WRITING PROBLEMS

A Personal Casebook

P.K. Rangachari

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Prolegomena to Problem Writing:

The role of "problems" in problem-based learning is largely to serve as a stimulus or focus for students to direct their learning. Much debate rages over the definition of "objectives". Although such arguments can be useful, it is sometimes more effective to be slightly more pragmatic.

I choose to follow the example of Eliot Eisner and broadly categorise "objectives" or "educational goals" into two broad categories (Instructional and Expressive). The former refers to what we conventionally regard as the "content" of a course C i.e. the items of information/ key concepts that student must acquire from a particular course. The latter on the other hand provides the student an opportunity to explore issues of specific interest to that particular student. Clearly many courses have both instructional and expressive elements, though as students progress with their learning in any particular area, the proportion of expressive to instructional elements should be greater. It would be particularly depressing if senior level or graduate courses were purely instructional. In a PBL course, problems serve as a focus for discussion.

Instructional objectives are the temptations of the devil and difficult to resist. Faculty often lay these on so thick that the poor student who gets buried beneath the weight of the Professor's erudition, surfaces periodically only to sink again. I prefer to look at the content of a course from a different perspective. I ask myself "Would I be embarrassed if a student who has completed my course does not even know this?" This permits me to frame a list of items that form the basis of a non-embarrassing curriculum and provides scope for the provision of more expressive goals.

In writing problems for ANY course it is pertinent to ask the following questions:

A) What are the overall goals of the programme?
B) What are the specific instructional goals of this particular course?
C) At what stage in their learning do students take this particular course?

The third question is particularly important, since the nature of the problems written and consequently the expectations would to some extent depend on the level of the sophistication of the students and their background in the area covered.

It is difficult to stipulate what is a good problem for such purposes. It may be useful to ask questions such as:

How long should this problem be?
How can I ensure that students do not miss key concepts?
How can I make this problem interesting, challenging?
How much data do I provide?
How "open-ended" should this problem be?

Before I begin to write any problem, I set down a few specific content elements that must be covered. To ensure that these cannot be avoided, I include key words, phrases in either the problem or the data provided. I then try to dress up the problem so that students can explore other issues if they so choose. I try to avoid inordinately lengthy problems. However, where a case evolves, a problem can be written in stages. Even then it may be better to keep individual sections brief. The open-endedness of any problem depends on the overall objectives of the course and the degree of sophistication of the students.

In the courses that I teach, I try to strike a fine balance between the requirements of the particular course and my own whimsy. In the following pages, I have included a set of problems that I have written for several different courses. In each case, I give the background of the course, the level of the students and the particular instructional objectives. In addition, I add brief comments about each of the problems. Comparison of the problems can give a flavour of the different styles that can be adopted.

Problems written for an Undergraduate Course in Pharmacology:

This is an introductory course in pharmacology taken by 3rd year undergraduate students enrolled in a combined Biology-Pharmacology Coop Programme. The students have had two years of biology at this University but have not taken pharmacology and this is the first small group tutorial based course for most of them. Time has to be spent in getting students to acquire some of the process elements.

The content objectives were described in the course outline as follows:

Pharmacologists are interested in providing answers to two central questions (a) WHAT does the DRUG do to the Body (pharmacodynamics) and (b) WHAT does the BODY do to the DRUG (pharmacokinetics).

To answer the first question, it is necessary to acquire information about: **dose-response relations, graded and quantal dose-responses, potency, efficacy, therapeutic and toxic effects of drugs, drug receptors, the logic underlying the classification of receptors, the experimental definition of receptors, agonists (the dimensions of agonism), antagonists, receptor-response coupling and the non-receptor mediated effects of drugs.**

To understand what the BODY does to the DRUG, you would need to acquire information about: **Absorption, distribution, biotransformation, excretion of drugs, orders of reaction (first, zero orders), routes of administration, different formulations, bioequivalence, definition and measurement of pharmacokinetic variables such as volumes of distribution, elimination rates, half-lives and areas under the curve**.

Once you have acquired these items of information you will be able to **apply** these to **specific categories** of drugs such as those acting **on the autonomic nervous system, central nervous system, chemotherapeutic agents, antifertility drugs.**

Malt does more than Milton can
To justify God's ways to man
A.E. Housman, A Shropshire Lad

DOES MALT DO MORE?

It had been a tough year. This PBL stuff was all right but it was becoming a bit of a strain. Self-direction was fine up to a point. Critical analysis was fine in theory, but to do it constantly was tiring. It would be really nice to sleep comfortably while the teachers droned on. And all that writing, the TRIPSES (what a juvenile term for something actually useful). Now the Wild One in 2J24 was demanding that they come up with a lab project. This was going a bit far. Why could he not do what others did. Have really simple cook book labs corrected by those who had little interest, less time and no knowledge of the language.

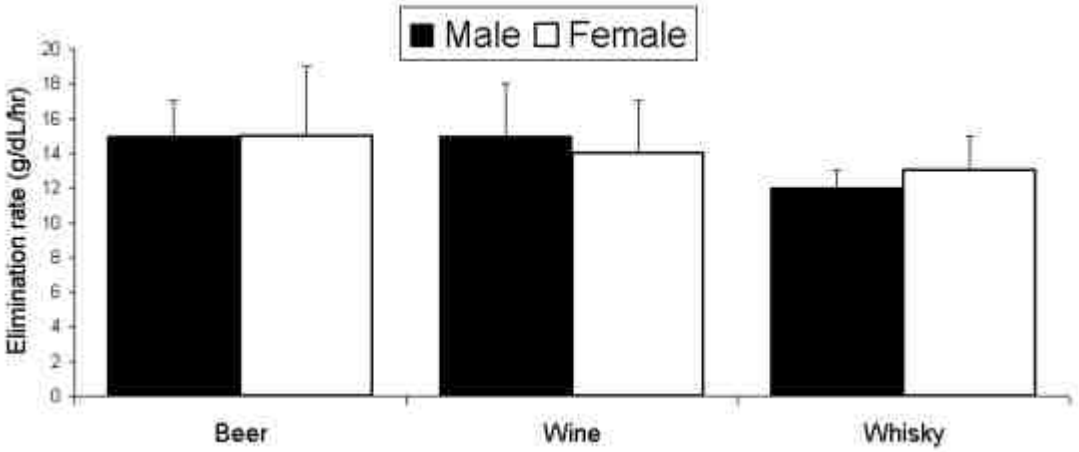
Well, if they had to show that they had learned pharmacology what better project than one dealing with man's best friend (beer, not as most think, some snivelling, panting, leg-lifting mutt). So David and Denise set out to entice their friends to sign up for a research project. Not that much inducement was needed. When the word got around that beer, wine and whiskey were being provided, the quads emptied fast. However when Denise started to talk about "a safe and ethical environment", most of them decided to baywatch. Seven (more women than men, in keeping with Bio-Pharm tradition) signed up.

The aims of the project were simple. The intrepid duo wanted to observe the effects of beverage type (beer, wine and whisky) on peak Blood Alcohol Concentrations (BACs) volume of distribution (VD) and elimination rate (Ke). The subjects drank different volumes of alcohol: beer (5% alcohol, Carling Lager), wine (11% alcohol, L=Epayrée) and whisky (40% alcohol, Seagram=s Canadian) that contained equivalent amounts of ethanol. After imbibing the said drinks with gusto, the subjects were required to have their breath tested with the Alcotest 7410 breathalyser, kindly donated by Drager Canada Ltd. through the courtesy of Monica Kelly. Each subject partook of all three beverages on three separate trials.

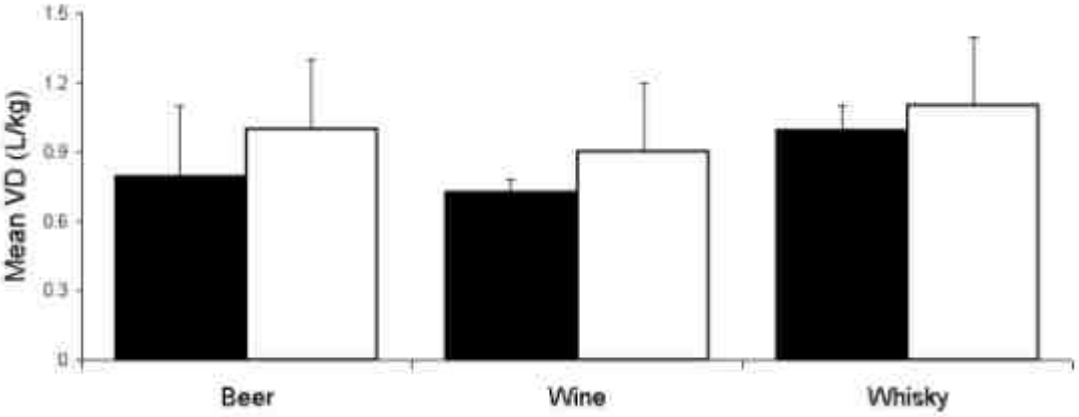
Some of the data obtained are shown below. The Wilcoxon sign rank test was used to determine the statistical significance of the results obtained.

Comments:

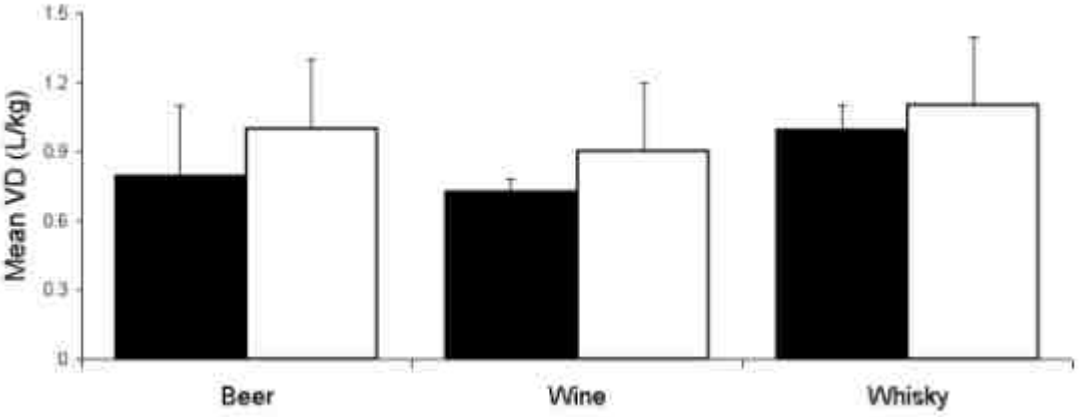
This problem served to introduce students to key concepts in pharmacokinetics. Data were provided that could have insured that crucial components such as volumes of distribution, elimination rate were not missed. Since the data had been acquired by students from a previous class, it served to provide an interesting departure point.


Male Female
Elimination rate (g/dL/hr)
20
18
16
14
12
10
8
6
4
2
0
Beer
Wine
Whisky

(a)


Mean VD (L/kg)
1.5
1.2
0.9
0.6
0.3
0
Beer
Wine
Whisky

(b)


Mean VD (L/kg)
1.5
1.2
0.9
0.6
0.3
0
Beer
Wine
Whisky

(c)

THE RIGHT FLOX

Jose has been suffering from recurrent bouts of chronic bronchitis. He had been a heavy smoker and coffee drinker for decades. He has given up smoking entirely, though he continues to drink 8-10 cups of coffee daily. Bacteriological examination of his sputum reveals the presence of H. influenzae susceptible to several fluoroquinolones. He is treated orally with ciprofloxacin. Although the patient responds to the treatment, he complains of restlessness and agitation at nights. The doctor advises him to cut down his coffee drinking. Jose protests that he cannot function without coffee and as he has been practically weaned on the beverage, it is unlikely to be the culprit. He tells the doctor that it is the drug that is to blame. When the doctor switches him onto ofloxacin, a related compound, the symptoms lessen and disappear.

Comments:

This problem served to reintroduce students to another key concept C drug interactions at a pharmacokinetic level. The problem is brief but the crucial elements are presented. The students are presented with a problem to solve but need to acquire a good deal of basic information before they can do so.

BREATHLESS

Kim Sung is a 26 year-old oboist who is practising for an International competition to be held in Seville in a few months time. He had been an asthmatic since he was two years old. He had been treated throughout his childhood with a variety of drugs C theophylline, salbutamol and even prednisone. He had been hospitalized several times during his secondary school years. Matters had improved at University with fewer exacerbations. The episodes when they did occur were treatable with salbutamol inhalation. He came to carry inhalers around wherever he went since attacks could still be precipitated by cold, exercise and exposure to cats and dogs.

Although, he was an excellent oboist, Kim suddenly became extremely tentative in his playing and had breathing difficulties and co-ordination problems. Relaxation techniques failed and he was seriously concerned about his performance.

A violinist friend of his suggested that he should try a small dose of nadolol, which appeared to work wonders by reducing palpitations and nervousness. Initially reluctant, Kim was assured by his friend that a number of musicians were using beta-blockers regularly. Kim got the tablets and decided to take them.

The following is a chronology of events that occurred on January 3rd:

2150: First dose of nadolol taken.

2210: Kim noticed a tightness in his chest and used his inhaler.

2220: The chest tightening became worse and he took more puffs of his inhaler.

2230: His wife tried to call the physician and had to leave a message on the answering machine.

2250: Kim was in agony and his wife decided to drive him to the hospital.

2315: He was brought to Emergency and pronounced dead on arrival.

Comments:

This problem served to introduce students to drug interactions, this time at a pharmacodynamic level. Once again students need to obtain background information about the drugs and the disease to Asolve@ the problem. Further, the issues of drug abuse and self-medication emerge as components.

A BOOSTER SHOT IN THE DRUG WARS?

Scientists at the Scripps Research Institute in California have been exploring the possibilities of suppressing the psychoactive effects of cocaine by active immunisation (Carrera et al. Nature, 378:727,1995). They have linked a hapten derived from cocaine to a carrier protein (keyhole limpet hemocyanin) to produce a conjugate that stimulated the immune system to produce antibodies in rats.

The efficacy of immunisation was measured in animals given cocaine intraperitoneally. The animals were immunised with the conjugate and booster shots given 21 and 35 days after the first injection. Control animals received only the hemocyanin. The drug produces a variety of effects including increases in locomotor activity which were measured on the 3rd, 7th and 10th day after the last booster shot (data given below):

	Total Activity (90 mins)	
Day	Control	Immunised
3	987.44 ∀ 149.5	555.07 ∀ 124.7
7	1035.19 ∀ 152.92	598.25 ∀ 121.46
10	719.23 ∀ 133.77	443.24 ∀ 199.50

The responses to an unrelated stimulant, amphetamine, were also measured on the 3rd day following immunisation (control 892.35 ∀ 177.51; Immunised: 948.75 ∀ 217.51)

Brains of the animals tested were removed and the content of cocaine in the striatal and cerebellar areas were measured. Levels of cocaine were found to be 52% lower in the striatal tissue and 77% lower in cerebellar areas from animals that had been immunised in comparison with controls.

Comments:

Publications provide ample resources for writing problems. In this case I have merely summarized data from a publication. Once again, the students will learn to struggle through to understand both the process of immunization and the mechanism of action of cocaine, amphetamines. Enough key words have been incorporated. The larger issue of drug abuse and procedures designed to deal with it form another component of the problem.

SENSE AND ANTISENSIBILITY

The steroids estrogen and progesterone modulate sexual behaviour in rats. When ovariectomised rats primed with estrogen are injected with progesterone, they demonstrate sexual behaviour in the presence of their male counterparts. One index of this activity is the Lordosis Quotient. A study by Mani et al (1994) tested the ability of antisense oligonucleotides to the progesterone receptor to alter these responses. They compared the effects of their oligonucleotides (ODNs) with standard progesterone receptor antagonists. Data from their paper (Endocrinology 135:1409, 1994) has been abstracted in the table shown below:

Conditions:	Lordosis Quotient (LQ)
Study 1	
E	10
E + P	100
E + P + RU3846	< 5
E + P + ZK98299	< 3
Study 2	
E	< 5
E + P	90
E + P + Antisense ODN	< 5
E + P + Sense ODN	88

E - Estrogen, P - Progesterone. RU3846, ZK98299 are progesterone antagonists. Both ODNs were administered in a dose of 4.0 nmoles.

Comments:

Here again published data have been reformatted to provide a problem for Asolution@. A number of key words and phrases have been thrown in. Students acquire not only information about steroid receptors (especially estrogen and progesterone), but also learn about the Aphysiology@ of estrus. The problem also serves to introduce students to antisense therapeutics, an emerging field in pharmacology.

HEARTBURN AT KRATERMED

Wasserhund Departs

Staff reporter

All is not well at KraterMed. Readers may well remember the fanfare with which that novel Research Unit had been established at Huronsville, just 5 years ago. It was hailed as the ultimate expression of Academic-Industrial collaboration which would usher in peace and prosperity to all citizens of Ontario. The Research Centre had been established by a consortium of pharmaceutical companies to investigate novel approaches to ulcer disease. The company had hoped to establish close collaborative links with the neighbouring medical school. Unfortunately these links were tenuous at best and the medical school had embarked on an ambitious but ultimately self-destructive Strategic Plan. Several key faculty had left for better climes. We have it on good authority that the real problem was the vicious infighting at Krater Med itself, particularly between the H. pylori group (referred to as The Buggers) and the group designing novel Proton Pump Inhibitors (Pumpers). Dr. Wasserhund, since his early association with Peter Mitchell in the late 60s, had been closely identified with the latter group. Unfortunately this did not mesh with the view of the parent Companies who saw little future in another proton-pump inhibitor. Zantac7, Tagmet7 and Losec7 had virtually cornered the market and even if reversible pump inhibitors were to be developed, it was really unclear what the ultimate sales would be. The Buggers on the other hand are riding the *Helicobacter* wave and appear to have fashion at least on their side. In reality, Dr. Wasserhund's problem was that he was an academic who never really comprehended the pressures under which the Drug Industry struggles. Perhaps both parties may be wiser for his departure. At the moment though, workers at KraterMed are reaching for their Rolaids7 (a whole lot cheaper than Zantec7 or Losec7).

Comments:

This problem is written in a different format, as a newspaper commentary. The students involved in this programme are required to complete 3 work terms. Many do this in labs attached to drug companies. Awareness of academic-industrial relations is important. This problem uses that as a starting point to explore the diverse treatments for peptic ulcer disease. Again all the key pharmacological terms are included as clues.

DELIVERANCE

Carmen is excited about her first work term interview. Although the job description at NEW DEL. Inc. looked interesting, she is a bit nervous when she hears that the VP of research, Dr. Delano, will be interviewing her.

However, the interviewer seems relatively benign and quite enthusiastic about their new products. He tells her that they hope to ultimately develop smart drugs. He tells her that if she is selected, she would join a group working on a very exciting drug code named DD45.

"In vitro studies showed good transfers across the gut," he tells her. "Unfortunately, the first pass effect was significant and so bio-availability was low. We set about to develop alternative formulations."

He shows her a table with some preliminary results:

Preparation	AUC (μg.hr/mL)
Oral (control)	5.8 ∀ 0.9 (10)
Transdermal	12.6 ∀ 0.8* (7)
Sublingual	9.9 ∀ 0.6* (6)
Nebuliser	8.9 ∀ 0.4* (8)
Metered-Dose Inhaler	8.0 ∀ 0.7* (7)
Nasal spray	7.2 ∀ 1.6 (4)

* Significantly different from control ($P<0.05$, 't' test). The number of trials is given alongside in parentheses.

Carmen looks at the data shown. She remembers what she had learned from PMCol 3A06 some eight months earlier and says: "This is quite interesting, but I would need some more information before I can properly assess the results shown here." Dr. Delano replies, "Good girl. Now what would you like to know and why?"

"Oh, there's another thing, I don't think a t-test is appropriate without a Bonferroni correction."

Comments:

This was the first problem in the Introductory pharmacology course and served as an introduction to several key concepts: routes of administration, first pass effects, bioavailability, absorption, distribution and excretion of drugs, areas under the curve and pharmaceutical formulations. Further it enabled me to reinforce some statistical concepts of particular relevance to experimental pharmacologists, namely the assumptions underlying "t" tests.

BLOODY GENES

Warfarin is a commonly used anticoagulant. The dose of warfarin is carefully adjusted to individual requirements using a standardised induction regimen. Certain patients require lower doses than others to maintain their anti-coagulant status.

A report in the *Lancet* (353:717-719, 1999) suggested an association between polymorphism in cytochrome P450 CYP 2C9 with dose requirements for warfarin. Part of the data reported are shown in Table 1 below:

Table 1

Genotype	Low-Dose Group (n=36)	Random Clinic Group (n=52)
CYP 2C9*1/*1	7	32
CYP 2C9*1/*2	12	9
CYP 2C9*1/*3	10	10
CYP 2C9*2/*3	5	0
CYP 2C9*2/*2	2	1
CYP 2C9*3/*3	0	0

Note: The wild type allele is CYP 2C9*1. Point mutations results in the two allelic variants B CYP 2C9*2 where cysteine substitutes for arginine at amino acid 144 and CYP 2C9*3 where leucine substitutes for isoleucine at residue 359.

The investigators also found that bleeding episodes (both minor and major) were significantly different in the two groups:

Table 2

Bleeding Episodes	Low-Dose Group	Random-Clinic Group
Minor (% per person-years)	5.27	1.93
Major (% per person-years)	8.28	2.25

Comments:

This problem used data from a study to get students to explore some fundamental concepts in pharmacology: pharmacogenetics, the biotransformation of drugs (specifically the role of CYPs), the adverse effects of drugs and hepatic function. Further many groups studied in fair detail the mechanism of action of warfarin and the clotting cascade.

THE MULE FROM MIAMI

Air Canada Flight 919 left Miami at 8:10 p.m. (about an hour behind schedule). The pilot apologized for the delay and promised that he would try and make up time en route to Toronto.

The young woman who sat in the rear of the plane seemed tense and agitated. She repeatedly pulled out a magazine, turned the pages listlessly and dropped it on her lap. She had refused to eat anything, asking only for a Sprite.

At about 10 p.m., the pilot announced that a snow storm in the vicinity of Toronto was forcing him to divert the flight to Dorval. He droned on about alternative flights but the young woman, who had been sitting with her eyes closed, jumped out of her seat and ran to the restroom. When she returned to her seat, she was seen to be staring straight ahead with her eyes open and repeatedly moving her legs back and forth. Within 20 minutes, she was having generalized convulsions. The crew on board attempted CPR. But by the time the plane landed, the woman was dead.

Autopsy revealed that she was 3 months pregnant, the fetus being found dead as well. 147 complete condoms and 40 condom fragments were found in her gastrointestinal tract (23 ileum, 61 ascending colon, 21 transverse colon, 42 descending colon). The packets were wrapped upon themselves numerous times and each contained 2 grams of cocaine. The purity of the compound was not determined. Gastritis, duodenitis and mild cerebral edema were noted.

Comments:

This was written in the form of a classic case, a narrative in which all the key components were embedded. The students explored both biological and sociological aspects of drug use. Much of the discussions each year have dealt with the mechanism of action of cocaine, the synthesis, storage and release of catecholamines, the receptors involved, the transit of materials through the gut and the reward systems in the brain. In addition, students have looked at the trafficking problem, the role of law enforcement etc. However, the course being an introductory one in pharmacology, much of the emphasis was on the biological issues. If the same problem had been used in the Arts and Sciences Inquiry course, there would have been a greater discussion on the behavioural and sociological aspects of the case.

Problems written for a Fourth Year Social Pharmacology Course

This is a course in Social Pharmacology taken by students in the same programme. This course is taken in the last term prior to graduation. By this time the students have taken a variety of courses in pharmacology as well as physiology and immunology. The goals of this course are to acquaint the students with the social dimensions of drug use. The list of elements that will be introduced is given below. Each problem is written to include both pharmacological and epidemiological components.

The content of the course and the expectations were described in the outline as follows:

Given that the scope is broad, it is impossible to cover all aspects. It is not my intention to produce either pharmacoepidemiologists or social pharmacologists in a span of twelve weeks. Rather, my objective is to acquaint you with the general principles and give you a flavour of the field. To that end, I have been selective in the content issues that I wish to cover.

It is expected that by the end of this 12 week course, you would be introduced to the terms and concepts listed below:

(i) Terms commonly used in epidemiology such as Incidence / Prevalence / Relative Risks / Odds Ratios / Specificity / Sensitivity etc.
(ii) The advantages / disadvantages of different Epidemiological Study Designs (Case Reports, Case Series, Analyses of Secular Trends, Case-Control studies, Cohort studies)
(iii) Methods of Data Collection
(iv) Post-Marketing Surveillance
(v) Adverse Reactions to Drugs
(vi) Drug Utilisation Studies
(vii) Legal Aspects of Drug Reactions
(viii) Economic Evaluations of Drugs (Pharmacoeconomics).

A RASH TO JUDGEMENT?

Heldane had been on the market for barely a year when numerous anecdotal reports began to appear suggesting that the drug produced lichenoid eruptions.

Marysia, a young clinician, at the Huronsville Clinic, obtained the following information from hospital records:

In a six month period, the eruptions have been observed in 6 out of 23 patients prescribed the drug. Similar rashes have been seen in 4 out of 50 patients who have not been known to take the drug. Marysia estimates the odds-ratio as 4.05. When she shows the data to Dr. Mammon, the Head of the Unit, he suggests that she contact the manufacturers of the drug.

Presented with the information, the manufacturers are concerned and offer to fund a larger cohort study to gather more evidence. After a year's intensive study the following data are obtained:

	Rash	**No Rash**
Drug Exposure	23	75
No Drug Exposure	16	91

This leads to an attributable risk due to the drug of 0.08. Although the manufacturers appear satisfied, Marysia is left wondering as to why she obtained such high odds-ratios in the first instance.

Comments:

This was the first problem used in the course. It provided an opportunity for students to explore epidemiological terms, consider appropriate study-designs and introduced them to the analysis of adverse drug reactions, which forms the basis of many studies in pharmacoepidemiology. The problem is a straightforward presentation of a limited set of data.

BITTER SWEET

The following confidential memo has been sent to Dr. G. Odnose:

THE QUISLING INSTITUTE OF COLLABORATIVE RESEARCH

Huronsville, Ont.

P.O. Box 69
Huronsville, Ontario
L0S 5T1

Date: June 10, 2007

To: Dr. G. Odnose

From: Dr. D. Cottenpurg, Interim Head, Toxicology Divn.

Re: "Expert Witness"

Thank you for your memo informing me about the invitation to act as an "expert witness" in a case involving aspartame. I am sorry that I cannot talk to you personally as I am rushing to catch my flight to Stockholm.

I am still puzzled as to why *you* were contacted. I am fully aware of your exciting studies on the effects of aspartame on glutamate binding sites in synaptic membranes, though that expertise may not be strictly relevant for the case at hand. I understand from your brief memo that the plaintiff has had both panic attacks and seizures following ingestion of aspartame containing soft drinks. I'm not sure from the material you sent me whether the patient was also a diabetic and/or was heterozygous for phenylketonuria? In any case, I feel that the plaintiff's lawyers should have contacted someone knowledgeable about epidemiological issues rather than a biochemical pharmacologist.

From the few cases that I know of, the experience of scientists in law courts has not been particularly happy. Toxic tort cases are particularly messy. Worse, the notion of causation that we have may not entirely coincide with that held by the legal profession. I have asked Brenda to pull together some material in a binder that is available in my office.

I hope that you have not committed yourself. I know that you are an avid reader of mystery stories, but real life is quite messy. Perhaps you could gather the relevant background information and talk to the group before you decide to participate in this exercise. I would prefer that you forestall any possible embarrassment for the division.

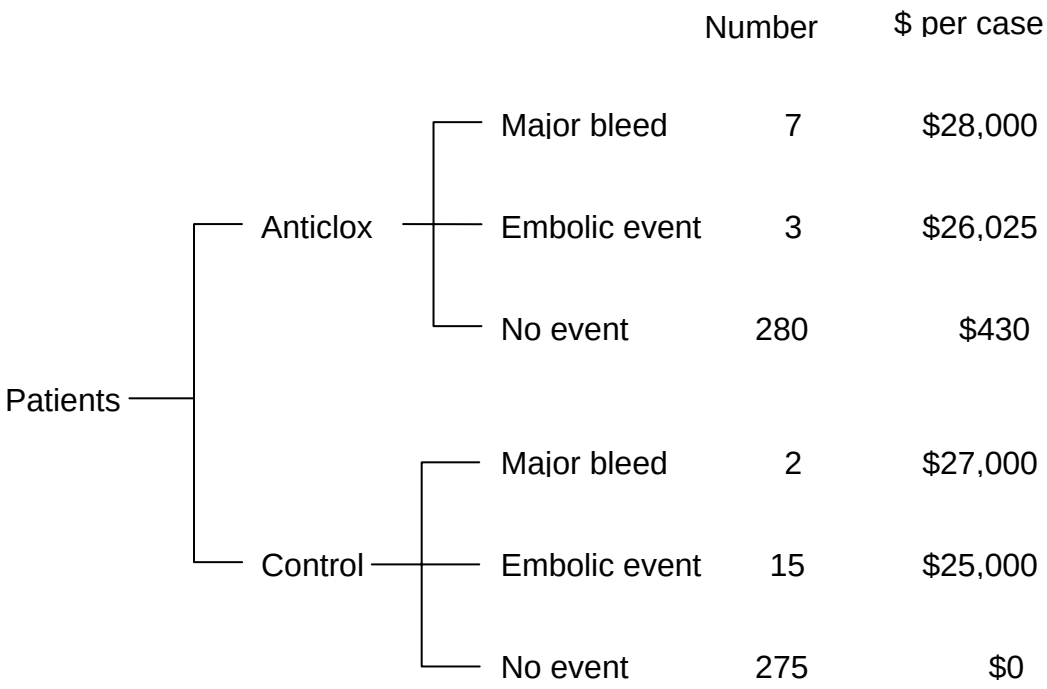
(Dictated but not read)

Comments:

This problem, written in the form of a letter, serves to introduce students to the legal aspects of drug use. Toxic tort cases serve as an appropriate vehicle for discussing the contrasting perspectives of the scientific and legal professions towards causality. In addition the problem serves to introduce students to the complexities involved in assessing the value of food additives, which normally bypass the drug regulatory process.

TOO BLOODY BAD

Dr. Hemat Klotz had received a substantial sum of money from Hemostats Inc. to investigate the effects of a novel antithrombotic drug on the prevention of stroke in patients with atrial fibrillation. The study had been in progress for a year, when a series of papers appeared testifying to the efficacy of warfarin in preventing strokes. The Ethics committee of the Hospital had recommended the study be terminated. Dr. Klotz believes that the data obtained could still have some value.



Comments:

This problem serves to introduce students to the elements of decision analysis and pharmacoeconomics. The data provided, though simplistic, led to a discussion of the relative merits and demerits of the different approaches used to gauge costs and resulting benefits. In addition they used this problem to study the coagulation cascade and anticoagulant drugs in the prevention of strokes.

A NOT-SO-HAIRY TALE

An astute family physician practicing in Huronsville is puzzled by a sudden increase in the number of patients who come to his practice complaining of hair loss. He has noted that over a six month period, there have 10 such cases and 6 of them have been prescribed Arzotec, a new non-sedating antihistaminic.

Through a contact at Huronsville Clinic, he finds that they too have noted a similar trend. In fact, an early look at their records shows that alopecia was noted in 6 out of 23 patients prescribed the drug. The same problem had been noted in 4 out of 50 patients who had not been prescribed the drug. The estimated odds ratio of 4.05 was worrisome enough to stimulate a larger prospective study .

A year later, the following results have been obtained:

Group	Alopecia	No Alopecia
Drug Exposure	23	75
No Drug Exposure	16	91

Based on the above results, the attributable risk due to the drug is 0.08.

Comments:

This problem is similar in format to an earlier one, A Rash to Judgement?. It serves to introduce students to basic epidemiological concepts, namely study designs and the rules of causation. It helps them tease out the meaning of a number of commonly used terms.

COURTING TROUBLE

Dr. Naif is a young patch clamper at Blast/Clast Enterprises, Inc. who has published exciting work on ion channels on osteoblasts. She is also an avid reader of detective stories and courtroom dramas and when asked to appear as an “expert witness” in a case, accepts with glee.

However her enthusiasm is dampened when she hears the Chief‘s comments on her voice mail:

Vera, this is David. I hear that Action Now want you to appear as an expert witness on their behalf in their case against the City. They claim, I am told, that the city is endangering their lives by fluoridating the water supply. I know that Fiona Physty, their leader, is a friend of yours, but she IS a certified flake. Also your expertise is far removed from what is needed. They need an epidemiologist, not an electrophysiologist. Also the legal view on causation is often at odds with ours and toxic tort cases are very, very messy. My advice to you, is DON’T. If you persist, at least get to know the issues at hand. Check out the Bendectin story. I wish I could talk to you personally, but I’m off to the Blast Conference in Capri. Hope this miserable winter will be over before I get back.

Comments:

Another problem that leads students to explore the legal ramifications of drug use. In this case, the issue of fluoridation raises a number of public health issues and the recognition that a "drug" could be more widely distributed than we think. Much of the emphasis in the discussions has focused on toxic torts, the role of expert witnesses, the contrasts between legal and epidemiological views of causation. I have occasionally invited a lawyer involved in class-action suits to come and talk to the students after they have completed the problem. This has served to reinforce what they had studied on their own.

EVIDENCE BASED MEDICINE: AN EMIC VIEW

Since the mid 1970's Nina Etkin has been studying the use of medicines in a rural Hausa village in northern Nigeria. When the studies began in the middle years of that decade, the Hausa used largely botanicals. By the mid 1980's, however, she noted the widespread use of pharmaceuticals bought either through the formal biomedical clinics and chemist's shops but also from itinerant herbalists. Despite the anticipation of health planners, the pharmaceuticals did not replace the existing pharmacopoeia, but became part of it. Also the use of the drugs differed significantly from that proposed based on biomedical knowledge (see Table below). The Hausa not only adapted Western medicines to their own use but demanded a different evidence for efficacy. The emic view of efficacy differed significantly from the etic one.

Drug	**Biomedical Application**	**Hausa Use**
Rifampin Capsule	Tuberculosis	Cough, Jaundice, Hepatitis, Schistosomiasis
Phenolphthalein tablets	Laxative	Jaundice, Hepatitis, Schistosomiasis
Chloramphenicol capsule	Bacterial Infections	Measles, Chickenpox, Abortion, GI disorders, Itching
Codeine Tablet	Pain, Cough	Energy, Strength
Ferrous Sulphate Tablet	Anemia, malnutrition, pregnancy	Blood Tonic, Jaundice, Hepatitis, Schistosomiasis
Tetracycline capsule	Bacterial infections	Measles, Chicken-pox

References:

Etkin et al (1990) Soc. Sci. Med 30:919-928

Etkin et al (1999) In *Anthropology in Public and International Health* Edited by Hahn, RA Oxford University Press, Oxford

Comments:

The term evidence-based medicine is bandied around with abandon these days, particularly at McMaster. I wanted students to confront this issue by forcing them to deal with the meaning of the term evidence as seen from different perspectives. Etkin's study offered an excellent opportunity. Students recognised that all systems of medicine, however primitive, were evidence-based. It is what constitutes evidence that was debatable. The problem also served to highlight the reason why people use drugs. Students in this course had dealt with the term efficacy in molecular terms and were now asked to look at it from a different perspective. Students used the information to look at a variety of issues, such as the WHO's list of essential drugs, the contrast between indigenous and modern systems of medicine, access to drugs, the role of pharmacists, herbalists and other health professionals etc.

AT WHAT COST?

Chloroquine-resistant malaria is becoming a major health care problem in much of Africa. Chloroquine though cheaper may not be effective and children treated with it may remain parasitaemic, febrile and at risk for complications and death. Alternative treatments are generally more expensive. Sudre et al (International Journal of Epidemiology 21:146-154, 1992) compared the cost-effectiveness of 3 different treatments, chloroquine (CQ), amodiaquine (AQ) and a pyrimethamine-sulfadoxine (PS) combination.

The authors used a decision-analysis model for their comparisons. The variables considered were the probability of *P. falciparum* infection, drug compliance, side-effects, level of drug resistance and case fatalities with each treatment. The measures of effectiveness were the number of malaria-related febrile episodes cured parasitologically with each treatment and the number of malaria deaths prevented in children 6-59 months old.

Data from their paper have been refashioned to produce the two figures (Fig 1 cure, Fig 2 prevention) given here.

Each figure relates costs to 3 levels of resistance.

I No resistance to ANY of the drugs
II Low resistance (low resistance to CQ, very little resistance to AQ and none to PS)
III High resistance (high resistance to CQ, moderate resistance to AQ and no resistance to PS)

Figure 1

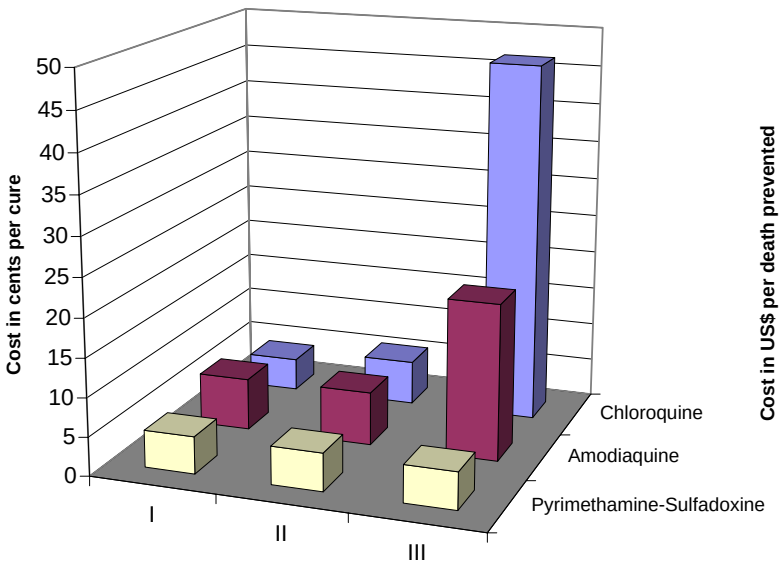
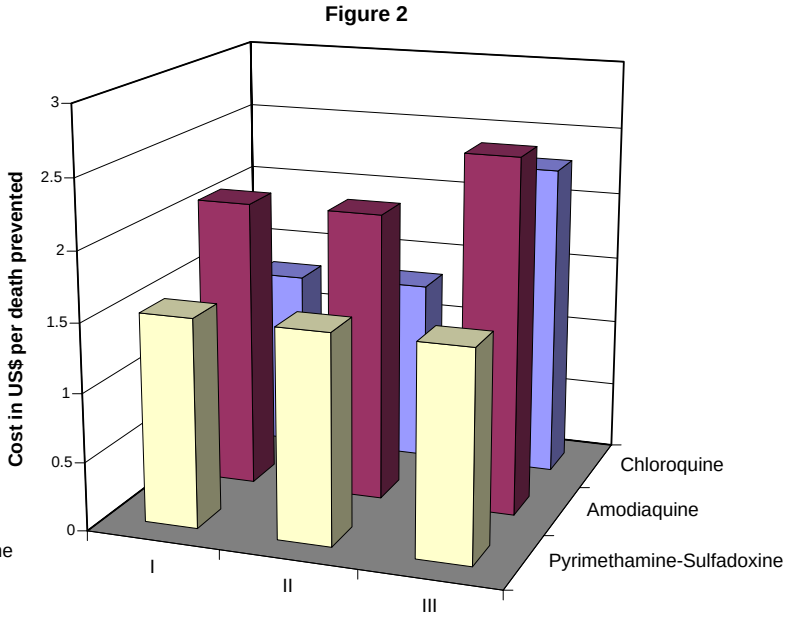


Figure 2



Comments:

This problem served to introduce students to basic concepts in pharmacoeconomics. Like the earlier problem, Too Bloody Bad, this problem introduced students to basic concepts in pharmacoeconomics, particularly the different sorts of studies that could be conducted. The notion of perspective was discussed and students learned to look critically at such studies using published guidelines. In addition, students studied the life cycle of the malarial parasite and the drug treatment of the condition.

Arts and Sciences Inquiry Course: The Curing Society

This course was taken by senior (third year) students in the Arts and Sciences Programme. This is an interdisciplinary programme that has a limited enrollment and attracts highly motivated students. The Inquiry courses in this programme provided a forum for exploration of complex issues of public concern.

In framing this course which ran from 1989-1995, I sought to provide these highly motivated students to explore issues related to health and illness. Students were told that in simplistic terms, issues of health and illness involved the dynamic interactions between providers and recipients of health care in institutional settings developed by individual societies in response to specific needs. The specific content of the course varied from year to year based on student interests. An initial session was devoted to developing a list of issues that the class considered crucial to understanding health care. Using that list as a starting point, I wrote problems to explore diverse issues. Thus the particular problems were tailored to student needs. In that sense several of the problems used may appear "dated". Nevertheless the core issues remained reasonably consistent over the 6 year period. These included amongst others:

THE SEARCHING

St. Mark's Hospital in Huronsville was planning to celebrate its 150th anniversary in 1993. As Huronsville's oldest hospital, the events were to be of great significance to the community. Plans had been made to produce a history of the hospital and funds were being raised to build a Ronald McDonald house as well.

The abrupt resignation of Dr. Bix Brendereich has, however, taken St. Mark's Hospital by surprise. As President, he had been abrasive and annoying, but few had doubted his abilities to get things done. The Board of Trustees had established an ad hoc Search Committee to recommend a successor.

The first meeting of the Committee proves to be a stormy one. The attempts of the Chair to have some agreement on the required qualifications for the post have been thwarted by members who had preferred to discuss other issues, such as the need for such a position, appropriate representation for all consumers on the Committee itself and the relations between the Hospital and the Community.

The Chair insists on focusing on the task at hand and emphasises the urgency. Some members feel that they are being railroaded into a quick decision and are concerned as to whether there will be a "Real Search" or the anointing of a candidate already chosen by the Board of Trustees. One member mutters "Are we seeing the operations of **true** democracy here, decisions first, input afterwards?"

The Chair abruptly terminates the meeting, hoping that the next one would be more fruitful.

Comments:

This problem, written in the standard scenario form, permitted students to explore issues such as the role of hospitals, their organisation, the role of different sectors of the community. Even more importantly, I wanted them to assess the relevance of "democratic" processes in decision-making under such conditions.

HIGH CHOLESTEROL - A NEW RISK?

The Artemesia Foundation has been established by a Group of Concerned Women Academics who feel strongly that the male-dominated scientific establishment does not permit the concerns of women to be adequately studied. Over the several years that the fund has operated, much of the funding has been geared to projects of a sociological nature. However, the Directors have asked for submissions from basic scientists as well.

Dr. Helmut Schwarzberg has proposed to study the relationship between serum cholesterol levels and serotonin receptors on platelets in battered women. He argues that studies have indicated that "a low cholesterol level among violent offenders in the younger age groups is a good and easily measured indicator of dangerousness," and that habitually violent tendencies and impulsiveness correlate with low concentrations of serotonin metabolites in CSF. Also recent animal studies suggest that "the aggressivity is related to reduced central serotonergic activity" (Biological Psychiatry 19: 435, 1984; Ann. Med. 22: 327, 1990; Lancet 339: 727, 1992). He thus wishes to test the possibility that the converse may be seen in victims of violence.

This submission has been received with mixed feelings by the board. The external reviewers of the complete proposal have been critical of the methodological details though they have recommended funding. Several members are, however, uneasy about the tenor of such approaches to the problem.

Comments:

This problem, again written in the standard format, raises another important set of issues for study. These include the nature and relevance of basic scientific research to solving social problems, the ethics of conducting such research and the role of special interest groups in funding research that appeals to them.

RANDOM HARVEST?

Students at the Huron Institute of International Health are discussing the statement that "War is not Healthy for Children and Other Living Things."

The notion that the civilian population bears the brunt of military operations is challenged by Hank who argues that those problems are unlikely to occur with the development of better weapons. He points out that during the Gulf War, the use of high-precision weapons with strategic targeting permitted the Allied Forces to produce maximal effect with limited damage to the civilian population.

This provokes a furious reaction from the other students and Professor Chernsky is forced to intervene. He suggests mildly that they should study the matter more carefully cautioning them to argue from a base of knowledge, rather than ignorance.

At the next session, Fatima brings along a map[1] showing the principal targets in Iraq as well as data (shown on the next page) from a recent study reported by an International Team in the New England Journal of Medicine (vol 327: 931-6, 1992) showing geographical variations in the mortality of infants and children, before and after the war.

[1] The map was taken from Hiro (1992) Desert Shield to Desert Storm: The Second Gulf War. Harper Collins, London.

Comments:

This problem was a corollary to the one on serotonin receptors. This problem focused not on individual but on institutional violence. The data provided a good focus for the brainstorming session as well as the subsequent discussions.

RANDOM HARVEST? (continued)

Data from a recent study reported by an International Team in the New England Journal of Medicine (vol 327: 931-6, 1992) showing geographical variations in the mortality of infants and children, before and after the war.

Region	Age Group	Mortality Rate (Reference)	Mortality Rate (Jan-Aug 91)	Relative Mortality
Baghdad	<1 mo	17.2	26.9	1.6
	1-<12 mo	14.8	28.1	1.9
	12-<60 mo	0.8	2.0	2.5
Central	<1 mo	13.8	12.1	0.9
	1-<12 mo	12.8	37.9	3.0
	12-<60 mo	1.8	5.1	2.8
South	<1 mo	19.8	37.8	1.9
	1-<12 mo	14.7	72.4	4.9
	12-<60 mo	2.6	13.3	5.1
North	<1 mo	18.3	51.1	2.8
	1-<12 mo	17.8	125.7	7.1
	12-<60 mo	4.9	16.9	3.4
Neutral	<1 mo	17.2	36.4	2.1
	1-<12 mo	52.9	307.7	5.8
	12-<60 mo	10.8	32.1	3.0

SCENARIO I

The following item appeared in a recent issue of the *Huronsville Gazette*

UNPLEASANTNESS AT THE ROYAL

Basil McClure
Special to The Huronsville Gazette

THE PLUSH PREMISES of the Royal Windsor Hotel was the scene of quite unseemly behaviour last night. Humana Corp., a recruiting firm from Mammon, Fla. had been discreetly organising seminars for local physicians to "acquaint" them with the benefits of practising "real" medicine south of the border. Tasteful dinners had been laid and doctors' wives had an opportunity to savour the joys of living in a warmer climate with year-round leisure activities. Dr. Marcus Whelpy had discussed fairly and frankly the "Calling" of the Physician and pointed out that a doctor should really do what is best in the interests of a patient rather than be dictated to by anonymous bureaucrats. Immigration lawyers were at hand as well as real estate agents to answer any questions that the physicians may have.

Matters went smoothly till members of the local chapter of the Medical Reform Group began asking awkward questions. They referred to a number of studies published in prestigious U.S. journals such as the New England Journal of Medicine comparing favourably the Canadian model with the American one. They demanded that Dr. Whelpy explain how the entrepreneurial system would provide equitable access to health care and noted that Clinton's new proposals involved HMO's to provide comprehensive coverage. The urbane Dr. Whelpy brushed aside their comments as meaningless socialist rhetoric that had now been discredited by entire nations. "Oh, yes," he noted, "I am well aware of those slogans and shibboleths such as Health for All by 2000. The Alma Ata Declarations are totally unrealistic. How can you achieve them if you manacle doctors who practice the best possible medicine?" This was greeted with enthusiastic applause.

Unfortunately for the organisers, a group of concerned citizens had infiltrated the gathering. They demanded that the doctors who wished to emigrate pay back substantial sums of money to compensate the taxpayers for the money spent on their education. This led to an incredible shouting match between several of the doctors and their families. A spouse shouted "Pay you back? WE killed ourselves, saving every cent and dime. What did YOU have to do with it?" The organisers abruptly closed the meeting—hoping for quieter sessions in Manitoba and Saskatchewan.

Comments:

This problem was written at a time when the Clinton administration was proposing a "different" model for U.S. health care. At that time, newspaper reports appeared about recruiting drives to entice Canadian doctors to more lucrative positions south of the border. This problem served to focus attention on the contrasts between two expensive systems of health care and in particular the role of the taxpayer in educating physicians. Since a number of students in the class were interested in applying to medical schools, I was particularly interested in their discussing such issues. These issues are still current as judged from media reports.

REDRESS OR REGRESS?

Given below is an excerpt from a recent Commentary published in THE HURON, dated September 24, 1991.

ZERO TOLERANCE: SIGNS OF A NEW REIGN OF TERROR?

by Jayne Ostenn

THE DELICATE RELATIONS between physicians and patients appear to be in grave jeopardy if recent trends continue. Physicians have been charged with a variety of offences broadly classed as sexual abuses. Attempts to streamline procedures to control what appears to be a pervasive practice have raised concerns. Dr. Colleen Clements writing in The Medical Post, September 24, argues that the College of Physicians and Surgeons of Ontario (CPSO) should have thought twice before sponsoring the Task Force on the Sexual Abuse of Patients. She is incensed at the hanging judge approach advocated by the task force. "The CPSO Task Force has entered the murky field of human sexuality and late 20th century feminism." She feels that the expressions used such as "zero tolerance" are "inherently unfair" and "the political correctness of this crusade seems to have gotten in the way of good sense, good ethics and good law and medicine." She notes that "the traditional standards of the legal system may not be perfect, but they do protect us from Kafkaesque ministries." These comments raise the spectre of a "New Reign Of Terror" with Madame Defarges running rampant denouncing physicians for sidelong glances or trifling comments. I asked a few of my more ardent feminist friends for their views. "What do you expect?" they asked, "These folks have been on their Power Trips for so long that they hate to see any challenges to their authority." A less strident note came from an older lady who chose to remain anonymous. "I have had a wonderful relation with my physician for twenty years. He has been friend, philosopher and guide through lots of troubles. He may have made a few "suspect" comments, but so what? I would hate to see that relation disturbed to correct a few mistakes. I'd rather be managed by a person than a soulless computer." Certainly the situation is complex and will not be helped by reflex ideological posturing on both sides. Given the temper of the times it is unlikely, however, that Sense and Sensibility will prevail over the Politically Correct but Mentally Bankrupt.

Jayne Ostenn is a writer and social commentator.

Comments:

This problem was written in the format of a newspaper clipping. I was interested in focusing discussion on physician-patient interactions, dimensions of sexual abuse of patients by physicians, the grievance procedures available and the larger issue of the impact of feminism in health care.

Arts and Science Inquiry Course:
Discovery: the Context of Biomedical Research

This was also an Inquiry course that is taken by the Arts and Sciences students. It has replaced the original course described earlier. In this course I sought to deal with the consideration of the "context" (antecedents and consequences) of scientific discovery in the experimental sciences, particularly in the biomedical realm.

As background material I wrote a brief commentary that loosely described the instructional elements of the course.

> ... In looking at scientific discoveries, one can adopt the “Small” View or the “Large” View (or in more pedantic terms Micro and Macro perspectives). In the former case, attention is focused on the immediate antecedents and consequences such as the status of knowledge at any particular juncture that gave rise to the ideas that provided the impetus for the action taken (experiments). The methods used can be interpreted quite broadly to include not only the judgements that scientists make about reliability and interpretation of data but the ways in which they work with each other and the strategies used to obtain information and justify it to the scientific community. These constitute the craft of science. The Large View focuses on the social forces that create the Institutions that permit research of this kind to occur, the investments and the returns of such activity, the mores and taboos of the communities involved. Scientific activity is not value-free. Biases inherent in society influence the selection of questions deemed worthy of pursuit and more importantly on those that are ignored. The methods used to obtain information as well as the justification procedures are coloured by the values and training of the individuals involved...

For this particular course, I used real cases since these were found to be more complex and rewarding than any that I could have invented.

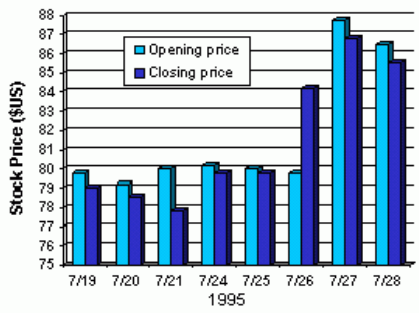
WAIT-LE$$NE$$

December 1, 1994. *Nature* publishes article entitled: "**Positional cloning of the mouse obese gene and its human analogue**" by Zhang *et al.,* from the Howard Hughes Medical Institute, New York, USA.

May 5, 1995. *Science* publishes a News and Comment Section: **Rockefeller Strikes Fat Deal with Amgen**: "In a deal soon to be completed, Rockefeller University will receive a $20 million payment from biotech giant Amgen for an exclusive license to develop products from a gene that may play a role in determining obesity...."

3 papers dealing with effects of the obese gene product submitted to *Science* (received **May 26**, **May 5**, **May 24**; accepted **June 28**, **June 29**, **July 5**.) Scheduled to appear on **July 28, 1995**. Journal embargoes news until the **evening of July 27** to permit reporters advance access to technical information to prepare accurate reports for the public.

At **9:19 a.m.** on **July 26**, a biotechnology analyst, Teena Lerner, from the brokerage firm of Lehman Brothers, breaks news of the impending publications over an electronic wire service.



Amgen stock prices

August 4, 1995. Editor-in-chief Floyd Bloom acknowledges that such events may force some changes in how journals operate.

Comments:

This problem traced the sequence of events over a 9 month period. Students used this problem to explore a variety of issues - the attitudes towards obesity in our society, the studies carried out to define the obesity gene, the publication process, the role of mass media in disseminating information about scientific breakthroughs and the emergence of biotech companies and academic-industrial relations.

JUST REWARD

PART 1

A number of scientists who are either US citizens or have done their major research in the US have been awarded the Nobel Prize in different categories. The list below separates them into 3 categories (A/B/C).

Category	Total	Prizes to US Scientists		
		A	B	C
Physics	152	57	1	0
Chemistry	127	37	0	0
Medicine/Physiology	164	66	5	0
Economics	42	24	0	0

PART 2

In 1993, the Nobel Prize for Medicine and Physiology was awarded to Richard Roberts (Cold Spring Harbor Laboratories) and Phillip Sharp (MIT) for the discovery of gene splicing.

J. D. Watson, Director of Cold Spring Harbor Labs said later in an interview with Science that there was another scientist (Chow) who should have had a share (Science 268, 23 June 95, p1708). He said "Louise did it, and it's terrible that she didn't win". The problem was at that time the role of another scientist, Berget, who was also deserving, "and including her would have made four – one too many for the Nobel rules".

Comments:

This problem was discussed by the students in December 1997, the month that the Nobel Prizes are awarded. I wanted to draw attention not only to the reward system in sciences but the larger issue of criteria, selection and ***exclusion****. The problem was discussed in two parts. The first part provided an opportunity to determine what categories A, B and C were. Although A and B (male and female) were relatively easy to discern, category C (black Americans) required some prompting. This led to a discussion of gender and race in science. The second part brought into sharper focus the political considerations involved. The problem was used to explore not only the Nobel Prizes, selection criteria, gender and race considerations in science, but also the actual studies carried out to demonstrate gene splicing.*

A SOUTHERN TALE

In the middle of the 18th Century, Don Pedro Casal described a condition in the Spanish town of Aveida in the Asturias region. The local term was "mal de la rosa" from the peculiar red necklace-like rash around the exposed regions of the neck. The malady, which later spread to several other countries (Northern Italy, Southern France, Romania, Russia and Egypt), was associated with poverty and the production of corn. The disease had a progressive course and was characterised by dermatitis, diarrhea, dementia and death (the 4 Ds).

It was only in the early years of this century that the disease began to reach epidemic proportions in the North American continent, forcing authorities in the US to take action. In 1914 Rupert Blue, the Surgeon General, assigned Joseph Goldberger, a little known officer of the US Public Health Service, to tackle "one of the knottiest and most urgent problems facing the Service" at that time. Dr. Goldberger, an immigrant physician trained at Bellevue Hospital Medical College, had by the age of 40 acquired extensive experience in investigating infectious diseases.

Given below is some of the information available to Dr. Goldberger from two institutions:

From the Georgia State Sanitarium for the treatment of insanity:

GROUP	Total Number	Cases	Percentage
Inmates	418	32	7.65
Employees	293	0	0

Note: The number of cases refers to those that developed the condition after admission to the sanitarium.

From the Orphanage at Jackson, Miss. on July 1st 1914, 68 out of 211 orphans had the disease, giving prevalence of 32%. A further categorisation by age group yielded the following data:

AGE GROUP (YRS)	TOTAL	AFFECTED	PERCENTAGE
< 6	25	2	8
6-12	120	65	54.2
>12	66	1	1.5

Comments:

From the perspective of this course, epidemiological studies prove particularly useful for exploring the interactions between science and society. I chose Goldberger's early studies into pellagra as they show how preconceived notions provide a stumbling block for acceptance of ideas that seem so obvious to us. The data taken from his early studies provided a particularly useful starting point for students to think through possible causes for the affliction. They also served to highlight some of the ethical issues involved in conducting such studies.

NUN-PAREIL

The Nun Study is a longitudinal investigation of aging and Alzheimer's Disease. The participants are members of the School Sisters of Notre Dame religious congregation. American sisters born before 1917 were asked to join the study between 1991 and 1993. The participants agreed to donate their brains for study after death. In a subset of participants, a study was conducted to explore the relationship between linguistic ability in early life to changes in cognition and the development of Alzheimer's disease in later life. All 93 participants in the study were white and born in the US.

To assess linguistic ability, the investigators used handwritten autobiographical submissions by the sisters, written by the nuns after 4 years training at the convent. The documents obtained from the archives were carefully analysed and indices of linguistic ability were developed. One of these was the term "Idea Density (IDs)". This was quantified as the average number of propositions expressed per 10 words. Based on their ID scores, the participants were categorised into 2 groups (LOW and HIGH).

Within the period of the study, there were 14 deaths. Autopsies were done to correlate brain changes with early linguistic ability. Since the sample size was small, another 11 sisters from other convents in the same area were included. There were autobiographical submissions available for those 11 which were subjected to the same analysis. Given below are the data from all the 25.

Neurofibrillary Tangles in Different Regions of the Brain by Linguistic Ability Demonstrated in Autobiographies written in early Life

	Mean number of Neurofibrillary tangles per 0.586 mm^2				
Idea Density	Temporal Lobe	Parietal Lobe	Frontal Lobe	Subiculum	CA1
LOW (n=10)	9.4	6.2	6.0	22.7	15.8
HIGH (n=14)	0.5	0.3	0.3	3.8	4.8

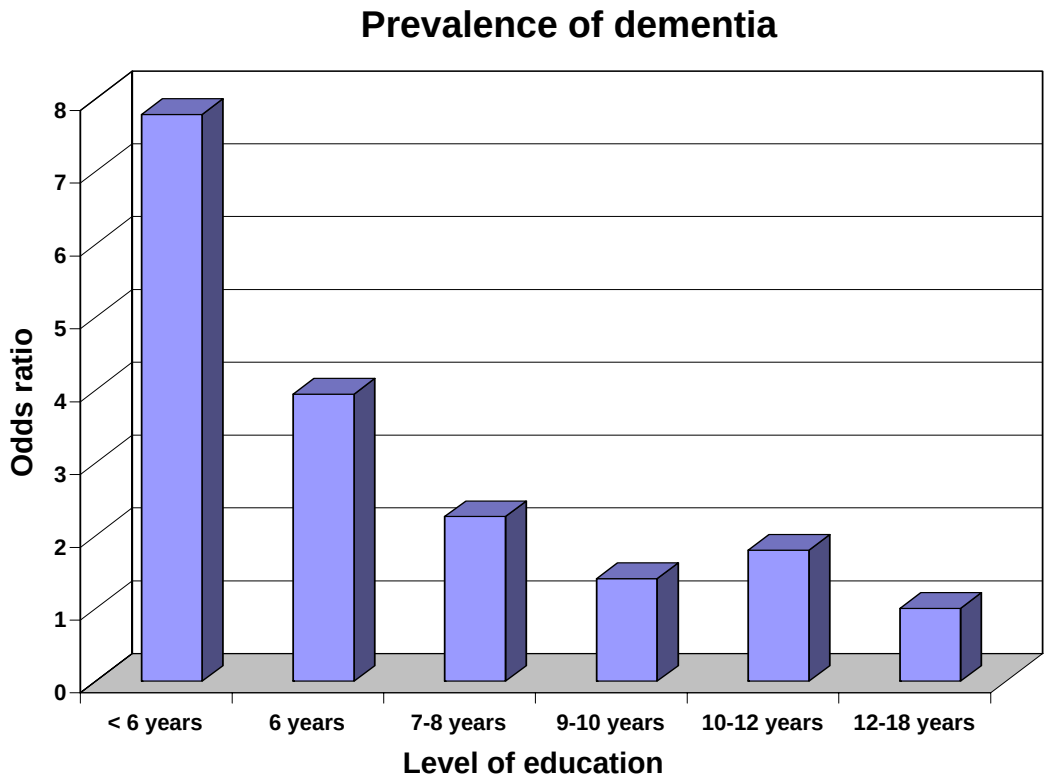
NOTE:
(1) Neurofibrillary tangles are an indication of Alzheimer's Disease
(2) The subiculum and CA1 form part of the hippocampus. The rest of the regions described are neo-cortical areas.

Comments:

This problem as well as the companion one (following) were used to explore the diverse approaches taken to study the problem of dementia. In both cases, I used published data.

SCHOOLING: DELAYED EFFECTS?

The AMSTEL Project (Amsterdam Study of the Elderly) is a longitudinal study on cognitive decline and dementia in a population (4039 subjects) between 65 and 85 years of age. Given below are data from that study (taken from J.Clin.Epidemiol.50:1025-1033,1997). Similar data have appeared from Israel, Shanghai, Sweden, Finland, Italy and France.



The highest level of education was taken as a reference.

TB OUGHT NOT TO BE

Part 1

A study was conducted by Ferguson and Simes using all Indian infants born in the Qu'Appelle Indian Health Unit in southern Saskatchewan during the period October 1933 to December 1945. Families of comparable social and economic status were paired and randomly allocated to one of two groups labelled A and B. All children born into families in group A were vaccinated with BCG vaccine in a given year and those born into families B were used as controls. In the following year the situation was reversed and this scheme was followed throughout the years of the study. Over a period of years there were 306 children in the vaccinated group and 303 in the unvaccinated group.

The data from their original study (Tubercle 30: 5-11, 1949) has been re-fashioned in the Table below:

Tuberculosis cases	Vaccinated	Not Vaccinated
YES	6	29
NO	297	274

The data includes information gathered up to August 1947

Thus the relative risk of non-vaccinated infants getting TB was 4.88.

Part 2

Half-a century later, Maureen Lux (CBMH Vol. 15, 1998, p. 277-295) looked at the Qu'Appelle BCG Vaccine trial from the perspective of the subjects themselves. She asked "How did an isolated, poverty-stricken agency in an equally isolated province come to be the site for a major medical experiment? Who were the subjects and how did they benefit?"

The last sentence read "The BCG trial was a success, but unfortunately the patients died."

Comments:

Historical cases provide an opportunity for students to reflect on changes in knowledge and attitudes. Using this problem, the students explored the biological aspects of tuberculosis, the routes of infection and pathological changes. They also delved into the social and economic context of the Qu'Appelle trial and also considered the design of clinical trials in general.

THE CULL OF THE WILD

A trial was conducted at Kruger National Park in South Africa to test the efficacy of immunocontraception using pig zona pellucida antigens (Fayrer-Hasek et al Nature 407: 149, 2000). Forty-one adult female elephants were located by helicopter and females identified as non-pregnant were anaesthetised by aerial darting. Twenty-one animals were vaccinated with 20 others serving as placebo controls. The animals were fitted with radio collars. Vaccinated elephants were located and received booster shots twice (once after 6 weeks and another at 6 months). The animals were recaptured 12 months after the initial vaccination and scanned for pregnancy. Two animals in each group were not located. Data from that study have been re-fashioned in the table below:

TABLE

Pregnancies	**Vaccinated**	**Placebos**
YES	9	16
NO	10	2

Thus the relative risk of pregnancies in the non-vaccinated group was 1.89

In a later study, the authors used a revised schedule to vaccinate 10 more elephants and ten months later found that only 2 were pregnant. If these numbers were used in the calculations, the relative risk in the non-vaccinated group would increase to 4.45.

Comments:

Immunocontraception in humans is a controversial issue. Placing the procedure in the context of wildlife populations enabled students to see the commonalities in approaches. They discussed the biological rationale for such approaches and compared and contrasted the technological and ethical aspects of applicability to humans and other mammals. A deeper exploration into the biology of elephant populations was undertaken by one group who considered the relations between elephants and humans and the impact of the trade in ivory. This proved to be one of the more exciting problems dealt with by the class that year.

BLOOD AND GUTS

Given below are excerpts from an article published in the British Medical Journal (18th Dec 1897) page 1386.

"For the last two years I have been endeavouring to cultivate the parasite of malaria in the mosquito. The method adopted has been to feed mosquitos, bred in bottles from the larva on patients having crescents in the blood. and then to examine their tissues for parasites similar to the hemamoeba in man. The study is a difficult one, as there is no a priori indication of what the desired parasite will be like precisely, nor in what particular species of insect the experiment will be successful, while the investigation requires a thorough knowledge of the minute anatomy of the mosquito.....

"On August 16th eight of them were fed on a patient whose blood contained fair to few crescents (and also filariae). Unfortunately four were killed at once for the study of flagellate bodies (flagellate cysts). Of the remainder two were examined on the 18th and 20th respectively, without anything being noted. The seventh insect was also killed on the 20th, four days after having been fed. On turning to the stomach with an oil-immersion lens I was struck at once by the appearance of some cells which seemed to be slightly more substantial than the cells of the mosquito's stomach usually are. They were a dozen of them lying among or within the cells of the upper half of the organ, and though somewhat more solid than these, still very delicate and colourless - so far it would have been impossible for any but a person very familiar with the insect's anatomy to have distinguished them from the neighbouring cells: but what now arrested attention was the fact that each of these bodies contained a few granules of black pigment absolutely identical in appearance with the well-known and characteristic pigment of the parasite of malaria (large quartans and crescent-shaped spheres)."

Five years later on the 12th of December, 1902, the author described his feelings on that day in August in the small laboratory in Secunderabad, India.

"Almost instinctively I felt that here was something new - but was so tired with work and had been so often disappointed before that I did not at the moment recognize the value of the observation. After mounting the preparation I went home and slept for nearly an hour. On waking, my first thought was that the problem was solved; and so it was."

Those comments were made by Ronald Ross on receiving the second Nobel prize in Physiology or Medicine. In later years that day came to be called "Mosquito Day."

Comments:

Another historical problem that led students to examine some of the older literature. One group dealt with Ronald Ross as a scientist and explored the development of tropical medicine, the role of Patrick Manson and the imperialism of British India and the attitudes toward "natives". Other aspects explored were the biology of malaria, knowledge of the condition at the turn of the century and our current awareness of the condition as well as the measures adopted to control it.

PRO BONO PUBLICO

Part 1

Given below are brief descriptions of two studies conducted to assess the relationship between tobacco smoking and lung cancer.

Study 1: was a survey-based retrospective case-control study. The author compared through questionnaires and medical histories, the smoking behaviour of lung cancer patients with that of a healthy 'control' group of comparable age. The questionnaires were sent to the patients' relatives, the histories obtained from medical records and diagnosis of death due to lung cancer confirmed by autopsy. There were 96 cases (86 males/10 females) and these were divided into 5 classes (extremely heavy smokers to non-smokers). The results showed that lung cancer victims were over 6 times as likely to be extremely heavy smokers. Further the healthy group had 4 times more non-smokers.

Study 2: Followed up and extended the earlier study. Questionnaires were sent not only to relatives of those who had died of lung cancer but also of other cancers (stomach, colon, prostate, esophagus and tongue). This sought to determine whether smokers were cancer prone or had a special predilection for lung cancer. Sampling was done of subjects of similar age who did not have any cancers. Data from their study has been refashioned and shown below:

Odds Ratios for Lung Cancer with Different Comparison groups amongst Smokers

Smoking Category	Group 1 (General Population)	Group 2 (All other cancers)
Very Heavy	16.6	8.8
Heavy	5.8	5.6
Medium	7.8	7.0
Moderate	1.6	1.4
Non-Smoker	1	1

Tested for Trends ($P<0.00001$ in both comparisons)

Part 2

The second study described above was conducted at an Institute for Tobacco Hazards Research set up by the Government. The state was concerned about the health and welfare of many of its citizens and undertook a series of steps to counter tobacco smoking. Some of the steps are given below:

- Smoking was banned in the offices of the Air Force, postal services.
- Smoking was banned by uniformed police
- Restaurants and cafes were prohibited from selling cigarettes to women
- Tobacco coupons were denied to pregnant women.
- It was illegal for anyone under 18 to smoke in public

- Advertisements for tobacco products were strictly regulated (both content/form)
    - *Ads that showed smokers as athletes were barred*
    - *Ads were not allowed to ridicule opponents of smoking*
    - *Images of masculinity were barred*
    - *Ads could not be directed at women*
    - *Ads could not be shown in films/billboards*
    - *Ads could not be used in text sections of journals/newspapers*
- Large scale production of nicotine-free cigarettes was started
- Research institutes were involved in developing nicotine-free cigarettes.
- Research was fostered into the psychology/psychopharmacology of smoking.
- Methods were developed to assist people to quit smoking.
- Tobacco manufacturers were pressured to convert their factories to non-tobacco ends
- Acreage for tobacco farming was controlled.

Part 3

The studies were conducted in Germany between 1939-1943. The Institute for Tobacco Hazards Research was established at the University of Jena by a grant of 100,000 marks from Hitler who not only abjured alcohol and tobacco but was also a convinced vegetarian.

Muller the author of the first study is regarded as the father of tobacco epidemiology and has been called "the Galois of tobacco science" (Proctor 1999). He was a member of the Nazi party and the Nazi motor corps. He presumably died in the war. The authors of the second study were Eberhard Schairer (a member of the Nazi party) and his student Erich Schoniger.

Reference:

Proctor, RN (1999) *The Nazi War on Cancer* (see chapter 6, The Campaign against Tobacco), Princeton University Press, Princeton, NJ, USA.

Comments:

I presented this problem to the class in sections. Each section raised a large number of issues. The students in general approved of the measures taken and when queried as to the locus of this study, almost unanimously felt it had to be either the United States or Canada since these had the most health conscious responsible governments. When presented with the final section, there was a sense of disbelief. We had an interesting discussion around unethical practices in one domain being counterbalanced by sensible, reasonable measures in another. This proved to be one of the more thought provoking problems used as it forced students to reconsider their assumptions.

SPRINGTIME IN THE SINAI

Part 1

Plants have long been regarded as a potential source for new drugs. Botanists from the Suez Canal University in Ismailia, Egypt sought to obtain antibacterial agents from plants growing in the Sinai region. Plant sampling was carried out in the growing season (March-April) of 1993 and 1994 in different districts of the Sinai peninsula. Bulk samples were air dried in the shade and after drying each sample was ground to a fine powder. The authors tried to gather flowering or fruiting specimens for taxonomic purposes. They used two different strategies to gather the plants studied.

In the laboratory, the samples were extracted with organic solvents, and finally dried under nitrogen and stored until bioactivities were assayed against Gram-positive and Gram-negative bacteria as well as yeasts and dermatophytic fungi. The results were reported in the journal of Ethnopharmacology 71: 365-376, 2000. Part of their data has been re-fashioned below:

Parameter	**Strategy A**	**Strategy B**
Total species	36	24
Active	15	20
Highly active	5	2
Moderately active	5	12
Weakly active	5	6

Part 2

Amongst the strategies used for selecting plants for pharmacological screening:

- Random approach (Strategy A) which involves the collection of all plants found in the study area
- Phyto chemical targeting entails collection of all members of a plant family known to be rich in bioactive compounds
- Chemo taxonomic approach is a method based on "specific plant parts"
- Ethno-directed sampling approach (Strategy B) based on traditional medicinal uses of a plant. In this instance, the authors selected plants based on the folk medicine of the Bedouins in the Sinai region.

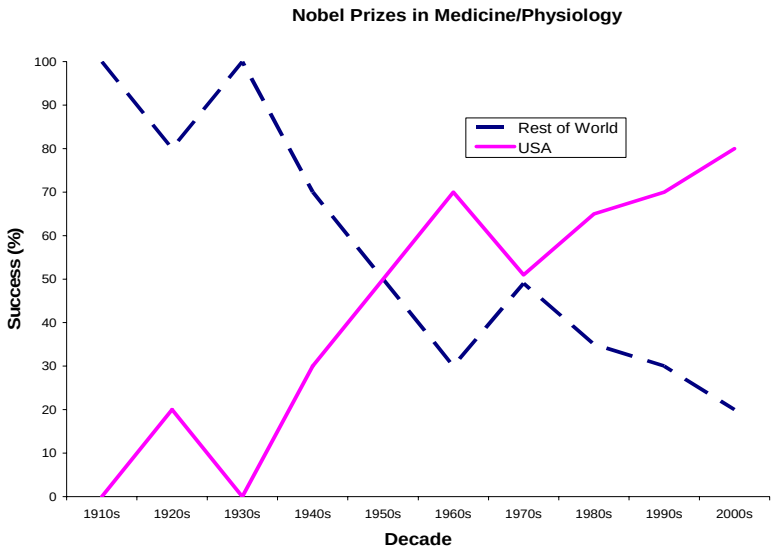
Comments:

The search for new drugs is a fertile field for discussing the context of discovery. It brings into focus the crucial interactions between ideologies, investments and ideals and sometimes individuals as well. There is always an ongoing debate between using high powered combinatorial chemistry approaches versus using ethnobotanical ones. With this problem, students considered a number of topics, the relative merits of ethnopharmacological approaches with specific reference to antibacterials, the contrast between traditional healing practices and modern medicine and the claims to knowledge, specifically whether indigenous populations should necessarily benefit when their traditional practices are exploited for profit.

WESTWARD HO?

Part 1

The first Nobel Prize in Medicine and Physiology was given to Emil Adolph von Behring in 1901. Since that time 171 scientists have either won the prize on their own or shared it with others. The figure below shows the success of American scientists in winning the prizes in comparison with those from other countries.



Part 2

Thirty of the US scientists were foreign born. Their countries of origin included England, France, Belgium, Austria, Australia, Canada, Czechoslovakia, Poland, Japan, India, Venezuela, Italy and the Ukraine.

Four of the Nobel laureates were women, two were born and had substantial training outside the US.

So far no African-American scientist has won the Nobel prize in any category.

References:

1. Schlessinger BS and Schlessinger JH (1991). *The Who's Who of Nobel Prize Winners*, 2nd edition. Oryx Press, Phoenix, USA.
2. http://www.nobelprizes.com

Comments:

The Nobel Prizes always provide a good starting point for exploration. With this problem, the students considered the interplay of institutional and individual factors (Nazi persecution of Jewish scientists, the availability of funds and the entrepreneurial spirit exemplified by American universities and research establishments etc) that led to the dominance of the US in the post war period. Some discussion focused on dominant paradigms and the exclusion of certain areas of research. Whether the provision of such rewards promoted competition at the expense of collaboration was debated.

CHICKENS - HIGHLY PRIZED

Part 1

July 10th, 1886, a mysterious illness breaks out in the chicken house attached to a small laboratory in Batavia in the Dutch East Indies. The lab has been set up to investigate the causes of beri-beri, an illness that is causing concern to the Dutch government. They are battling guerillas in the Malaysian archipelago and their troops have been ravaged by the disease. A team from Utrecht attempting to define the causative organism had not made much progress. The neurologist on the team has established that the disease is some form of polyneuritis. The senior investigators have returned to Europe, leaving Christiann Eijkman, a military medical doctor in charge of a small unit.

Eijkman is intrigued. The disease amongst the chickens appears similar to the human condition. The birds become unsteady, have difficulty in perching and frequently fall over while walking. The wing muscles become weak and the paralysis continues. Attempts to transmit the disease from an affected bird to another fail. Mysteriously the disease disappears by the end of November. The affected chickens recover.

Part 2

The laboratory has been housed provisionally at the military hospital, although it had been administered by the civilian authorities. Eijkman discovers that for a period, the laboratory keeper, for reasons of economy, had been feeding the chickens with cooked rice from the hospital kitchen. But a new cook refuses to allow civilian chickens from eating military rations and so the normal chicken diet had resumed by the end of November. The suspicion that something in the food was responsible leads Eijkman to undertake feeding experiments. Chickens fed cooked rice develop the disease, whereas controls fed unpolished rice do not. The condition seems easily treatable by altering the diet.

Part 3

In 1929, Eijkman is awarded a share of the Nobel Prize in Physiology and Medicine. He is unable to attend the ceremony due to illness, but his co-recipient Sir Frederick Gowland Hopkins does. They are recognised for their contributions to the role of accessory food factors (now known as vitamins). Casimir Funk who has coined the term and has isolated the active principle that cured beri-beri does not get a share of the Prize.

Comments:

The discovery of accessory food factors later termed vitamins provides students an opportunity to explore many aspects of research in practice. With this problem, students discussed the nature of beriberi, the role of experimental models, the current awareness of dietary deficiencies and Nobel Prizes. The role of dominant paradigms in delaying recognition of new ideas was discussed given that proponents of deficiency diseases had to counter the prevalent paradigm of germs as major causative factors.

LIVING MORE

"I think of myself as a six-foot-tall, blond, blue-eyed male" says an MIT trained physicist to an ethnographer in the waning years of the Cold War, "The work (I am doing) is quite interesting and that was definitely a consideration. But I decided to work in the lab, I think, because I had a fear of big weapons. I really wanted to see what was happening for myself. I wanted to see what was going on, rather than take other people's word."

The speaker is in reality a much shorter, dark-haired, dark-eyed Japanese-American woman who is the only non-white member of an elite group, Warhead Designers at the Livermore National Laboratory. Sylvia (to give her her code name) is quite proud of her Japanese heritage. Her aunt had witnessed the bombing of Hiroshima and suffered radiation sickness as a consequence.

Sylvia considers herself a feminist but one who is "fighting for everybody's rights, not just women... I think I'm protecting children. I feel as if I'm protecting the country." As a weapons scientist, she is opposed to the suspension of nuclear testing that was being strongly advocated, as that would be risky. "I would like to see testing of things that have already been built, just to make sure that nothing has happened like the quality of the sample, because things change..... I like to poke things and tear them apart. I would like these systems to be as predictable as possible."

It is the fall of 1987, and an ethnographer has chosen to live at Livermore, a small town forty miles east of San Francisco. He has gone to study the patterns of culture of an exotic but powerful tribe – those who design and test nuclear weapons. The town, though somewhat unprepossessing, has some good features for those who want to raise a family, a low crime rate, a very good school system, parks and churches. It has the second highest proportion of PhD's per capita of any community in the US.

In standard fashion, the ethnographer sought out informants (Sylvia being one). He is struck by the diversity of political opinions and religious views. The weapons scientists included atheists, Jews, Catholics, Episcopalians, Presbyterians, Methodists, Lutherans, Unitarians, Baptists, Mormons, Evangelists and even three Buddhists.

References:

Gusterson, H. (1995) 'Becoming a Weapons Scientist' in *Technoscientific Imaginaries* edited G. E. Marcus, U. Chicago Press Chicago

Gusterson, H. (1998) *Nuclear Rites: A Weapons Laboratory at the End of the Cold War.* U. California Press, Berkeley, L.A.

Comments:

Many of the students who take my course have their sights set on medical school since they believe that by becoming doctors they would "help" people. This problem forced them to reconsider the meaning of that word. They realised that many scientists may become weapon designers for the same reason. The topics discussed ranged from the profile of weapons scientists, the case for and against nuclear disarmament, the proliferation of nuclear weapons, the creation of the bomb and the effects of nuclear explosions.

GUTS AND GLORY

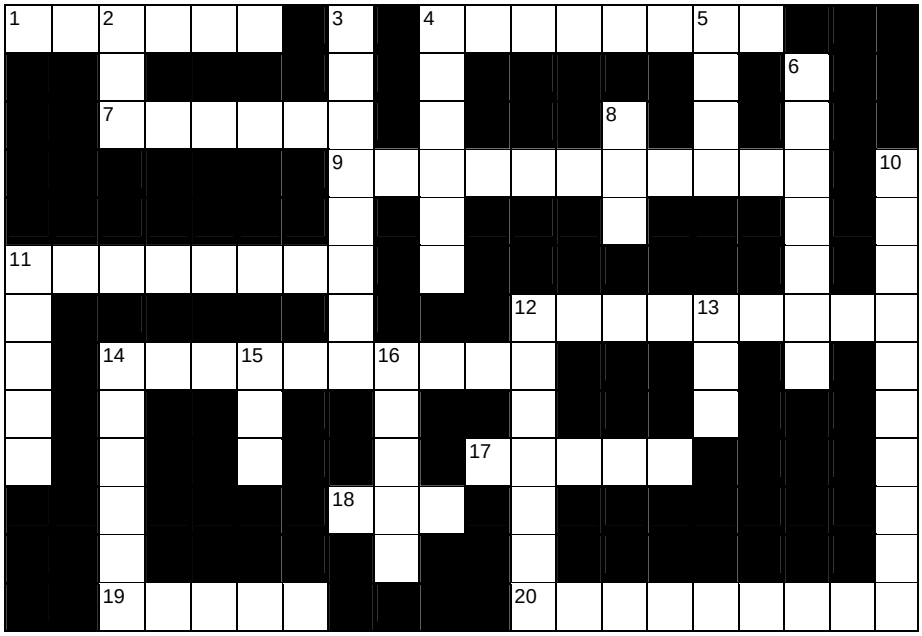
Modern science is a cooperative enterprise. Items of information add to the sum total of knowledge on any subject. Operationally science in practice is like solving a puzzle. Using clues that are obtained from diverse sources, scientists piece together a picture of how they believe the world operates. The fruits of their labours can on occasion be remarkably profitable. Vexing diseases can be tackled and cured, much money can be made. One of the more spectacular achievements of modern medical science has been in developing drugs for stomach ulcers.

You have been given a crossword puzzle with a set of clues. All the clues relate in one way or another to the problem of stomach ulcer disease. Try tackling the puzzle either individually or in groups and at the next session we will discuss the answers and flesh out your findings.

(See Crossword on next page)

Comments:

The students quite liked this approach. The Internet was quite useful and they cooperated with each other in tackling the clues. The information gathered then generated much discussion.



ACROSS:

1. Good for aching joints but they hurt your guts. (6)

4. This cell may be a bit to the side – but that does not matter, does its job well. Keeps the acid flowing. (8)

7. Cave in Greek but part of the stomach for those who speak English only. (6)

9. Maybe good for anthrax and similar conditions -but why are they used for ulcers? (11)

11. U.S. Army surgeon stitched up 3 down – did not do it well, but got glory anyway. (8)

12. Strong stuff, makes you itch, burn, flare and wheeze. (9)

14. Found in 4 across – keeps the action going. Stopping it, good for heart burn. (6,4)

17. His name may sound a bit dark, but he is a shining white knight for those who had heart aches and heart burns. Was well rewarded (see 10 down) (5)

18. Common term – can cause disease or just annoy. Spies may plant one. (3)

19. Vital nerve - 10th of 12; keeps the heart and stomach working. (5)

20. Five membered ring contains nitrogen – central part of 12 across. (9)

DOWN:

2. Common over-the-counter drug - belongs to the same class as 1 across. (3)

3. Tough French Canadian – brought glory to 11 across, outlived him too. (2,6)

4. Another cell close to 4 across, adds another component to flowing juices. (6)

5. Maybe against, but added to 12 across soothes itch. (4)

6. Like 12 across, stimulant for 4 across. (7)

8. Acronym for important ubiquitous enzyme – can be affected by 1 across. (3)

10. Reward for work well done. Given to 17 across and 14 down. Not to 11 across, 16 down since they died too soon. (5,5)

11. First name of down-under scientist – swallowed bugs to prove his point – may get 10 down. (5)

12. Spiral critter – causes much damage. (1,6)

13. Short for powerful "Stuff" released from 19 across. (3)

14. He did a lot more than ring bell for slobbering dogs. Got his just rewards though. (6)

15. Had a hole in his stomach. Was studied by a Dr. Wolf. (3)

16. Found what made stomach juices acid. Foresaw a version of the Periodic Table. (5)

Solution on p. 64

VIP LASH

Helmut Vipkracker has had enough. He knew from the outset that it had been a mistake for his company to become involved with those sanctimonious academics from MuckMaster U. But the Company was under attack and they needed to show that they were responding to global needs. A PR ploy had become desperately needed. MAC-SYMIZE was the name of the new endeavor to foster research into drugs that may benefit the worthless losers of the Third World. The company was to follow the tradition of the Rockefeller foundation and make the peaks higher. They chose to select individuals with promise and fund operations to seek out novel drugs against intestinal parasites. Several collaborative groups had been established: the Ethnopharmacology Division, the Parasite-Genetics group and most contentious of all, the Zoopharmacognosy initiative.

Many years earlier, Vipkracker had fled the back-biting of academic politics with its trivial stakes for the larger blessings of industry. He wanted to be free of carping students complaining about their grades and giving flimsy excuses for late submissions. He had reluctantly chosen to involve himself with the tenured nobodies, whom he utterly despised. Now, as he took stock of the five years wasted, he shuddered. He felt that a strong hand was needed, even a whip. So he called the heads of the various divisions along with some of their minions for a Strategic Plan Initiative.

As he watched them jostling around the table in the Board room, Vipkracker could barely conceal his disgust. The ethnopharmacologist seemed to play to the image of the intrepid adventurer, with his bushy eyebrows, ear-rings and neatly trimmed beard. He had been known to spend as much time searching out exotic women as he did hunting rare plants. His shady dealings with shamans had been briefly mentioned in a local tabloid, but the University moved quickly to hush it up. The Head of the Parasite Genetics group was an expert in knocking out diverse genes from a variety of parasites, but her reputation was less as a genes-knock outer than as a jeans pull-downer. Her rapid ascent up the academic ladder had been noted. The Chief of the Zoopharmacognosy Division elevated publicity seeking to a fine art. His observations of self-medication amongst monkeys in Borneo had been televised ad nauseum. Not a month passed, without the local rag doing yet another feature on his “discoveries”. He wandered the halls surrounded by deluded groupies who believed that they had finally found a sensitive, “holistic” scientist in tune with Nature and not one of those run-of-the mill reductionists. Being a synthetic organic chemist himself, Dr.Vipkracker had thought these new fangled novel approaches quite silly and fruitless at the best of times, worse when they were being fostered by a mediocre, self-serving bunch intent on furthering their own careers.

“Your progress has been pathetic”, Dr. Vipkracker told the assembled group, “Yes, yes, you have publications and invitations to conferences. That is irrelevant. Nothing is coming through for us. We are not a charity designed to promote your life styles and build your petty empires. You have two weeks to present a coherent strategy to find new drugs using your particular skills. If you can’t, you are out. Get to it.” Not waiting for any questions, he stormed out of the room.

Commentary:

This piece was deliberately provocative to highlight the practice of science in the "real" world. The unflattering portraits were composites drawn from readily recognizable types (some of whom I have known personally). The students focused on several key issues in the drug discovery process.

La Fin de Siecle: Une Nouvelle Blague?

On Wednesday the 10th of March 1999, the Cavendish Physical Society met in the Pippard Lecture Theatre attached to Cavendish Laboratory in Cambridge, England to hear Dr.Jacques Benveniste. His talk was entitled AElectromagnetically Activated Water and the Puzzle of the Biological Signal@.

The Cavendish Laboratory at Cambridge, England is one of the world=s most remarkable scientific institutions. The first Director, James Clerk Maxwell laid the foundations of electromagnetic theory which spawned the information revolution. Later research done there opened up the inner world of the atom and irretrievably altered the face of modern science in the early decades of the 20th century. Soon after the Second World War with Big Science destroying the "string-and sealing" wax style of physics fostered there, Cavendish revitalised itself with two new divisions, molecular biology and radio-astronomy. Both ventures led to much greater glory. No single institution has gathered more Nobel Prizes; laureates included Rayleigh, Thomson, Rutherford, Cockroft, Walton, Wilson, Aston, Bragg, Chadwick, Kapitza,Josephson, Crick, Watson, Klug, Perutz, Kendrew , Milstein and Ryle.

The speaker that day had attained legendary status of a very different sort. He was not only a legitimate card-carrying immunologist, discoverer of PAF (platelet activating factor) but also the recipient of not one but two AIg Nobel A awards given for those doing outstanding work that could not be replicated. He had incurred the scorn of the scientific community in a paper where he claimed that infinite dilution of an antigen solution could serve to degranulate basophils. That smacked of homeopathy and in fact he did receive funding from such an agency. Nature, one of the best known amongst peer-reviewed publications, published his paper and then promptly set out to investigate his claims. The investigating committee included a fraud expert and a magician. The author was cleared of fraud but his judgment still remained questionable.

Benveniste claimed that his results were very real and invoked a mysterious Amemory of water@. He lost his peer reviewed funds and set up on his own establishing a company Digital Biology. In his later efforts he has gone in the view of many quite Beyond the Fringe.

In his presentation, to a packed audience including some very eminent names, such as Sir Andrew Huxley, Nobel Prize winner and past president of the Royal Society, Benveniste suggested that specific biologically active molecules (adrenaline, nicotine, caffeine, antigens) could be recorded and digitised using a computer sound-card. These signals can then be transferred to distant locations via the Internet, so that responses can be elicited elsewhere, by simply playing back the recordings. Molecules in this view need not be in close proximity to affect each other. After all one can listen to Pavarotti from a CD and experience the same emotions.

Josephson, a Nobel Prize winner at the ripe old age of 33, was in the audience and later defended the decision of the Society to give Benveniste=s views an airing. The Nobelist has also been known to insist that quantum physics can explain telephathy and other paranormal phenomena.

In 1897, when J.J. Thomson had announced his discovery of the electron from his work done at the Cavendish Laboratory, several prominent physicists had thought that he was pulling their legs. The concept seemed beyond the fringe then. A hundred years later, scientists at Cavendish were being presented with what appeared to be a new joke for a fast fading century.

Comments:

This scenario raised a large number of issues---dogma in science, stifling of creativity, legitimate versus non-legitimate explorations, the Cavendish Laboratory, Nobel Prizes, the rewards and punishments meted out by the Scientific community. In the class-room discussions, many aspects were touched on, ranging from Popper to Feyerabend (I have personally a sneaking admiration for the latter!)

MORE THAN LUKE WARM

1. And it came to pass that Hieronymous, the Orthodox Metropolitan did write to Antonio Mattiazzo, Bishop of Padua, to donate part of the relics that lay in a tomb there to be placed in another in the good city of Thebes.

2. And the relics that lay in the said city of Padua had travelled far and wide. The bones came from one, who born in Antioch in the Roman province of Syria, had travelled wide spreading the word, till he died in the Greek city of Thebes some hundred and fifty years after the birth of the Lord. The remains were taken thence to the golden capital city of Byzantium where they lay some eight hundred years. They then found their way to the said tomb in Padua.

3. And it came to pass that the Bishop of Padua did consider the request and found it good. And so he caused the seals to be broken and the tomb to be opened. And a rib was sent forth from the tomb to be buried in the empty tomb at Thebes.

4. Now there were in nearby Ferrara, certain men wise in many ways. They could from bits of bones say who begat whom, whence they came and where they went. The Bishop said unto them -- tell me whose bones these are. Are they his whom we revere here. Give us the teeth they said and we will tell you. When he did the wise men rejoiced. In their telling could come much glory for them all.

Comments:

This problem was based on the paper by Vernesi et al (2001) Proc Natl Acad Sci 98(23):13460-3 dealing with the classification of the body attributed to the evangelist Luke. A number of interesting issues were reused - the obvious was such as anthropology and molecular biological approaches the relationship between religion and science, the meaning of and motivations to undertake scientific experimentation.

The United Weigh

Fellini=s Satyricon, new Millenial style. Slobs of all shapes and sizes slouch side by side on sofabeds strong and sturdy, slurp slushing soft drinks smiling. Globs wipe ketch-up of greasy chins. Joe, the Pudge, fast approaching the perfect shape, the Platonic Sphere beams at them all. He made it happen with his lottery winnings. Instant wealth meant not luxury cruises and down payment on a fancy house but a wild party to right years of wrongs. His luck would be shared with his fellow orbs. Jocks not welcome.

The Sea of Slobs part as Pudge oozes his way to the podium.

AFriends! Glad you could come. Hope you are having a great time.@

Wild cheers. Pudge! Pudge! Pudge!

Fat hand rises. ***Silence*.**

AWe have work to do. The time has come for us to join together. We have suffered long enough. We are held to ridicule day and night. Jocks jog along as though they own the world. Gyms abound. What have we done wrong? We are what we are? We don=t point fingers at any one. We don=t ask others to follow our lifestyle. We may die sooner. So what? We have a good time don=t we?@

Wild shouts. Yes, yes, yes.

AThey may live longer, but they lead such boring lives, it just seems long. No fries, no chocolates. Lacing life with garlic and broccoli. Sweating and smelling on treadmills. Those silly jocks laugh at us. They are to blame. It is those slimy scientists and pompous doctors with their Wellness studies and health fads. We have to fight them.@

Chants of AFight , fight , fight! Sue, sue, sue!@

AFriends. No. Suing won=t help. Yes they can discriminate against US with impunity. They won=t dare do this against other visible minorities. We ARE Visible. We ARE a Minority! Law suits don=t help. Only lawyers win. No we will fight them by funding them.@

Puzzled silence. A What? What did he say? Fund them@

A I am creating a Foundation B The United Weigh that will fund research into the benefits of indolence and weight gain. Call for research proposals will be going out soon. I can feel that saliva dripping on campus floors when the announcements are made. I know those guys. They will do a cut and paste job on their old grants, change the focus and beg for money.@

Shouts of laughter. Smart Pudge, knows the enemy well.

Comments:

Much like the previous problem “wait-le$$ne$$”, this served as a stimulus to the discussion

of obesity and the attempts to control it. Although the role of foundations and finding of research was raised as an issue, much to my disappointment, the class did not frame it as a major learning task. Two students felt quite offended by my flippant remarks about obese individuals and felt it was discriminatory. It is difficult to be anything more than bland and boring in these politically correct times.

TEXT ----- WORDS

AIn the past, war was confined for the most part to men in uniform, but with increased mechanisation of armies and the introduction of air forces, there is an increased dependence on the home country, and eight to ten people working at home are now required to keep one man in the fighting line. This state of affairs alters the complexion of war.... It is just as effective to kill or disable ten unarmed workers at home as to put a soldier out of action and if this can be done with less risk, then it would be advantageous to employ any mode of warfare to accomplish this.@

AIt is a war of scientist against scientist. This war above all in history will be one in which the application of science to warfare will give one side or the other the advantage.@

AFor some weeks experiments have been in progress on bacterial warfare..... These experiments have now (Oct 8,1940) reached the point where field work must be carried out on the means of distribution from the air. When this information is obtained, further laboratory experiments on drying, preservation and production as well as selection must be carried out.@

AThose Huns at home, those huns of HitlerBIt is our job to kill them.@

CONTEXT---- DEEDS

The words are those of Sir Frederick Banting. By the time they were written, he had attained considerable eminence for the discovery of insulin.

The last excerpt is from his diary in the fall of 1940 after he had watched a plane making low passes over Balsam Lake, in cottage country north-east of Toronto , sprinkling saw dust from various altitudes to see how far those particles would spread in the event that they would be carriers of infectious agents. He is credited with having been one of the prime movers in getting Canada started on a biological warfare programme in the early years of the Second World War.

The initial investments for Canada=s forays into germ warfare came from the corporate sector. Three civilians participated in the early development and formed part of the War Technical and Scientific Development Committee. They were John Eaton (head of T.Eaton Co.), Sam Bronfman (head of Seagrams) and R.E. Stavert who represented Sir Edward Beatty (president of Canadian Pacific Railway).

All information taken from John Bryden=s Deadly Allies: Canada=s Secret War 1937-1947 (McLelland and Stewart 1989)

Comments:

Students were presented this problem in two steps. The first part raised a number of issues ranging from germ warfare, to scientists' contribution to the war effort, our responsibility and the targeting of airlines as legitimate targets. Some concern was expressed at the

sentiments expressed in the last sentence.

The second part came as a shock to most students. The general mythology of Banting as the great saviour is embedded deep in the Canadian consciousness. The realization that he was one of the pioneers of biological warfare in this country was new to them. The involvement of major industrialists in the effort was also a revelation. I was able to get Mr. Bryden, the author of the book and a Member of Parliament, to talk to the students as well.

Problems written for an Inquiry Course in Philosophy

Between Jan-April 2005, I participated in an Inquiry course on philosophy co-ordinated by the Dept. of Philosophy at the University of Calgary. The course was aimed at first year undergraduate science students in an undergraduate health sciences programme. The students who took this course have already taken an earlier Inquiry course where they dealt with the problems of communication between scientists themselves and between scientists and the public through the mediation of journalists.

For this particular course, the course co-ordinator (Dr. M. Ereshefsky) wanted students to appreciate the general approaches taken by philosophers and tailor it to students who were in a science based program. The course was taught by 3 separate Faculty members who took slightly different approaches. Though the course itself was not problem-based, I chose to teach my section in a PBL format.

The entire class was divided into 3 sections. We adopted a rotation format whereby each large group of 24 students would spend 3 weeks with each preceptor wrestling with specific issues. I chose to get students to struggle with the notion of distinguishing what was termed disease and non-disease. Since there were 3 sets of students, I had to write slightly different problems so that even if the students talked amongst themselves, each set would get to see only one of the problems. In the pages to follow, I give the 3 problems that I wrote.

PATHOLOGICAL WASTE

Rudolf Firkow is quite incensed. As a pathologist who had devoted his life to liver dysfunction, he was certain that he could tell the differences between normal and diseased tissues. But a current issue of Arch. Histopath carries a bizarre article by some obscure philosopher stating that the concept of disease is irrelevant. He cannot believe that a reputed journal would publish such arrant nonsense. It seemed to be a waste of precious space, almost pathological. He feels strong that if they continue to publish such rubbish, he should cancel his subscription. He would like to write a rebuttal, but is perplexed by the philosophical jargon and does not even know where to start.

Comments:

A number of questions were raised following the brainstorming session. Some of these are given below:

Does disease require a biological basis? Will absence of clear pathological signs exclude disease? Is the concept of a disease relevant? Do pathologists define disease differently? Does an altered histological picture denote disease? Can a disease that remains undefined not be treated? Is a disease only a label of convenience? Does abnormaility at a tissue level denote disease? Does absence of an abnormality denote health?

AGGRAVATED ASSAULT

Agro Inc. had acquired a reputation for undercutting their competitors and obtaining international military contracts. Their aggressive policies and competitive streak made their stockholders wealthy, but did not lead to good interpersonal relations with their staff. Many employees had been summarily dismissing for non-performance and others quit in disgust. When several employees were given pink slips for frequently falling sick, they filed a suit against their employers. They claimed that the time they had spent in the Middle East exposed them to toxic chemicals and they were thus suffering from the Gulf War Syndrome. Not to be outdone, Agro Inc hired sharp lawyers to contest these claims.

The lawyers, in turn, called on several philosophers to act as expert witnesses on behalf of the defendants. They felt quite cynically that the plaintiffs would have no chance. One of the lawyers quipped, “Put the Philosophers in court and the judge will scream for help.”

Comments:

This problem provoked much discussion. Amongst the questions that were asked were the following: How can one distinguish between slacking off and being really sick? Is inability to function a definition of illness? Conversely dose ability to function equate to health? Dose the Gulf War Syndrome exist? Who defines a disease? Do these definitions matter? To Whom? Do Insurance companies consult philosophers? Do doctors take philosophy seriously? Can philosophers act as expert witnesses? If there is no concept of a disease, can there be a concept of compensation? What determines a disease? How dose it differ from a syndrome? Is it just a term? What are the boundaries?

Amongst the Philistines?

The proposal to establish a new veterinary school has generated a great deal of interest. Many committees have been struck to frame a suitable curriculum. The participants include basic scientist, educators, veterinarians and medical doctors. The proposal is to use a clinical presentation approach. Thus students would tease out the underlying pathophysiology using as triggers clinical cases that are exemplars of the problems they are likely to face in practice. The early discussions are going well, though the jargon used by some of the educational experts is jarring to the ears. Someone suggests that it would be good to invite a philosopher to discuss the more theoretical aspects of health and illness.

Dr. Ludwig Van Witlesstein is excited at the offer. He arrives with a stack of notes and some well thumbed texts. His shuffling presence and earnest gaze seem quite out of keeping with the sleek, well fed bets and sleeker docs. His forays into essentialism, nominalism, normativism and social construction are met with stony faces and glazed eyes. When he begins to wax eloquent on Hesslow, and asks rhetorically "Do we need a concept of disease?" the silence is broken by a horsy snort.

"This is #$%^$@!$%, pardon my French", bursts a burly vet from the front row, "We have no time for this. We are REAL doctors practicing real medicine. We cannot hand out placebos to vomiting cats or %$#@^$!ling cows. That rubbish is fine for family docs or psychiatrists, not for us".

Dr. Van Witlesstein is stunned at the outburst, even more by the applause that follows.

Comments:

This problem too provoked much discussion. Given are some questions that emerged: Does a concept of a disease matter if the patient cannot understand? Why is the concept of a disease relevant for veterinarians? Can placebos be used in vet practice? What do the terms nominalism, essentialism, etc really mean? Is philosophy relevant for practice? Do practicing vets have a different concept of disease?

Writing problems for “solution”

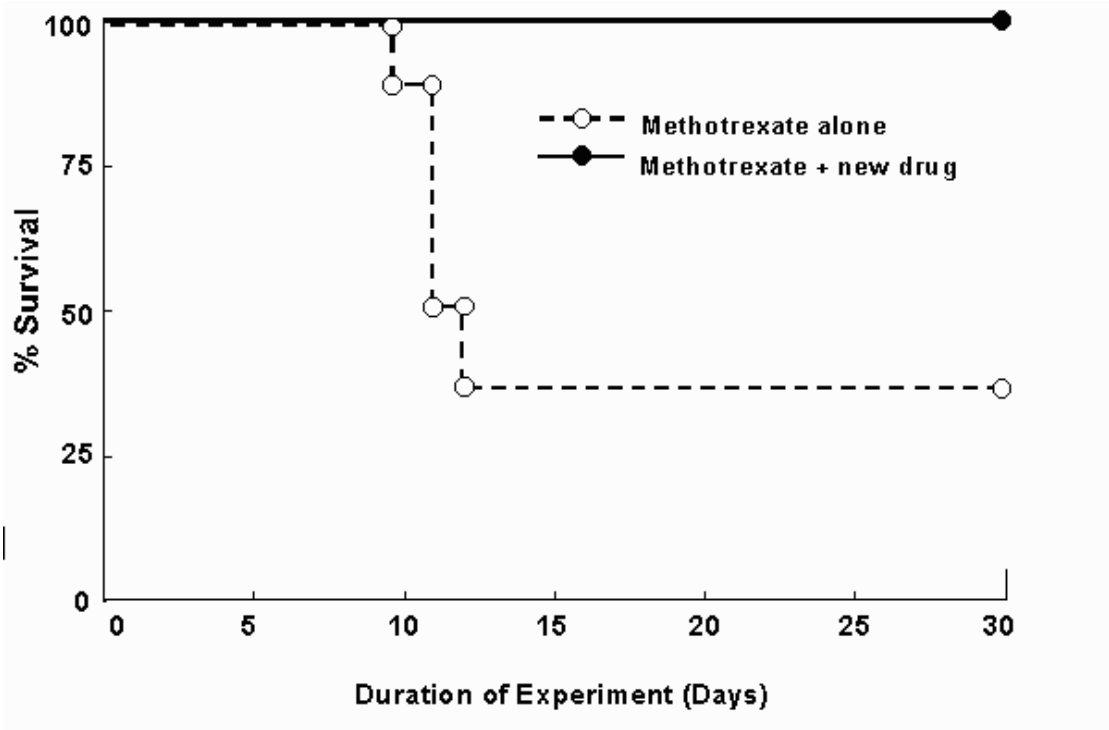
In the Pharmacology course, problems have been developed for purposes of evaluation. These problems present a limited set of data. Students are asked to provide suitable explanations for the data provided within a limited time. They are then asked to select their best explanation and either design experimental tests or suggest avenues for further exploration. In the third phase, the students are provided with more information and asked to reassess their original explanations and approaches. I include examples from two Pharmacology courses.

Writing such problems is tricky as, under pressure, students tend to misunderstand/ misread. I permit students to take the problems with them, which makes it difficult to re-use them for another year.

OF MICE AND MEN

Resistance to chemotherapy reduces the effectiveness of many anti-cancer drugs. Since many tumours show a steep dose response curve to chemotherapeutics, it is possible to overcome this resistance by increasing the dose of the drug. However, this in turn poses another problem as toxicity to the drug develops. **If** the toxic effects can be either reduced or eliminated, it is possible to increase the dose of the drugs used to treat cancer. Investigators have explored such possibilities.

Given below are data from an investigation designed to test the abilities of a new drug to reduce the toxicity of a standard anti-cancer drug, MTX. Two groups of mice were used in the study. Both groups were injected with a single intraperitoneal dose (LD50) of MTX. The treatment group received **in addition**, the new drug, (twice daily by the same route). The investigators charted the survival of both groups over a 30 day period (see Fig below).



Comments:

This problem was given as a final evaluation in the Introductory Pharmacology course. Students had not done cancer chemotherapy as part of the course, but that was not the issue at hand. They were asked to deal with the issue of toxicity. The majority of the students performed well and had many interesting explanations. However, some students misread the problem and did not realise that the mice used were ***not*** *tumour-bearing ones. The addition of the single word "normal" would have avoided that difficulty. Unfortunately I failed to spot that until I saw the answers.*

OF NUDE STRIPS AND PEPTIDES

Bradykinin is a peptide that is a potent bronchoconstrictor and could thus be an important inflammatory mediator in asthma. A research group at BioPharmacol Enterprises have been studying the effects of a novel drug BP239 on the responses of human bronchioles to exogenously added bradykinin.

They dissected out the bronchioles and cut them spirally to obtain strips which were mounted in organ baths and the tension generated in response to different drugs was recorded. Two kinds of bronchiolar strips were used. In the normal strips the bronchiolar epithelium was left intact whereas in the denuded set, the epithelium was carefully removed and the removal checked by histology. The responses were tested in the presence and absence of the drug BP239. The results are shown below.

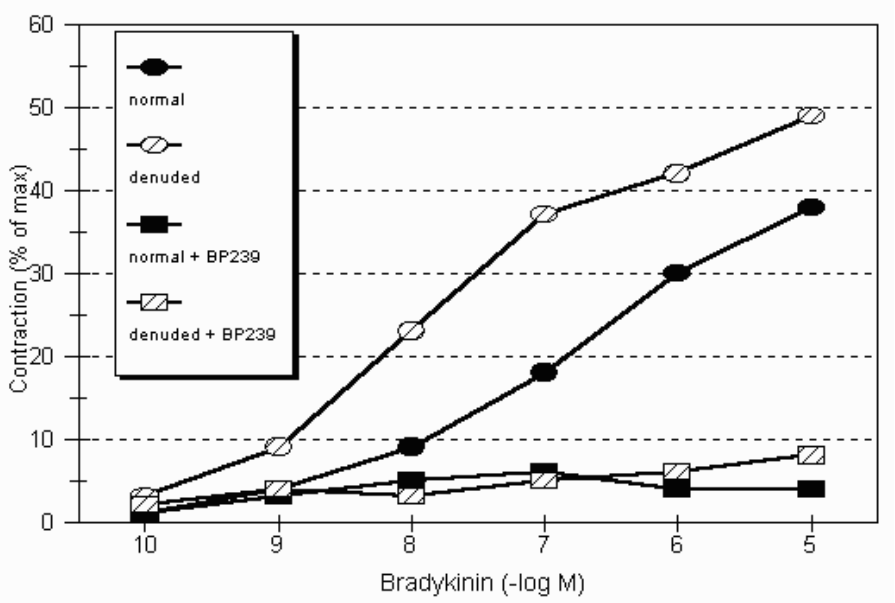


Figure shows the cumulative responses of bronchiolar strips to exogenously added bradykinin. The data are expressed relative to the maximal tension developed in response to a standard agonist, methacholine (a cholinergic drug). Both normal and denuded strips were tested in the presence and absence of a novel drug (BP239). The data are mean values, the error bars have been deleted for the sake of clarity. The responses of normal and denuded strips in the ***absence*** of BP239 were significantly different from each other. However in the ***presence*** of BP239 no differences were noted between normal and denuded strips.

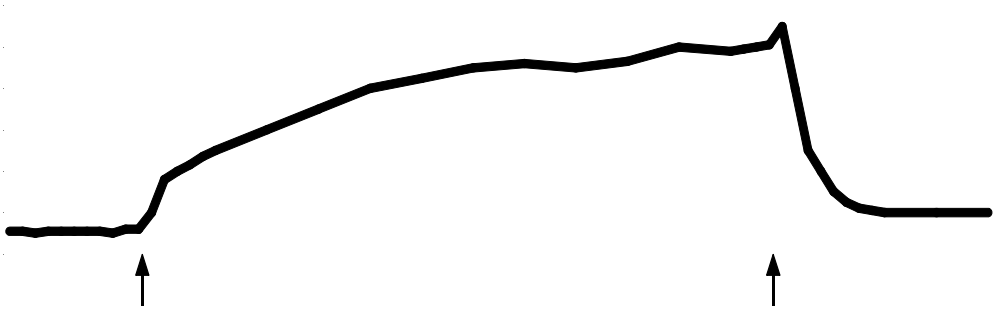
Comments:

Several possible explanations can be given. For instance, the epithelium could be producing an inhibitory substance that either limited responses to the peptide or even degraded it, it could have acted as a mere barrier to the access of bradykinin to the receptor, etc. Again the novel drug could be a general antagonist to bradykinin or to the production of some substance released by bradykinin that was responsible for the contractile effect.

TUNDRA RED SHIFT

Jorge Luis is now a consultant with Tundra Wines, who have used the wonders of biotechnology to develop the Supreme Grape. They expect to produce a healthy red wine that would entice Canadians to give up on imported wines. As part of their scientific approach to the problem, they have set up a Vascular Lab to explore the effects of grape products on smooth muscle function, since there is evidence that consumption of red wine is protective against coronary artery disease.

Jorge Luis sets up rat aortic rings in physiological salt solutions and records isometric tension in response to different agonists. He finds that arteries precontracted with norepinephrine (NE), promptly relax when treated with a 1:100 dilution of Tundra Red Extract (TREX) (see Fig 1).



He compares the responses of intact aortic rings with those that have been denuded of endothelium by gently rubbing the luminal surface with curved forceps. In these experiments, the rings were **pre-incubated** for 15 mins with a 1:100 dilution of the Extract.The results are shown in Table 1.

TABLE 1

Tundra Red induced relaxation of aortic rings

Condition	% Relaxation
Endothelium Intact	88 ± 3
Endothelium Removed	5 ± 2

.../continued

Finally he compares the relaxing effects of a variety of products, all used in the same concentration (see table 2).

TABLE 2

Vascular Relaxing Effects of Different Grape Products

PRODUCT	% Relaxation
Grape Skin Extract (red)	100
Grape Skin Extract (white)	96 ± 4
Tundra Red Extract	100
Cabernet Sauvignon (red)	86 ± 3
Burgundy (red)	88 ± 3
Bordeaux (white)	0
Chardonnay (white)	10 ± 2

Comments:

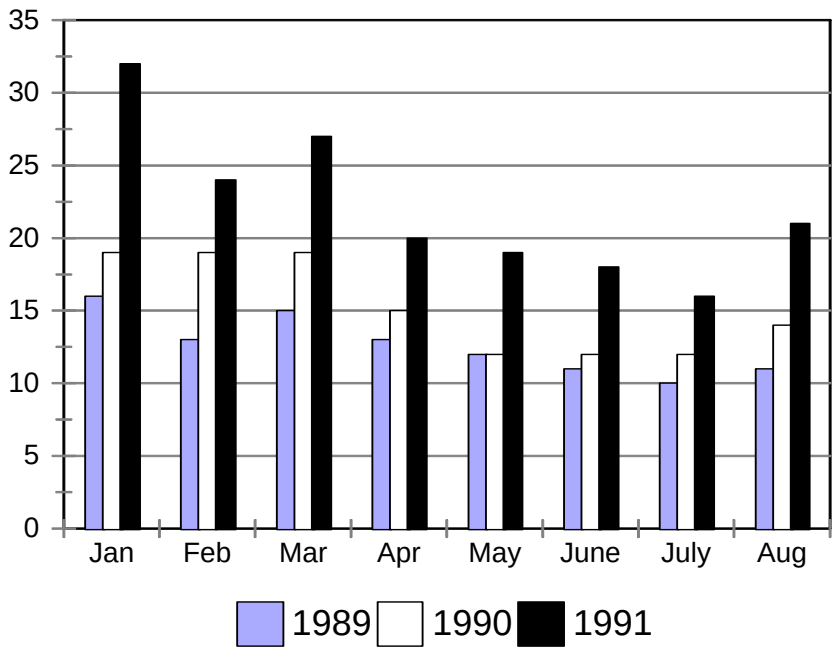
This problem used a study that had been published in the American Journal of Physiology (Fitzpatrick et al, Am J Physiol 265: H774-H778, 1993). I reworked it to use the character Jorge Luis who had appeared in one of the earlier problems. Again many different explanations are possible.

A SECULAR TREND?

Given below are data gathered on the number of prescriptions for albuterol (Ventolin) in four health centres in Bahrain during the first 8 months of the years 1989-1991.

Bahrain is an archipelago located in the Arabian Gulf, 320 km to the southeast of Kuwait. The population (516,444) is served by a well-developed medical system provided by a combination of a government health service and the private sector. In the government health care centres, acute asthmatic attacks are treated with albuterol nebulisers. The data are obtained from the centres in Muharraq, Nai'm, Hoora and Sheik Sabah.

Number of prescriptions per 1000 medical visits



Comments:

This problem was used in my 4th year course which dealt with social aspects of pharmacology. Here students were expected to find possible explanations for the variations in prescriptions written. Many explanation were given ranging from the appearance of the drug in the formularies, aggressive marketing, non-availability of other medications, some even remembered the Gulf War!

A LEADING CAUSE?

Marnie, a graduate student in Behavioural Sciences, uses a well validated rating scale to assess the prevalence of antisocial behaviour amongst Grade 3 students in all 5 elementary schools in the city. She finds that 27 out of 246 can be labelled "antisocial". Closer attention to the data shows that 7 out of the 27 students come from the same private school (The Vanguard).

Millicent, who is Marnie's roommate, suggests that she approach the problem epidemiologically by listing the school as a "risk factor" for the production of antisocial behaviour. She shows Marnie how to tabulate the data to estimate an odds-ratio.

	Antisocial behaviour	Normal behaviour
The Vanguard	7	18
All other schools	20	201

The estimated odds-ratio is large enough to cause concern. At Millicent's urging, Marnie decides to explore the issues further.

She finds that the school is a private one, run by a Society dedicated to improving the lot of women. Many of the mothers who send their children to the school are adamant about self-reliance. To that end they not only promote self-medications with herbals rather than prescription drugs, but also advocate that women undertake training in using firearms. A large number of them are practising artists and craftspeople. Marnie is also intrigued to find that 5 of the 7 students on her list live in the same large house — an older building which had been extensively remodelled several years ago by the parents themselves. The house not only has several pottery studios but also an attached indoor shooting range.

Comments:

Another problem used in my Social Pharmacology course. The format is similar to that used in A Rash to Judgement, A Not-so-Hairy Tale. Here attributable risk can be assessed but also students were expected to tease out potential causes. A number of clues were given pointing to lead poisoning, though many other explanations were possible.

COSTLY ODDS

Pharmacoeconomic evaluation of new drugs is becoming increasingly important for health care planners. Favourable or unfavourable comments about cost-effectiveness could play a significant role in determining whether certain drugs or classes of drugs get widely used.

A recent study sought to review economic analyses of new drug treatments in oncology. The authors searched MEDLINE and Health STAR databases (1988-1998) for original English-language research articles of cost or cost-effectiveness analyses of 6 breakthrough cancer drugs in 3 categories. These included hematopoietic growth factors, serotonin antagonist emetics and taxane chemotherapeutic agents. In the studies analysed, a novel treatment was compared to either standard treatment or placebo.

The authors looked at qualitative conclusions regarding the new drug. Favourable or neutral comments included statements such as the new drug "reduces costs" or "is cost-equivalent" or "may be cost-effective". Unfavourable comments included statements such as the new drug has "higher costs" or is "not cost-effective".

Data from their paper have been re-fashioned to produce Table 1 below.

TABLE 1

Data Sets	Unfavourable Comments	Favourable/Neutral
A	9	15
B	1	19

Comments:

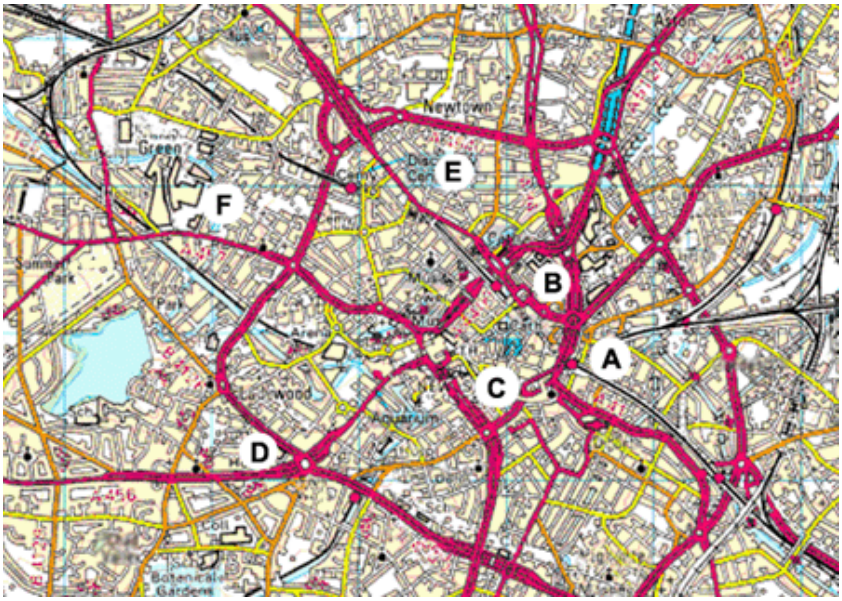
This was a problem written as a TRIPSE for my 4th year Pharmacology course. I expected students to apply their knowledge of pharmacoeconomic issues to a new problem. Students were presented with two sets of data that appeared to reach different conclusions regarding a new drug. There were many different explanations possible (different perspectives, different sources of funding for the studies, different outcomes being measured etc). Having identified possible explanations, students were required to suggest possible avenues for further exploration. The data were abstracted from a publication in JAMA 282: 1453-1457, 1999. The authors were in reality comparing pharmacoeconomic analyses sponsored by pharmaceutical companies with those sponsored by non-profit organisations. This was a difficult problem to write since I had to extract the information without giving away too many clues. Unfortunately, the wording was quite ambiguous and students were quite confused by the term data sets. Although many students did identify perspective or source of funding as a potential explanation, they thought that data set A comparing the novel drug to a standard drug whereas the drug was being compared to a placebo in B. I had not thought of that explanation, but seemed reasonable enough given the ambiguity in the wording.

MORE OR LESS

Oligoanalgesia is the term that denotes under-use of analgesia with painful conditions. A study was carried out to assess the risks of patients receiving inadequate analgesia in emergency rooms in several hospitals in a large North American city. Two hospitals were unwilling to participate and so data were obtained from only 6. Records were reviewed for a 2 year period and all patients who received treatment for fracture of the long bones (humerus, radius, ulna, femoral shaft, tibia and fibula) were included. Information was gathered about the type of analgesic used (non-narcotic, narcotic) and the route of administration (oral, parenteral). With respect to dosage, two categories were used, low or high (less than or equivalent to 10 mg of parenteral morphine sulphate).

The proportion of patients receiving inappropriate analgesia in each of those places is tabulated below. The location of each of these hospitals is indicated on the map.

Emergency Room	Oligoanalgesia (% of treated patients)
A	56%
B	49%
C	51%
D	12%
E	19%
F	15%



Comments:

This problem was based on two papers suggesting that ethnicity was a risk factor for oligoanalgesia is in the emergency rooms of an American city (Annals Emergency Medicine 35:11, 2000, JAMA 269: 1537, 1993). The students were shown a non-descript map with the hospitals in different locations. Three of the hospitals were clustered close to the city centre and the others were spread out. Again many different explanations were possible and the students became quite imaginative.

These included public versus private hospitals, differences in competencies, different formularies, variations in numbers, sampling errors, larger volume of patients in inner city hospitals, ethnicity etc. Once explanations were given, it was not difficult for the students to define the ways and means they would use to gather more information. The open-endedness of the exercise permitted students to explore a variety of options.

DISTINCT: AT ANY PRICE?

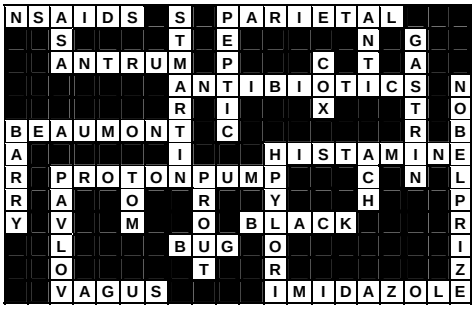
A study reported in Canadian J. Clinical Pharmacology (vol 2, no 4 Winter 1995, p 167- 174) provides support for M. Bouchard's repeated assertion that Quebec is a "Distinct Society". The authors Hogan, Ebly and Fung used data collected as part of the Canadian Study of Health and Aging to determine factors significantly associated with use of potentially inappropriate medications across different regions. They divided the country into 5 such regions: Atlantic, Quebec, Ontario, Prairies and British Columbia.

For the purposes of their study, they regarded inappropriate prescribing as including 'overuse', 'underuse' and 'misuse'. They found that overall 7.6% of all Canadian seniors were taking one or more medications that could be labeled inappropriate. From their paper, I have selected and re-fashioned some of their data. As the authors were from Calgary, I have normalised the data to that observed in the Prairie provinces to get a "Flat rate" (see Table).

PROVINCE	Inappropriate Medication	Inappropriate Benzodiazepine
Atlantic	1.75	1.71
Quebec	2.7	3.23
Ontario	1.29	1.35
Prairies	1.00	1.00
British Columbia	1.02	1.19

M. Bouchard's Quebec may be even more distinct than he thinks.

Comments:

The data provided suggested regional differences in prescribing patterns. Once again a number of explanations can be given and students came up with a variety of explanations ranging from differences in formularies, fiscal problems leading to inadequate care in long term facilities, problems in gathering data, language difficulties leading to incomplete translations of guidelines for prescribing, more aggressive marketing strategies in some provinces etc.

Solution to crossword p. 45