Discussion

DR J L DECKER (NIH—USA)
We have had a very edifying morning, hearing a very thorough review of the latest available information, which I think most of us are trying to apply practically to our patients. I solicit your questions, or your comments, on anything that you have heard today.

DR BEGUIN (PARIS, FRANCE)
I would like to ask, in view of the time during which these drugs have been used, and we now have five or six years’ experience, which are nevertheless very dangerous, why are experiments continued in humans? We know that there is a certain percentage of deaths and a higher percentage of complications, which may be serious, and which leave the patient much more worried by these complications than by their polyarthritis. I wish to know how we may press for these experiments to be limited; they are also very expensive for the laboratories.

DR DECKER
As I understand it, the commentator categorises much of what you have heard this morning as experiments and asks if they should be continued. My response would be that rheumatoid arthritis is a terrible disease and patients need something. Accordingly, I suppose that most of us in the room feel that the risks that have been described today, the expense, the laboratory studies, etc. are justified in an attempt to make their lives more bearable. You have to die somehow...

DR B CORRIGAN (SYDNEY, AUSTRALIA)
Could we hear something of the effects of time on treatment. In other words, is there an optimal treatment time, or time after which azathioprine should not be used at all? Are there any data on the effects of time on the side-effects? We had one particular instance of malignancies tending to occur early. It strikes me that everybody is looking now for tumours occurring later. What is the effect of time and dosage on the problem of malignant side-effects?

DR DECKER
The time to begin treatment would presumably be a function of the disease. I suppose that there are some people who have got into enough trouble with gold, or something else, within the first year of their rheumatoid arthritis, so that it might be appropriate to begin drugs of this category then. When should we begin to look for malignancies? We have heard Dr Urowitz suggest that these neoplasms were already in the incipient phase, in three females with genital neoplasms, when the drug was begun. As they were followed, one might say that the incidence of malignancy was dropping. Do I interpret your remark correctly.

DR M B UROWITZ (TORONTO, CANADA)
That might be reading more into the data than is there, that is what the data show. The malignancies that occurred, occurred early, and this is similar to the experience seen in the renal transplant situation, when the malignancies tend to occur within the first two years. I mentioned those two women who insisted on going back on azathioprine after they had their hysterectomies for treatment of carcinoma of the uterus and cervix. They have been followed now for almost a further two years and have not developed a recurrence or another malignancy. From that, I drew the inference that, maybe, they had a premalignant lesion there. I don't think that we can ever let up our vigilance. If, after 1½ or two years, there is no malignancy, you cannot stop looking. The purpose of these large, on-going, and often retrospective studies, is to see whether the incidence is at all increased and, if it is increased, is it increased early or late? I think only large studies will give us these answers.

DR DECKER
This to some extent depends on the drug involved as well. I think that with alkylating agents more extended concern is warranted, even after the drugs are stopped. I think Dr de Silva has made it very clear that the dose of chlorambucil over time is also very pertinent to the potential development of malignancy.

DR H DEICHER (HANOVER, GERMANY)
I have a question relating to the increased incidence of lymphoreticular tumours which has been referred to by some of the speakers here this morning. I mean the increased incidence of lymphoreticular tumours in diseases like lupus and others. Since we have Dr Denman with us, who has already provided us with a
number of interesting assumptions, I should like to
ask him whether he has an explanation of the
increased incidence of this type of tumour in these
so-called autoimmune diseases.

DR DECKER
Dr Denman, before you respond, Dr Barnes would
like to add to your troubles.

DR C G BARNES (LONDON, UK)
I wonder if I might also ask Dr Denman what he
thinks is the relevance of Sjögren’s syndrome in
association with rheumatoid arthritis in these
patients. We know that some patients with Sjögren’s
syndrome have an increased propensity for lym-
phoreticular problems. I find it difficult that in many
reports of such tumours in patients treated with vari-
ous agents the incidence of Sjögren’s syndrome is
never stated.

DR A M DENMAN (NORTHWICK PARK UK)
I think that it is evident from what has been said that
we are speculating about the nature of diseases such
as rheumatoid arthritis. Thus, I can only pile specula-
tion on speculation. But let us start with two clear
observations. The first point is that the incidence of
lymphoreticular tumours in patients who have re-
ceived cytotoxic drugs following renal and other
transplants is much higher than that observed in
patients receiving the same drugs for the treatment of
autoimmune and chronic rheumatic diseases. The
transplants provoke persistent lymphoproliferative
activity which, in combination with mutagenic drugs,
leads to neoplasia. The second point is that even pot-
et carcinogens in animals have a long latent
period before tumours are evident, and even then
only certain organs are affected. Thus if one takes a
very potent carcinogen such as O⁴ méthylnitrosourea
(MNU), and gives it to strains of mice which are
either sensitive or resistant to the oncogenic effects of
this agent, there is a long latent period before
when emergence and only certain sites are involved,
as Phil Lawley has clearly shown. His studies have
emphasised that two factors predispose, above all, to
the development of cancer in these mice. The first is
the extent of proliferative activity which goes on in
the target cells for neoplastic transformation. Thus,
the thymus has a high level of lymphoproliferative
activity and is particularly susceptible to tumours
induced by MNU. It is interesting to reflect that
lymphoreticular tumours are more likely to occur in
younger patients and in systemic lupus erythematosus
(SLE) rather than rheumatoid arth-
ritis, since in the former conditions there is a high
rate of spontaneous lymphoproliferative activity.
Thus, cultured B lymphocytes from patients with
SLE produce large amounts of immunoglobulins
spontaneously.

The second factor is the extent to which different
tissues can repair the damage induced by MNU in the
experimental system and by cytotoxic drugs such as
alkylating agents in clinical practice. More attention
has to be paid than in the past to such repair mech-
isms. What is peculiar about the thymus, which is
cancer-sensitive in mice receiving powerful
mutagens, as opposed to other organs which appear
to be resistant to tumour induction, is the poor ability
of the thymus to remove promutagens from the DNA
of thymus cells. The thymus in mice which are cancer
prone is inefficient at removing alkylating agents,
whereas other tissues like the liver are extremely
efficient. What may save human patients from the
oncogenic effects of cytotoxic drugs is the much
greater efficiency of human lymphocytes, compared
with murine lymphocytes, in removing promutagens.
This point has been emphasised by the results of
collaborative studies with Phil Lawley and Gilmour
Harris of the Kennedy Institute. Lymphocytes from
patients with autoimmune diseases may show
improvisioned ability to remove promutagens com-
pared with lymphocytes from normal subjects, but
this deficiency is not absolute. Lymphocytes bearing
potentially malignant mutations may also be killed by
continuous exposure to cytotoxic drugs. These are
the sort of areas we should explore in the future, but
for the moment what I have said remains mainly
speculative.

DR DECKER
In connection with Dr Barnes’s remarks, you would
count Sjögren’s syndrome as a disease of lymp-
phoproliferation, in some degree, in its own right, and that
makes patients more prone, perhaps.

DR DENMAN
One is always worried that an audience like this could
contain people such as Keith Whaley or Norman
Talal, who know far more about the subject than I do.
However, it is most people’s impression that the
emergence of lymphomas in Sjögren’s syndrome is
the end stage of a lymphoproliferative process, which
is initially polyclonal and ends up as a B cell lym-
phoma originating in a single malignant clone. If one
believes that there is some association between the B
cell aberrations which produce autoantibodies and
those which produce lymphoma, it is not unexpected
that one process should evolve into the other in some
patients.
DR W BUCHANAN (HAMILTON, CANADA)

I think one should inject just a word of caution about these drugs. They are described as ‘slow-acting’ drugs, but they are also, we should remember, weak-acting drugs. When one looks at the clinical trials that have been done, for instance of gold, which was Dr Ward’s standard ‘second-line’ drug, one finds in fact that the results indicate it limping ahead of placebo. The Empire Rheumatism Council trial showed a difference between the means of the number of active joints in the gold treated people of nine, and in the control group of six, which is hardly a dramatic effect. Grip strength increased by 30 mmHg in the gold treated patients and 10 mmHg in the placebo treated patients. So I would first make the point, we are really dealing not only with a slow-acting but a weak-acting drug.

The second point is the toxicity of gold which Dr Paulus reviewed so well: one death in 10 000 prescriptions. We should recall that chloramphenicol does that at the rate of 1 in 30 000 and it was removed from the pharmacopoeia in the UK as a result, and phenylbutazone in fact kills 1 in 80 000. So this, then, from that data, would be a very toxic drug indeed. One should recall that the data that he was basing that on was voluntary, not obligatory, recording of deaths so in fact we may be dealing with a much more toxic drug than we would like to believe.

DR DECKER

I thought Dr Paulus made the point very well that these drugs were, in fact, hardly perfect for rheumatoid arthritis. We are all aware of their failures, Dr Buchanan, and one of the reasons, I think, we try them is because there are small numbers of patients out there, on the far extreme away from the mean, that do magnificently and one is always hoping that each patient will do magnificently. Certainly the population is not uniform in behaviour. This is a very interesting issue which we have been running into in the lymphopheresis work. It is quite clear that what we describe as active rheumatoid arthritis is not the same thing in all patients. I mean, the immunological events going on in 15 patients with active RA—nodules, systemic involvement, synovitis—are different and we are going to have different effects of these medications. This is one of the reasons why it is so important to try to look for predictors, so that we can pick out people who will respond, and not subject the others to the risk of whatever form of treatment you are dealing with.

DR S ALEXANDER (CALIFORNIA, USA)

Pursuing the first question of Dr Corrigan, there was a report from Dr Isomaki’s group from Heinola, Finland, indicating that the gold salts were much more effective if used in the first two years, that is when used early, and in fact when used after the disease process had been present for longer than two years were not effective at a statistically significant level. I wonder if any of the panelists have any information to bear on this, as to whether this would be confirmed; because if it is true, it would seem that it would invalidate the results of most of these studies and perhaps the effectiveness would not be as bleak as Dr Buchanan has pointed out.

DR DECKER

Would anybody care to respond to that?

DR H A ISOMAKI (HEINOLA, FINLAND)

I would like to comment. As to the effect of gold, we don’t know if it depends on the effect of the drug itself or if it is that patients come frequently to the doctor who sees and takes good care of them. I think that at least part of the therapeutic effect of gold is the result of good care of patients. The doctor sees them very often and, of course, if you start treatment early, at the beginning of the disease, you must get better results than if you start it later. If you start after erosions occur you cannot prevent them.

DR M D SKEITH (SEATTLE, USA)

A practical point, since we’re always looking, Dr Decker, for the patient who responds very well to these medications. Is there anyone on the panel who would like to comment about the duration of time that one should persist in the use of any of these individual drugs—say azathioprine for instance—before one abandons it as being an ineffective drug? Would that be three months, six months, or two years?

DR DECKER

I suppose we could have a good long discussion on just that point. Dr Paulus, would you care to respond?

DR H E PAULUS (LOS ANGELES, USA)

That is always a difficult decision to make when one runs along for three months, or six months, or a year with a patient on a particular drug and who still has active disease. One of the points that I was trying to make in my talk was that the sequential use of a number of slow-acting drugs is of little benefit. It may take a year before you see a major benefit from a drug. If you stop at that time or earlier and then you start another one, it takes another six months, or
longer, before you can expect to see a response. In a totally non-statistical way, in patients that I follow, I frequently see patients on gold, say after a year of therapy, who continue to have symptomatically active disease and they are not very happy with how they are doing. Usually I try to carry on, but sometimes the patient convinces me to stop. So we stop and switch to something else, and the patient often gets a lot worse within the next three or six months, before he sometimes gets better with the second drug. So my tendency would be to try to carry on a lot longer than we usually do.

DR WHISNANT (BURROUGHS WELLCOME, USA)

In the US prescribing advice, the data allow you to treat for 12 weeks and, if there is no response by that time, current studies say that you are at the limit of the data. Let me just remind you that Dr Ward’s co-operative study was designed to try to extend that to a six-month treatment period, which we think has probably got to be a minimum time to try to assess an individual patient’s response.

DR BARNES

I remind you that one follow-up study in the United Kingdom showed progressive improvement up to sometimes as long as one year.

DR M DE SILVA (CAMBRIDGE, UK)

We have evidence of the continued effect of azathioprine after five years of continuous use. We have withdrawn azathioprine and we have shown that even after five to eight years of continuous use, in a double blind manner, if you discontinue the drug the disease reactivates and it responds to the reintroduction of the drug. So the answers to the first and subsequent questions are that azathioprine continues to exert a beneficial effect over a prolonged period—and our study also included combination with gold—and after withdrawal and reintroduction it can again be effective.

DR UROWITZ

I think that there is a little confusion here with the question. One question is, what do you do with the patient who does not respond? I think Dr Whisnant’s comments are right, that the data would indicate that by 12 weeks there is definitely some response if there is going to be a response. If there is not any clinical response by 12 weeks, it is probably not worth pursing azathioprine. On the other hand, if a patient does get a response, how long should you continue that drug? Of the patients who have already begun to respond, all the studies have now shown that as you follow them further and further down the line they maintain and even improve on that response. So there are two answers: if they respond, continue; if they have not responded by 12 weeks, you are probably at the end of the trial.

DR GONZALEZ (CANARY ISLANDS, SPAIN)

When a patient with rheumatoid arthritis does well with gold, do you stop or do you maintain the gold therapy? How long do you maintain the gold therapy?

DR DECKER

The question is, with a good response to gold therapy, how long does one continue it? I suppose that everyone in this room would have a different response to that question. For myself, when I have got a solid remission, I have continued it for life at the rate of 100 mg sodium aurothiomalate (Myocirsin) every three months. It may be a placebo, but I would continue gold until I got a complete relapse that demanded a change to go to something else or I got into toxicity—which, as a rule, you don’t get after years like that, although you can. You did not examine any x-rays in that AB study, Dr Ward?

DR WARD (SALT LAKE CITY, USA)

No!

DR A J GOLDBERG (LONDON, UK)

I wonder if I could ask a question of the panel about second courses of treatment with the same drug. It is our experience that a second course of gold is very often not as successful as the first. The question would first of all be, why does the panel think that might be so, and secondly what is the panel’s experience with second courses of other disease modifying agents as far as success is concerned?

DR UROWITZ

In terms of the cytotoxics, I think that I’ve probably answered, as if I haven’t had a response after 12 weeks, I give up a cytotoxic.

DR GOLDBERG

But what if a patient had been doing well and wanted to go back on it?

DR UROWITZ

Oh yes, I would have no hesitation in restarting. And then your question is the specific side-effects it was stopped for?
No, my question is, what is the likelihood of a successful response to a second course of therapy if the first one was successful and was stopped for side-effects, but the patient, for example, wanted to start again. We know that with gold, the second course is often not very successful. What is the experience with other cytotoxics—other disease modifiers?

For instance, with azathioprine, patients who have been stopped for leucopenia and have flared, or patients who have stopped because we were afraid to carry them on beyond one or two years in our early studies, and then flared, have been restarted. They have responded and we have actually reported that. So that the patients who stopped, because of our fear, have been recaptured.

I would agree. I think that a fair number of patients with gold will have a second response if they are restarted carefully following the resolution of a toxicity.

I think that we are reaching the end of our comments. Dr Hitchings.

Much of what we have heard today, including empirical studies of a clinical nature, shows that even after two or three decades we have not come to definitive treatments. We are beginning to see glimmers by sorting out cell types—cell types that are responsive to specific drugs. We are beginning to find glimmers of what kind of biochemistry goes on in these responding cells. I would like to predict that the next decade is going to see some revolutionary changes in this field.

I am sure they will be welcome.