading either provides an understanding of this topic or presents information relating it to the next topic up the scale of the hierarchy. Following are four examples of the core of information presented under headings used in this hierarchy:

Homeometric Autoregulation H15-16

When arterial pressure is elevated, stroke volume is initially decreased resulting in an increase in end-systolic and end-diastolic volumes. The ventricular myocardium will develop greater tension and do more work. If this condition is maintained the myocardium will undergo an intrinsic change which results in an enhanced contractility. The enhanced contractility will enable the ventricle to increase its stroke volume returning end-systolic and end-diastolic volumes toward control level. The change which renders the ventricle better able to pump blood against the elevated arterial pressure is called homeometric autoregulation. The mechanism for this change is not known. Associated with homeometric autoregulation is a reduction of ejection time. This assists ventricular filling (17).

Korotkoff Sounds B13-14

The Korotkoff sounds are caused by audible vibrations of blood and/or vessel wall when blood flows intermittently under the occlusion cuff during its decompression. The first intermittent flow, and hence the first sound, occurs when cuff pressure falls just below systolic pressure; the last intermittent flow, and hence the last sound, occurs when cuff pressure falls just below diastolic pressure.

Myocardial Compensation E18-19

Myocardial compensation may be accomplished by the following mechanisms:

1. Myocardial hypertrophy due to increased work load.
2. Heterometric autoregulation.
3. Homeometric autoregulation.
4. Neural influences on myocardial contractility.

If the work load is excessive and the above mechanisms do not compensate, cardiac output will fall below normal.

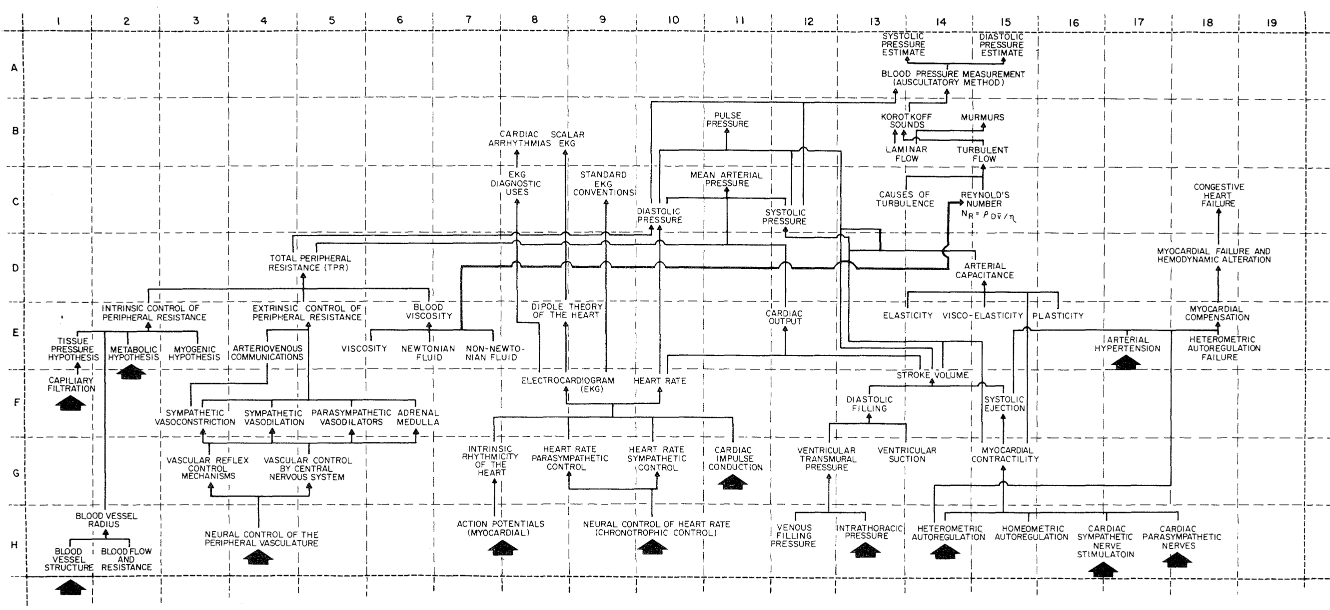

Fig. 1. Hierarchy of major topics relating to blood pressure, EKG, and congestive heart failure. [arrow symbol] indicates that this portion of the hierarchy is incomplete.

Sympathetic Vasodilation F4-5

Sympathetic vasodilator fibers can be demonstrated in resistance vessels that distribute to skeletal muscles by first blocking adrenergic constrictor effects with pharmacologic agents and then electrically stimulating sympathetic nerves. This technique provokes an active vasodilation. The vasodilation is caused by release of acetylcholine and can be blocked with atropine. These fibers do not appear to be tonically active. Their pathway originates in the motor cortex and then advances to the supraoptic hypothalamic area, the medulla and the spinal levels. They are activated during anticipatory fear or exercise (5,18).

Note that there is a capitalized letter-number combination following each topic heading which refers to the location of the topic in Figure 1. For example, Homeometric Autoregulation has the label H15-16 following it. An inspection of Figure 1 shows that this topic is found in blocks H15 and H16. An individual can refer from the hierarchy in Figure 1 directly to the core information by following the alphabetical order of the topic headings. The reverse is possible by using the letter-number labels. The topic Myocardial Compensation is given as a list of undefined terms because these terms are defined in detail at a lower hierarchial level.

DISCUSSION:

We have used two constraints as guides in the selection of material for this core of information on the cardiovascular system. 1) Only the information which is essential for the understanding of contemporary methods of diagnosis and treatment should be retained for the teaching of medical students. 2) A physician, because of his decision-making responsibilities, should be the most broadly trained member of a health care team. Selection of content is dependent on whether or not the information is supportive to the understanding of a clinical decision. "Understanding" is a key word with respect to the training of a medical student because a physician's task does not end with the recording of a single information bit; he must simultaneously evaluate many physiological and also pathological variables. Such performance requires knowledge in depth. On the other hand one must guard against the addition of excess information to the hierarchy. For instance, related to the core of information on Korotkoff sounds, there are several theories that can be used to explain their origin. These include fluid and wall vibrations caused by systolic impact (3), turbulent jets (2), stenotic flow (3), turbulent wakes (1), protodiastolic recoil (3), cavitation (11), arm resonation as the pulse enters (4), Bernoulli effects (16), and others (12). The decision to omit this information was based both on the lack of a generally accepted theory for the genesis of Korotkoff sounds (12) and, more importantly, on the fact that an understanding of these theories does not contribute to the performance of a physician.

DIRECT CLASSROOM APPLICATIONS:

An instructor may decide to use a prepared content hierarchy in a variety of ways. Since it is logically prepared to show prerequisite knowledge for subsequent teaching, the instructor could use the outline directly for the planning of lecture sequences. The hierarchy could be used no matter what method is chosen for the delivery of the information. Accordingly, an instructor preparing any programmed or audio-tutorial instruction could also use a content hierarchy. It is merely a matter of taking the outlined information and fitting it to the delivery method. The core content hierarchy could be given directly to the students in a similar form as in this paper. Under these circumstances the students could follow the logic of the instructor's pattern of presentation and also have a source of reference to cover for any omissions.

Medical instructors are traditionally independent. Hence, they might find a content hierarchy confining. If this is the case there would be a tendency to omit information or to expand on certain principles. The omission of essential information is not compatible with the use of a content hierarchy. It is important that there be no information left out of an individual instructor's presentation because the instructor who next teaches the student should be able to assume that the students have had the essential prerequisites. It is very important that instructors feel obligated to identify new concepts that are not as yet found in the hierarchy but may be applied in the future to tomorrow's clinical medicine. This responsibility is one method for overcoming the rigidity of the definition of "core" information. It is a safeguard that would prevent locking the student into a "No Change" learning environment. With periodic revision the new concepts should become part of the core as it becomes essential for the understanding of contemporary methods of diagnosis and treatment.

PSYCHOLOGICAL ADVANTAGES:

Hierarchies of core content not only prevent the omission of essential knowledge from the curriculum but have other salient features as well. For instance:

1. A content hierarchy shows the student how seemingly useless bits of information will be applied later to medical problems.
2. A hierarchy of knowledge is especially useful as a teaching aid for slower learners and forgetful individuals because it provides an outline of previously learned knowledge. The recall of this knowledge is required before an individual can learn something new or solve a problem (8,10).
3. A mastery of the knowledge within a content hierarchy enhances the student's ability to generalize and to transfer information to new uses (8,13).

PSYCHOLOGICAL LIMITATIONS:

The mapping of learning sequences to form a content hierarchy is not necessarily the ultimate answer for curriculum development and student learning. The major disadvantages are:

1. Hierarchies of knowledge, as the one presented, are not designed to replace books. For example, this hierarchy does not provide for the discussion of different forms of experimental evidence and hypothesis. They are prepared to show what knowledge is prerequisite to specific student performance.
2. Hierarchies of core content are psychological maps as opposed to being purely logical maps. Logical maps are prepared as sequences of deduction that can be followed by the student. However, students cannot take deductive steps just by following a content hierarchy because these maps show only sequences of content needed for learning steps. Sometimes a psychological map may also be logical and vice versa, but this is not necessarily the case.

PRACTICAL USES:

Content hierarchies have many practical uses. Seven major ones are listed below:

1. A content hierarchy can be applied directly to the planning of sequences of instruction because it is prepared by mapping sequential levels of knowledge.

2. Hierarchies prepared to the "presumed" level of the entering medical student can be tested against the actual knowledge that the students have at their command. If the presumed knowledge level of the hierarchy does not fit that of the students it can be corrected.

3. Content hierarchies are ideally suited for developing a rational basis for testing prospective medical students for scientific preparation.

4. The very sequential nature of a content hierarchy shows that some types of knowledge are prerequisite to certain forms of learning experiences. Similarly, it can be shown that some forms of clinical experience can be learned concurrently with physiological instruction, whereas others require physiology or some other discipline as a preclinical science.

5. A hierarchy of knowledge provides a defined point or level at which the intern or resident is ready to begin his applied training.

6. Hierarchies can be used as a reference for correction and change within the medical curriculum. They also provide a rational basis for allocation of teaching hours.

7. Teachers need to cross interdepartmental lines and jointly prepare a content hierarchy of broad scope. One of the major purposes of a content hierarchy is to bring information together where a student can see interrelationships of knowledge rather than isolated information in separate blocks.

CONCLUSION:

Core content hierarchies aid in student learning as well as in the practical problems of curriculum content selection and the allocation of teaching hours. The methods described in this study are reasonable, objective, and are appropriate for preparing hierarchies of core content for medical school use.

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INFORMATION FOR AUTHORS:
The Laboratory Experiment

Those of you who have developed new laboratory experiments or interesting modifications of classical experiments in physiology and would like to share them with your peers and their students may find the following instructions helpful in organizing information for publication in The Physiology Teacher.

1. The title should be short and informative.
2. Give author(s) name, department and institution, city, state and zip-code.
3. Submit two copies of the manuscript so that one copy can be sent to a referee for critical review.
4. State the general objective of the experiment and present the subobjectives in the introduction.
5. If the physiological process being tested or demonstrated has an interesting history, write up the background to give the student some insight into the evolution of the concepts regarding the process.
6. Give a detailed and specific list of the materials that will be needed to perform the experiment successfully. For instance:
   a. Identify the test subject.
   b. When used, identify the type and concentration of the anesthesia and the method of administration.
   c. List all required instruments, equipment and reagents. Identify the source of any special items.

d. When new drugs or chemicals are used, the chemical name should precede the trade name and information given as to the availability and the source.

e. Give the concentration and the pH (if necessary) of all solutions.

5. Describe the procedure completely, preferably in numbered steps. Remember that a student doing the experiment for the first time needs guidance over possible pitfalls.
6. Give typical results and observations and discuss them.
7. Illustrate sample data in graphic or tabular form. Photographs of animals are not acceptable; use line drawings. Include a legend with each figure and identify each with a figure number.
8. Chemical and biochemical terms and abbreviations should be in accordance with the recommendations of the IUPAC-IUB Combined Commission on Biochemical Nomenclature. Refer to the CBE Style Manual (3rd ed., AIBS, 1972) for commonly accepted abbreviations, word symbols, etc.
9. Cite references as follows: last name of first author, followed by initials; initials and last names of each coauthor; title of article (first word only capitalized); name of journal (abbreviated as in *Chemical Abstracts List of Periodicals);* volume, inclusive pages, and year.

LETTERS

Dear Dr. ___________:

The Education Committee of the American Physiological Society intends to establish an "Educational Materials Review Board" to assist the Committee in the search for and evaluation of materials useful to teachers of physiology. The purpose of this letter is to ask whether you would be willing to serve as a member of the Board.

As you are no doubt aware, the Society has been involved for several years in an on-going evaluation of audiovisual and related teaching materials in the various sub-specialties of physiology. As a member of the Board, you might be called upon, from time to time, to review materials in your particular area of specialization.

Another function of Board members would be to provide, one each year, brief abstracts (see enclosed example by Arthur Guyton) of review articles or other educational materials in your physiological specialty that would be of particular value to teachers of physiology. We would hope to receive these abstracts by April 1 of each year for publication in the May issue of The Physiologist and The Physiology Teacher. This information would then be available to teachers planning courses for the coming school year.

We earnestly hope that you will be willing to serve the Society in this endeavor. I shall look forward to hearing from you.

Sincerely yours,

Jack L. Kostyo
Chairman, APS Education Committee

MEMBERS, EDUCATIONAL MATERIALS REVIEW BOARD
Educational Materials Abstracts

As described in Dr. Jack L. Kostyo's invitational letter of September 8, 1975, as a Board member you are called upon once a year to provide abstracts of valuable educational materials and review articles for publication. This year you abstracts will be published in the April issue of *The Physiology Teacher.* This in turn will be provided to the membership of the Society as a complimentary issue in the mailing of *The Physiologist* in May.

Enclosed are self-explanatory abstract forms which when submitted constitute the camera-ready copy to be entered directly into the photo-offset reproduction system. Multiple copies of the form are enclosed so as not to inhibit the number of abstracts submitted by any Board member. Surplus copies may be returned with the completed abstracts.

Will you please provide one or more abstracts of the best reviews available in your fields of special competence, whether they be journal review articles, chapters of books, monographs, or whatever form of publication they exist in, so long as they are generally available to interested users. I emphasize that to meet our rather tight publications schedule, we should receive your abstracts by March 29.

This is the first effort to provide teachers of physiology with material of this nature. We believe the program's value and significance will gain immediate recognition, and we sincerely appreciate your interest and cooperation in making this possible.

Orr E. Reynolds
Executive Secretary-Treasurer

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