Problem Solving Learning: Applications in Medicinal Chemistry

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This study describes the implementation of a didactic methodology in medicinal chemistry known as problem solving learning. Students were divided into groups of four to nine students predicted to have varying aptitudes in these classes based on their performances in previous chemistry courses. Prior to coming to each class, students are required to read a specific portion of the class notes and answer the questions posed at the end of each reading assignment. A problem set based on the designated reading is distributed to all students who then work in the small discussion groups. At the commencement of the next class, answers to the problem set are presented by the instructor or alternatively by students from one or more of the groups. This approach is viewed positively by the students as a stimulating and challenging way to understand medicinal chemistry.

INTRODUCTION

For a number of years, the author has taught half of a compulsory medicinal chemistry course in the penultimate year of the 1+4 undergraduate program at the University of Saskatchewan, as well as an elective on drug design in the final year. The presentations were made using a traditional “chalk and talk” method whereby the information was placed on a board and dutifully copied by the students.

However a number of factors caused the author to re-evaluate this teaching methodology. In the first place, could not the time be better spent than the teacher honing skills of dexterity with chalk and the student in developing note-taking skills? Secondly, little time was available for the students to think about the subject matter, to ask questions or to discuss the material with fellow students or the instructor. Thirdly, the closed book examinations consisted of multiple choice questions. Although this method of evaluation presented novel problems to the students, it inflicted excessive emphasis on memorization of the material and in addition only right or wrong answers were permitted. Students did not have the opportunity to explain why they had reached various conclusions which, if ultimately incorrect, would deny them some credit for at least thinking correctly part of the way. Clearly the point had been reached for some radical changes in both teaching methodologies and examinations.

Recently an episode provided sufficient motivation for changes when the attention of the author was arrested while reading the introductory comments of Medieval Church History. This book was written in the 19th century by Dr. R.C. Trench who at that time was the Anglican Archbishop of Dublin. He was a prolific writer and possessed an incredible wealth of knowledge. Yet in discussing teaching church history to “girls of the upper and middle classes,” his approach to the matter seemed inordinately unimaginative as illustrated by the following partial quotation from a 155-word sentence.

“How far the wearers of bonnets would bear the strain of competition with those thus assumed to be in exclusive possession of brains... on this I give no opin-

A red flag was raised, i.e., is this all there is to teaching namely to have students receive, assimilate and reproduce knowledge? Thus commencing with the 1995-96 academic year, didactic lectures were eliminated and instruction was given solely by a procedure which may be called problem solving learning (PSL). The aim of this presentation is to describe how PSL has been applied to teaching medicinal chemistry at this institution although the principles involved are applicable to other subjects including all of the disciplines in pharmacy schools.

MODUS OPERANDI OF PSL

A description of the various stages in utilizing PSL follows.

Division into Groups

The first action to be taken prior to the beginning of the academic year is for the students in each class to be divided into groups. In the opinion of the author, the ideal size of the group is four to six students which is the situation in the drug design course. However the dearth of available small rooms mandates that the medicinal chemistry class of 75-80 students be divided into nine groups each containing eight to nine students. Self selection into groups would likely lead to markedly divergent levels of ability and attainment(2) and the clusters of students should have similar capabilities. The division into groups is based on their performance in specific classes taken in preceding years namely an organic chemistry course for those students commencing the medicinal chemistry class while individuals electing to take the drug design course are divided into groups which are determined by the marks obtained in the medicinal chemistry class taken one year previously. The way in which students are divided may be illus-

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Table I. Objectives of the medicinal chemistry and drug design courses

1. The objectives of the medicinal chemistry class are to enable the student to gain an understanding of the following general areas of study
   - The structures of different drugs
   - The modes of action of certain drugs
   - Solubilities of organic molecules
   - Chemical reasons for the toxicities of drugs
   - Metabolism of organic compounds
   - Nomenclature of drugs
   - Physicochemical properties of some drugs
   - Various correlations between chemical structures and bioactivities

2. The objectives of the drug design class are focussed to enable the student to achieve the following goals
   - Gain an understanding of the history behind the evolution of new drugs
   - Obtain a grasp of different general approaches to designing new drugs such as the prodrug concept and the limitations of such techniques on occasions
   - Achieve an understanding of different terms used in drug design such as soft drug and obstructive halogenation
   - Obtain a familiarity with various physicochemical techniques for predicting bioactivity including QSAR and molecular modeling approaches
   - An awareness of the chemical, biochemical and physicochemical properties of specific chemical groups such as halogens
   - To be able to design candidate drugs

The Problem Set

The situation so far is as follows. The students will have been given a reading assignment at the beginning of the previous class. This task should have been completed along with the PCSE. At the current class, each student receives a problem set and proceeds to the group to which assignment has been made previously. Some general comments on the questions posed will be made followed by specific examples.

The nature of the problem set will vary. Generally the questions will be based on the class notes. For example, if the general principles of the solubilities of organic compounds was the subject of a reading assignment, the students will be presented with the structures of drugs hitherto unencountered and asked to make predictions of their solubilities in pharmaceutically acceptable solvents such as aqueous sodium bicarbonate solution. However on occasions prior to the current problem set being tackled, one student in each group will have been deputed to obtain some information from the library such as the structure of an organic compound which is not found in the class notes. The information will be required in order to answer one of the questions on the problem set.

In the case of the medicinal chemistry course, often there is only one correct answer to the question such as when the problem requires assigning the stereochemistry to a molecule or indicating how the drug will react with a certain class of cellular constituents. However some speculation is necessary on occasions when, for example, the prediction of a metabolic route of a molecule is required and naturally a variety of plausible answers may be given. On the other hand in answering the problem sets in the drug design course, there is little likelihood for the same groups producing identical answers. In other words, generally there are no specific answers to the problems which have been posed. Thus the questions may pertain to the design of compounds which will gradually release an acid which has pronounced biological activity and to this poser a myriad of answers could be given such as controlling the rate of release by steric, electronic and other physicochemical means. Alternatively the answer may require designing a molecule to react with a specific receptor site and there are almost unlimited ways in which an answer may be achieved. Thus the students are being taught to think in a creative and original fashion. Specific examples of the questions posed on the PCSEs and problem sets in both the medicinal chemistry and drug design courses will be given in order to clarify the PSL approach.

In the case of the medicinal chemistry course, one of the reading assignments outlined the use of nitrogen mustards in cancer chemotherapy. This section of the class notes commenced by indicating the structure of mechlorethamine hydrochloride \( \text{I} \). The mode of action of this drug was presented namely its conversion in vivo into a cyclic ethyleneimmonium ion and subsequently a carbonium ion which then alkylates various cellular constituents including position 7 of the guanine residue of DNA. A disadvantage of \( \text{I} \) is its rapid inactivation by hydrolysis. The reasons for and examples of various structural modifications of mechlorethamine hydrochloride designed to lead to superior products were outlined including the preparation of various aryl nitrogen mustards such as chlorambucil which has lower chemical reactivity than \( \text{I} \) and is less readily inactivated by hydrolysis. The structure of \( \text{I} \) and examples of a PCSE and examples of a PCSE and questions on a problem set are given in Figure 1.

In the case of the PCSE, the students will be challenged to

Introductory Booklet and Class Notes

At the commencement of the first lecture, an introductory booklet is disseminated describing the objectives, format and outlines of the courses as well as some of the relevant resource materials in the libraries and details of the examinations. The objectives of the two courses are summarized in Table I. An important segment of the booklet is a description of the method of undertaking peer evaluations (Table II); this procedure will be discussed subsequently.

All students are required to obtain the class notes which are divided in such a way that each reading assignment is equivalent in content to one lecture period (80 minutes). At the end of each reading assignment there is a preclass self examination (PCSE). These questions serve as an indicator to the student as to how well the material has been understood and may also provide assistance in preparing the student for the problem set. The PCSE is designed to be undertaken on an individual basis but if time permits, it may be discussed in the groups after the problem set has been completed.
describe the way in which \( 2 \) will react with a different cellular constituent than the one stated in the class notes. The second part of the PCSE will bring into focus the fact that chemical reactivity (and bioactivity) can be controlled by the electronic nature of the aryl substituents. If the students have worked diligently at the PCSE before coming to class, they will be in a good position to reflect how \( 3 \) will react with the amino acid \( 4 \). However they should be sufficiently alert to the fact that attack of the carbonium ion derived from \( 3 \) on the carboxylate anion of \( 4 \) will liberate a certain proportion of molecules possessing a free amino group which can then be alkylated. For the second question of the problem set, answers should indicate a realisation that the chemoprotectant mesna can attack at the \( \alpha \beta \) unsaturated keto group as well as the nitrogen mustard function.

Some examples of the type of questions asked in the drug design course are as follows. An important subject in this class is gaining an understanding of the important contributions that various physicochemical constants make to bioactivity. This area includes familiarity of the noncomputerized method of Topliss using a potency order table(4). In this procedure five compounds having the same side chain are prepared, namely the unsubstituted compound as well as those analogs possessing 4-chloro, 3,4-dichloro, 4-methyl and 4-methoxy substituents; an example of such a series is compounds 6-10 in Figure 2. These molecules are examined for bioactivity and arranged in order of potency. A table is consulted designed to reveal the contributions of the Hammett \( \sigma \) or Hansch \( \pi \) values of the aryl substituents to biological activity. When this information is to hand, a second table is examined which indicates new aryl substituents predicted to yield derivatives of equal or greater activity.

Thus in the example of a PCSE in Figure 2, students should be able to discern from the potency order table given in the class notes that there is an inverse correlation between antimicrobial activity and the magnitude of the Hammett \( \sigma \) value \( i.e. \) a \( -\sigma \) parameter is operational. In the case of the problem set, a different cluster of compounds with varying bioac-
tivity would normally be presented. However in the interest of brevity the same series is retained in Figure 2. The students would be expected to determine the parameter dependency from the potency order table i.e., $\sigma$, and then consult another table which indicates the selection of new substituents. Thus since a $\sigma$ parameter has been noted arising series 6-10, the 4-amino or 4-hydroxy analogs are rational choices since both compounds have aryl substituents with lower $\sigma$ values than 10 which is the most active member of the initial series. Acylation of the 4-amino or 4-hydroxy compounds would produce the corresponding ester or amide, respectively, and these resultant prodrugs are capable of liberating the parent compounds in vivo by hydrolysis. Thus in this example, students should gain an appreciation of the use of various physicochemical constants in drug design in addition to reinforcing the importance of prodrugs which is covered in another portion of the class notes.

At the time that the students in the courses give their responses to the questions, the author believes that encouragement is important whereby correct answers are applauded and those whose original thinking has led to erroneous conclusions should be redirected in a gracious and constructive manner. Under no circumstances should creativeness be squelched by unduly harsh words from the instructor.

The instructor visits each group of third year students to inquire if there are any queries, to ask and/or answer questions and to redirect those who are off on the wrong track. In general, the students interact well and teach each other.

In the medicinal chemistry class, the author gives answers to the problem set and the PCSE. For the drug design elective, the groups take turn in providing the group responses; these presentations can be by one or more of the students in the group. The reasons for the different approaches in the two courses are as follows. A number of students in the third year class struggle initially (and some continually) with the material. Hence as much time as possible is spent in the group discussions. On the other hand, students taking the elective course will need to combine a knowledge of general metabolic pathways with some ability in organic chemistry. Thus the metabolic steps leading to the formation of 12 from methadone(5) include N-demethylation and oxidation processes while the dehydrogenation steps, possibly by nonmetabolic processes, lead to ring closure and formation of the ethylenidene group. In order to answer the bonus question in the drug design course satisfactorily, the student should recognize that some of the structural features of 13 are present in ampicillin sodium. Polymerization can occur in concentrated solutions of this antibiotic by reaction of the side chain amino group of one molecule and the $\beta$-lactam ring in another molecule(6). In the case of 13, the primary amino group could react with the cyclic amidino function leading to polymerisation. Inhibition of polymer formation

### Table II. Peer evaluation of group discussion

1. Marks should be allocated for each member of the discussion group except themselves in each of the following four categories listed below. These marks should be out of 10 per category i.e., a maximum of 40 points is possible.

   **Category A:** Preparation: Has the student read the class notes and understood the material? Was the PCSE completed and, if so, how was it undertaken?

   **Category B:** Discussion: Was there a willingness to contribute to the group discussion or not?

   **Category C:** Value of Contribution: What was the value of the verbal contribution to the group? Were the comments correct and/or constructive?

   **Category D:** Attendance: In this regard, absenteism should be noted on the basis of the loss of 1 mark per absence unless reasonable excuses were proffered. It is expected that students will be firm and allocate the appropriate marks since PSL depends significantly on the input of all members of each group.

2. This peer evaluation is part of the student’s training for professional responsibilities when, in the future, assessment of others with whom one works will be necessary. This evaluation must be fair, honest and impartial. For those students who have taken their responsibilities seriously and have made sustained, significant efforts to solve the problems, high marks should be given. Conversely, students who have displayed inertia regularly and/or been inconsistent in their attendance should be allocated marks which reflect these shortcomings.

3. Any evaluation in which all students in the group are awarded full marks will be rejected.

4. The evaluation should be completed at home and definitely not in the groups. After completion and signature, it should be placed under the door of the instructor by 5:00 PM on December 5. Marks will be deducted if the peer evaluations are late.
could occur by forming the corresponding acetonide; this molecular modification has been undertaken with ampicillin leading to heticillin(7).

The reasons for creating a bonus question are as follows. First, the exams are designed for the average student and not for the superior ones for whom the subject matter presents few difficulties. Hence the presence of a bonus question provides a mechanism whereby those who excel in the subject may be duly compensated. Second, the regular part of the examination will not accurately reflect the potential complexities of the subject matter. A bonus question will therefore ameliorate this false impression.

Normally two midterms of one hour duration and a final examination of two hours are held in the 13-week term. These evaluations count 90 percent towards the final mark in the course. The remaining marks come from peer evaluations vide supra.

**BENEFITS AND PROBLEMS OF PSL**

The benefits of PSL are perceived to be as follows. First, in general the students enjoy the interactions in the small groups. They teach each other and learn together; in short, it is an active learning process rather than the traditionally passive approach of note taking. Second, verbal and written comments from different students indicated a belief that retention of the material was greater with PSL than other didactic models. This viewpoint is in concert with a recent report stating that when students taught each other, the retention rate was 90 percent in contrast to a figure of five percent when the lecture format was utilized(8). In addition, the situation may arise when a group thinks about a problem for a while and draws an erroneous conclusion. It is likely that when the correct answer is given, it will be impressed on the knowledge bank of the student to a greater degree than if the student was simply taught the material. Third, PSL will prepare pharmacy students for their participation as a member of the health sciences team in which working together with a view to solving various problems takes place. In other words, the interactions in groups (as well as peer evaluations vide supra) afford excellent training for professional responsibilities.

What are some of the difficulties noted with PSL? The American humorist W. C. Fields in his scintillating monograph having the intriguing title of “Fields for President” entitled the third chapter as follows.

"How to beat the federal income tax - and what to see and do at Alcatraz "(9).

Beneath the humor lies the grim reality that while something may be a good idea in theory, practical realities are otherwise. Nothing is perfect in this imperfect world. The principal drawback noted in this experimental method of teaching is not so much with PSL (although doubtlessly this process will be altered and refined in the future) but with those students whose commitment to active participation was very poor. In some of the groups in the medicinal chemistry class, the instructor became aware of a few passengers whose input was minimal and unfortunately their performance was not reflected in the peer evaluations. However the difficulties being endemic are unlikely to be overcome by organizational means. Initially no marks for absenteeism were deducted in the peer evaluations. However this problem soon surfaced since the students were in possession of the notes and could obtain answers to the problem sets from their classmates. Hence certain of the marks of the peer review refer to attendance at the group discussions. The problem of absenteeism has now virtually been eliminated.

**COURSE EVALUATIONS**

Monitoring of the teaching in the College is undertaken using a course evaluation sheet which rates the instructor as well as the lectures and examinations from different perspectives as indicated in Table III. Currently there are no procedures in place to attempt to correlate retention and comprehension of material with variation in didactic methodologies. For a con-
CONCLUSIONS

This overview of PSL is presented along with an aspiration for its consideration as a teaching methodology for instructors in post-secondary centers of learning. PSL is a somewhat different strategy than problem based learning (PBL) whereby a problem is presented initially and self-directed learning ensues(10). The strategy of PBL has been incorporated into a number of curricular changes in pharmacy schools(11) and both PSL and PBL have the aims of increasing student participation in the learning process and encouraging critical thinking. It is the belief of the author that students should be exposed to a mosaic of didactic methods which will enliven the learning process and for those students who will subsequently become instructors, an appreciation of different approaches will have been gained.

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table III. Student course evaluation in the medicinal chemistry course for the 1996-1997 academic year

<table>
<thead>
<tr>
<th>Instructor’s Group</th>
<th>Mean value</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Knowledge of his/her subject</td>
<td>4.3</td>
<td>0.26</td>
</tr>
<tr>
<td>2. Interest in his/her subject</td>
<td>4.7</td>
<td>0.54</td>
</tr>
<tr>
<td>3. Skill in presenting subject</td>
<td>4.5</td>
<td>0.79</td>
</tr>
<tr>
<td>4. Self-confidence</td>
<td>3.9</td>
<td>0.83</td>
</tr>
<tr>
<td>5. Stimulating intellectual curiosity in students</td>
<td>4.0</td>
<td>0.90</td>
</tr>
<tr>
<td>6. Providing opportunities for questions in class</td>
<td>3.9</td>
<td>0.99</td>
</tr>
<tr>
<td>7. Ability to answer questions</td>
<td>4.3</td>
<td>0.80</td>
</tr>
<tr>
<td>8. Willingness to consider views which differ from his/her own</td>
<td>4.4</td>
<td>0.74</td>
</tr>
<tr>
<td>9. Instructor’s overall performance</td>
<td>4.4</td>
<td>0.72</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lecturer’s Group</th>
<th>Mean value</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Organization of subject matter</td>
<td>4.2</td>
<td>0.14</td>
</tr>
<tr>
<td>11. Incorporation of up-to-date subject matter</td>
<td>4.5</td>
<td>0.60</td>
</tr>
<tr>
<td>12. Speed of presentation</td>
<td>4.2</td>
<td>0.71</td>
</tr>
<tr>
<td>13. Overall rating of this course as a learning experience</td>
<td>3.8</td>
<td>0.93</td>
</tr>
<tr>
<td>14. Course outline well defined</td>
<td>4.0</td>
<td>0.95</td>
</tr>
<tr>
<td>15. Lectures follow course outline</td>
<td>4.4</td>
<td>0.66</td>
</tr>
<tr>
<td>16. Subject matter easily understood</td>
<td>4.4</td>
<td>0.63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluation Group</th>
<th>Mean value</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Ability of tests, examinations to evaluate understanding of class material</td>
<td>4.2</td>
<td>0.77</td>
</tr>
<tr>
<td>18. Lack of ambiguity in wording examination questions</td>
<td>4.1</td>
<td>0.66</td>
</tr>
<tr>
<td>19. Fairness in grading</td>
<td>4.2</td>
<td>0.85</td>
</tr>
<tr>
<td>20. Fair proportions of final grade based on tests, examinations and assignments</td>
<td>4.3</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*The rating is on a scale of 1 (poor) to 5 (excellent).

executive period of three years prior to PSL being implemented namely 1991-1993, the evaluations for the instructor in the medicinal chemistry course were 4.0, 4.0, 4.0, 3.8, respectively, (average of 3.9) and in the drug design class, the relevant figures were 4.3, 4.6 and 4.3, respectively, (average of 4.4). For the next academic year, the author was on sabbatical leave and hence no data are available for the 1994-1995 year. Four academic sessions have been completed using PSL and the figures for the overall performance of the author during this time frame in the medicinal chemistry course were 4.5, 4.4, 4.1 and 3.4, respectively (average of 4.1) and for the drug design class the values were 4.8, 5.0, 4.1 and 4.8, respectively (average of 4.7). Thus apart from an unusually low evaluation during the 1998-1999 academic year in the medicinal chemistry course, there has been a perceptible improvement in the review of the instructor by the students.