Manipulatives Help to Teach Molecular Diagnostic Concepts

Learning involves coordinating sensory input with neurophysiologic and mental phenomena to foster thinking, intelligence, and learning. Although many theories exist for learning, educational psychologists Piaget and Thorndike developed theories based on constructive or incremental-stage learning. Fundamental to their theories is the belief that knowledge and understanding develop in stages in which the learner moves toward a goal in an organized manner. Piaget firmly believed that knowledge acquisition was a continuous process of self-construction and reinvention.

Students of clinical laboratory science (CLS), cytotechnology, and histotechnology enter their courses and training with a general education. Clinical instructors build on this foundation to lead the student into the application, interpretation, and evaluation levels of thinking required of the clinical professional.

Meaningful learning should: (1) facilitate the linkage between the new information and what is already in the cognitive structure, (2) facilitate the student's ability to discriminate new ideas and their application, and (3) increase the stability and clarity of anchoring old ideas. Through well-planned lessons, learning objectives, and curricula, instructors proved incremental steps for learning to help students acquire large bodies of knowledge while providing "safe" practice episodes that stimulate higher-level thinking.

Molecular-based clinical testing permeates all laboratory disciplines. Our understanding of it advances rapidly, and instructors must continually educate themselves so they can include the new technology in their curricula. A gap between cutting-edge technology and existing curriculum often exists until the instructor integrates the new methods into didactic lessons and acquires instructional materials and instrumentation for laboratory experiences.

ABSTRACT
Changes in technology and diagnostic health care challenge clinical laboratory science program administrators to meet the diverse needs of students, affiliated training institutions, and prospective employers. In particular, molecular techniques, which permeate all disciplines of clinical and anatomic pathology, are forcing instructors in clinical laboratory science, cytotechnology, and histotechnology to ensure that students have technical and clinical skills in this area. We developed lessons that use manipulatives—hands-on learning tools that students can physically manipulate to develop conceptual foundations during guided activities—to integrate molecular theory, practice, and application into a clinical laboratory science curriculum. Results gathered from student projects, assignments, and examinations indicate that students are better prepared to interpret molecular-based data and to apply molecular techniques to new clinical test systems.

Lessons that incorporate the use of manipulatives can bridge the gap and provide an avenue for continual change and rapid accommodation of new technologies into the curriculum. Manipulatives—powerful tools used to teach geometry, fractals, discrete mathematics, and language skills to learners at any level—allow students to play freely with concepts and ideas (as children do while learning mathematics) and learn through trial-and-error practice. They offer opportunity for remediation and peer tutoring without the added expense of reagents or instrumentation. Manipulatives can also be used to assess learning because they lead to measurable outcomes.

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This article presents teaching strategies successfully used in CLS instruction, student activities, and problem-solving exercises. Students worked in pairs, groups, or independently to complete learning packets that included molecular biology manipulatives designed to develop fundamental molecular theories while allowing for exploration, trial-and-error strategies, and data interpretation.

**Materials and Methods**

**Restriction Fragment Length Polymorphism Mapping**

We obtained Popsicle sticks from a local hobby shop and dyed them different colors. Each stick represented an enzyme restriction-digested DNA fragment prepared from genomic DNA. (A restriction enzyme cleaves the DNA at a certain base sequence.) Each Popsicle stick was labeled for patient identity and fragment length. Each patient had a set of Popsicle sticks that represented all DNA fragments generated from enzyme restriction digestion of their DNA.

To prepare a DNA molecular weight ladder, we labeled plain Popsicle sticks with DNA fragment lengths corresponding to commercially available DNA ladders (Promega, Madison, WI). We then glued these molecular weight marker Popsicle sticks to a 44 × 88-cm piece of white construction paper in a pattern corresponding to the size-separation pattern for the DNA ladder published by Promega.

In this learning unit, we gave students learning objectives and lectures on genomic DNA isolation, enzyme restriction digests, Southern blotting, and DNA visualization techniques and associated reading assignments in their text. We then gave the students prepared case histories for each set of Popsicle sticks, the Popsicle sets, DNA molecular weight ladder, and questions to answer.

Working in groups of 3 to 5, the students arranged the Popsicle sticks next to the molecular weight ladders to generate the restriction fragment length polymorphism patterns for each person (Fig 1A-C) and then analyzed the patterns to answer case history questions. (Polymorphisms are variants associated with a genetic locus in the same species, e.g., ABO and Rh blood groups.)

**Bioengineering**

To make plasmid models, we used a string of polyester-covered cotton (a string of 1/8-inch diameter), highlighters, and colored electrical tape. (A plasmid is a circular DNA strand that exists outside and separate from the chromosome of a bacterial cell.) The string represented the DNA sequence within the plasmid and the yellow- or blue-highlighted regions corresponded to antibiotic resistance genes or genes of interest, respectively (Fig 2A).

To indicate enzyme restriction sites, we wrapped colored electrical tape around the string at strategic locations. One of the sites was used to connect the ends of the string with electrical tape.

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![Fig 1. Mapping with manipulatives. Popsicle sticks represent restriction digested genomic DNA fragments isolated from each person in the case history. A, Students in groups of 3 to 5 lay out the Popsicle stick sets that generated restriction fragment length polymorphism (RFLP) patterns for each person. B and C, Students interpreting the RFLP patterns to answer case history questions.](https://academic.oup.com/labmed/article-abstract/31/9/513/2657135/Manipulatives-Help-to-Teach-Molecular-Diagnostic/514)
to make an intact plasmid. Colored electrical tape represented the following restriction enzyme sites: EcoRI (orange), EcoRV (black), Hind III (brown), SacI (green), and Smal (red).

An animated plasmid picture was generated by computer to correspond to the plasmid models. We prepared plasmid digests by cutting the string at the restriction digest sites (Fig 2B). We used a large resealable plastic bag to contain a single plasmid digested with a single restriction enzyme. We labeled each bag with the color-coded restriction digest enzyme. We left 1 plasmid intact and cut another to use as an answer key.

We gave the plasmid map, bagged plasmid models, and intact plasmid to the students. Their assignment was to transfer a DNA fragment (corresponding to a signal sequence peptide) within the gene of interest into another plasmid or expression vector so the gene could be characterized.

We allowed students to work in groups or independently while they simulated DNA restriction digests and did gel purifications to separate the DNA fragments for subcloning. Students then formulated an experimental plan and checked their answers with the plasmid answer key.

DNA Probe Synthesis and Hybridization
After purchasing unmarked, colored cardboard puzzles from an art supply center, we taped 5 pink puzzles together on their backsides. The combined puzzles represented double-stranded DNA. To denote unique sequences within a specific gene, we handwrote the 5′—>3′ DNA sequences and complementary 3′—>5′ DNA sequences (including sugar phosphate backbone) onto the front of the linked puzzles (Fig 3A). We removed a portion of the complementary 3′ — > 5′ DNA sequence, filled in the vacancy with yellow puzzle pieces, and labeled yellow pieces with the complementary 3′ — > 5′ DNA sequence (the phosphates contained an asterisk to indicate a radioactive label). The yellow pieces corresponded to a synthesized radioactive oligonucleotide (a polymer of a few nucleotides) used as a probe to detect the gene of interest in a hybridization experiment. The yellow puzzle pieces were then separated from the pink puzzle as an intact oligonucleotide. The pink puzzle was then put back together to represent double-stranded DNA.

The students were then given hybridization conditions, and the intact pink (double-stranded DNA sequence) and yellow (radioactive oligonucleotide) puzzles and asked to explore the processes associated with probe hybridization and detection of specific gene sequences (Fig 3A-D). We referred the students to Genbank,10 a database of DNA, RNA, and protein sequences at the Web site: http://www.ncbi.nlm.nih.gov/) for a computer-assisted instructional unit. The students were asked to search the database, identify a gene of interest (and a unique DNA sequence within that gene), and formulate an experimental design that includes the preparation of a radioactive oligonucleotide (probe) and the hybridization conditions. Students had to search Genbank for related sequences to show that their probe was specific for the gene of interest. They also had to discuss limitations and sources of error of the hybridization conditions.
Results and Discussion

When integrated into student learning packets, manipulatives have been successful aids to teaching mathematics. Public school teachers report increased student involvement and mastery.\textsuperscript{11-13} We had similar success with CLS students, who were eager to use molecular manipulatives (in groups or independently) and showed great interest in the concepts and processes depicted in the manipulative exercises (Fig 1A, B; 2A, B; 3B, D). Group discussions were intellectual and collaborative (Fig 1A, B; 2A, B), with all students offering opinions and rationalizations for their interpretations. Similar to results reported in teaching mathematics with manipulatives,\textsuperscript{14} CLS student discussions (held while students worked with manipulatives) expanded each student’s literacy and enhanced the correct use of terms.

Manipulatives integrated into learning packets tend to incrementally build student learning. When our students completed the learning units, they could think (and work) at higher levels, which showed their ability to transfer concepts to new scenarios or create experimental designs of their own. They easily completed the assessment task, which included developing a new diagnostic assay for an infectious disease. Test scores (data not shown) revealed that students (1) understood molecular principles, (2) could interpret data, and (3) could formulate conclusions or make a diagnosis.

According to K-12 educators,\textsuperscript{15} manipulatives must be part of the teaching strategy but are “not for all students” or all-inclusive. In our study, manipulatives helped students to solidify concepts through visualizing and physically exploring topics covered in lecture. Most students accepted and enjoyed using manipulatives, but others may learn best through other learning styles such as lecture, observation, reading, or independent study.
Parameters for using manipulatives were suggested by an experienced educator to increase the successful use of manipulatives in the classroom. These parameters—setting ground rules for manipulative use, allowing time for free exploration and group discussion, clear descriptions or demonstrations of how to use the manipulatives, and clear expectations for student learning and evaluation—improve the effective use of manipulatives.

According to another educator, manipulatives can also be part of the curriculum for education because instruction on how to use them improves their usefulness in teaching. Future instructors need exposure to such alternative teaching styles. In addition, teaching strategies that include manipulatives not only augment learning units, they provide another avenue to reach out to individual learning styles.

Manipulatives have also bridged the gap between theoretical methods and physical instrumentation. This is fortunate because training program administrators cannot afford to purchase new molecular instrumentation—it changes as rapidly as our understanding of molecular biology. Manipulatives also allow students to practice new technology at no added program expense, and students gain understanding and confidence when they take up the new technologies at the clinical affiliate sites where molecular clinical diagnostics are used.

References
10. Genbank Database, National Center for Biotechnology Information, National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894.