

NATHAN B. EDDY AWARD LECTURE

J. Lewis

University of Bristol, Bristol, London

“In Pursuit of the Holy Grail”

I have attended every CPDD meeting since the Nathan B Eddy Memorial Award was established and each year I've been interested to find out who was to be the recipient without ever dreaming that it could be me. This is without doubt the greatest moment of my career and I am honored that the College has bestowed on me its premier award. We all owe an enormous debt of gratitude to the great man whom I was privileged to meet, for he, more than any other individual, laid the foundations for the field of drug abuse research.

My surprise that I am now in the company of some of the giants of this field probably relates to my position outside the mainstream of drug abuse research as a non-American medicinal chemist with a career spent largely in industry. For though I have worked in the University of Bristol for six years, for the previous 27 years Reckitt and Colman paid my salary and gave me the opportunity to develop a career among the opioids. My Reckitt and Colman career of course had a focal point in buprenorphine. It is given to relatively few scientists in the pharmaceutical industry to be involved in the discovery of a drug but to be involved in the discovery and then to be allowed to be responsible for its development was a stroke of good fortune for which I am deeply grateful. I hope you will not be too bored with these personalized reminiscences particularly of the early days of the odyssey which has been the story of buprenorphine.

The research and development activity in industry is very much a team effort; I am conscious that I will not have the opportunity to acknowledge by name a great many Reckitt people who made enormous contributions to the development of buprenorphine. But in the best traditions of the Oscar ceremony, there are individuals whom I must mention because their influence on the progress of buprenorphine and on my career has been so fundamental.

The first of these is Kenneth Bentley who established the chemistry of Diels-Alder adducts of thebaine and had the vision in the 1950's that opioids with structures substantially more complex than morphine could selectively retain the desirable actions whilst shedding undesirable side effects. Though this was a simplistic view, it was nevertheless borne out to a substantial extent with the orvinols. Ken Bentley laid the chemical foundations upon which we were able to build a successful development program.

I had first met Ken Bentley in 1950, in my first term as a freshman at Oxford. The Oxford tutorial system is based on a weekly one to one meeting between the student and his tutor. Ken Bentley was my designated tutor for that first term's tutorials in organic chemistry. I remember the first tutorial to this day. The question was: how many methods did I know for the preparation of aldehydes? I managed two, or was it three? Ken then proceeded to write down two dozen other methods! He made so much of an impression on me that fifteen years later when he was Head of Chemistry at Reckitt and Colman, I jumped at the opportunity to join him as his deputy.

In those intervening years, I had graduated and completed my D.Phil. in natural product organic chemistry. After a two year stint in the chemical industry, I had moved back to academia as a lecturer at Loughborough and established a research program in organic synthesis methodology but at that time, Loughborough was in transition from technical institute to university and the opportunity to join Ken Bentley was too good to turn down. My career in drug abuse research was thus not planned and I owe it primarily to Ken Bentley.

Loughborough continued to be involved from time to time in my career. In 1973, Bentley left Reckitt to become Professor and Chairman of the Department of Chemistry at Loughborough giving me the opportunity to succeed him as Research Director. The Loughborough connection was renewed five years ago when after my move to Bristol, I started a collaboration with John Traynor which has continued now that he is ensconced with Jim Woods at Ann Arbor.

How did Reckitt and Colman, a consumer product company whose main business is in grocery stores get involved in opioid research? It happened because among their consumer product lines, the company had some over the counter

pharmaceutical products including two dispersible aspirin formulations - Disprin[®] and Codis[®]. Codis is a combination product containing 300 mg aspirin and 8 mg codeine. In fact, Codis was the key to Reckitt's venture into discovery research. To find an improvement on codeine was the rationale for the opioid program and to replace aspirin we set out to discover new non-steroidal anti-inflammatory drugs.

Reckitt set up a joint research program with McFarlan-Smith, a long-established producer of opium alkaloids. Bentley had started working on Diels-Alder adducts of thebaine as a lecturer at Aberdeen University and was hired with his research program by McFarlan Smith on behalf of the joint venture. In 1964, Reckitt took over the program and Bentley moved to Hull; I joined a year later.

By then, not only had Bentley assembled a group of about twenty organic chemists of varying levels, but they had synthesized about 200 orvinols and thevinols and filed patents. Inevitably, in such a situation, pharmacological evaluation lagged behind the synthesis but some fantastically potent morphine-like opiates including etorphine had already been identified. These orvinols were several thousand times more potent than morphine in the rat tail pressure test (Bentley and Hardy, *J Amer Chem Soc*, 1967, 89: 3281-3292). The popular scientific press were excited by news that doses of a few milligrams of etorphine could immobilize an elephant or rhinoceros. This turned out to be very bad publicity for etorphine for it convinced the World Health Organization (WHO) that etorphine was extremely dangerous and therefore should be controlled in Schedule 4 of the Single Convention, the most restrictive level of control. At about that time, fentanyl, a synthetic opiate of not dissimilar potency to etorphine was being developed by Paul Janssen as an intravenous anesthetic for human use. Fentanyl and its analogs have been huge commercial successes whereas etorphine, which I'm sure could have been an equally successful clinical anesthetic, has had very modest sales as a veterinary anesthetic. I think we must conclude that etorphine arrived too early for the consumer marketing people of Reckitt to appreciate how it should be commercialized.

When I joined Bentley, the group was starting to explore the effect of replacing the N-methyl group in the orvinols particularly with allyl and cyclopropylmethyl (CPM) groups. This structural manipulation had been shown to be an important step in the conversion of opioid structures into analogs of lower abuse liability. The pharmacology of nalorphine was becoming understood and pentazocine and cyclazocine had been disclosed by the Sterling group directed by Lou Harris and Syd Archer. The first N-CPM orvinol to attract attention was M320 which was discovered by my new colleague Alan Boura who was in charge of the pharmacology group. M320 produced very potent antinociceptive activity but was also a powerful CNS depressant. These effects could not be reversed by nalorphine which was the only morphine antagonist available at that time. This pharmacological profile of M320 was described in detail in a paper published in 1966 (Boura and Fitzgerald, *Brit J Pharmacol*, 26: 307-321).

If you read this paper you will realize that the profile described is that of a full kappa agonist. This report predates by nearly ten years the descriptions of ketazocine and ethylketazocine by Bill Martin as the first kappa agonists. Later, when the full battery of isolated tissue tests, guinea pig ileum, mouse vas deferens, rat vas deferens and rabbit vas deferens were available, so that mu and kappa affinity and efficacy could be evaluated, we were able clearly to show the high efficacy kappa agonism of M320. It also has some mu efficacy and substantial affinity for mu and delta receptors so that its opioid receptor profile is quite similar to that of ketazocine and EKC. Just after I arrived, M5050, or diprenorphine was synthesized. It was our best morphine antagonist at that time though it was later shown also to have kappa partial agonist effects. It has proved a very useful pharmacological tool and is still the preferred "universal opioid ligand."

The orvinols provided not only exciting opportunities for opioid pharmacologists, but for the organic chemist the chance to observe some spectacular molecular acrobatics as these complex molecules rearranged themselves simply by treatment with acids or bases. After a year or so of self indulgence with the exciting chemical toys I had been given, I decided that we had to get down to the serious business of finding candidates for development.

A number of N-CPM derivatives had been selected by the pharmacologists for clinical evaluation. Soon after I arrived in Hull, we received a report from Arthur Keats on his evaluation of two orvinols in a small number of patients with post operative pain. These candidates, designated M278 and M285 were administered to patients after only acute toxicity tests. How time have changed! Since both candidates showed signs of the dysphoria and psychotomimetic effects which had first been seen with nalorphine, neither candidate was seriously followed up. The company was thus spared further

development costs but one might ask whether the patients were exposed to significant risk by the lack of multiple dose toxicity studies? Clinical studies without such toxicity data could not take place today but in truth, it was extremely unlikely that a single low dose of an opioid with good acute safety would cause any conceivable harm. When I think of how much of my subsequent career was involved with regulatory authorities over the minutiae of safety issues, the procedures of the early sixties seems light years away.

At that time the pharmacological screening of new opioids was almost totally based on rodent antinociceptive tests. Morphine was active in tests which used heat or pressure as nociceptive stimulus, but nalorphine was inactive in these tests though it had been proven to be an analgesic in man. It was argued that any compound having antinociceptive activity in the heat and pressure tests would display the full range of morphine-like effects including the main unwanted effects - respiratory depression and physical dependence. Our primary screen was the tail pressure test in rats which was used to eliminate candidates which would be too morphine-like. We were looking for morphine antagonists in the tail pressure test and an antinociceptive response in the anti-writhing test, which we now call the abdominal stretch test. Our other priority was good oral activity because we particularly wanted to compete in the codeine and oxycodone markets. At that time, oral morphine was not established as the analgesic of choice for advanced cancer pain.

After M278 and M285, the first candidate which appeared to satisfy all these criteria was M5205. It was put through a preclinical safety program and after brief Phase I evaluation it was tested in a single dose study in post-operative patients. It was not particularly effective and produced some dysphoric effects. A further blow for M5205 came when in studies in rhesus monkeys at the University of Michigan, Deneau and Seevers showed that it substituted for morphine in withdrawn morphine-dependent monkeys and in a direct dependence study gave rise to a withdrawal syndrome that was morphine-like.

At this point around 1968/9, our corporate masters were getting distinctly cold feet. I had succeeded Ken Bentley as Head of Chemistry and assumed responsibility for the orvinol project. The pharmacology group was then joined by a bright young Ph.D. from Strathclyde who became the second key influence in my opioid career - Alan Cowan. I quickly discovered that Alan shared my commitment and enthusiasm for the orvinols. He was given responsibility of the analgesic testing program and together we set out to select what we realized would be the last candidate - we had one last throw of the dice and we had to win.

Our strong feeling was that among the many orvinols rejected earlier because of their activity in the pressure test some, particularly those having the N-CPM substituent, must have morphine antagonist activity which would indicate that their abuse liability might be lower than that of morphine. If they had such activity it had been missed possibly because the pressure test had been relatively insensitive to antagonist activity. Some of the orvinols had been tested in the rat warm water tail withdrawal test and of these a small group of N-CPM derivatives had shown bell shaped dose response curves. Though we weren't sure how to interpret this effect, we associated the descending arm of the curve with an antagonist effect and concluded that the tail withdrawal test may be more sensitive to morphine antagonist activity than tail pressure. This proved to be the case and we showed that this group of orvinols indeed were antagonists of morphine in the tail withdrawal test.

So the breakthrough we had been seeking was made. We had found that this group of orvinols were relatively weakly active as agonists in the thermal antinociceptive tests so that their antagonist actions could be identified. We recognized that the activity of our candidates in the pressure model could give them a distinct edge as clinical analgesics but might be associated with unacceptable abuse liability. Thus, the primary criterion for choosing our single candidate had to be the assessment of abuse liability which at that time effectively meant physical dependence. Though the significance of reinforcing effects was becoming recognized, tests involving self administration and discriminative techniques were in the early stages of development.

Alan set up mouse and monkey models of physical dependence and evaluated the leading candidates. His primate model using groups of three patas monkeys housed in large cages was perhaps slightly less sophisticated than the established model of Deneau and Seevers at the University of Michigan but it allowed Alan to differentiate the morphine abstinence syndrome from the cyclazocine syndrome - what nowadays we would call mu and kappa. We decided to characterize the primary physical dependence associated with each of our candidates. We would reject those that showed significant morphine-like abstinence and hoped that any cyclazocine-like effects would be mild.

The results of Alan's study showed that we now had two serious contenders M6007 and M6029. M6007 produced a mild, delayed cyclazocine-like abstinence syndrome whereas for M6029, there was no evidence of abstinence either precipitated by naloxone or on abrupt withdrawal. This convinced us that M6029 was our candidate and from then on most of our effort was concentrated on this exciting compound which later we named buprenorphine. Incidentally, the first indication the buprenorphine was a kappa-opioid receptor antagonist was obtained by Alan from his dependence studies in those patas monkeys. He showed that buprenorphine could precipitate the characteristic abstinence syndrome in cyclazocine as well as morphine dependent monkeys (Cowan, *Advances in Biochemical Psychopharmacology* 1974, 8:427-438)

The first disclosure of the pharmacological profile of buprenorphine, subtly designated as RX6029-M was made by me at the 1972 Scientific Meeting of CPDD at Ann Arbor. In this report, we detailed the performance of buprenorphine in a battery of antinociceptive tests, physical dependence in mice and monkeys, cardiovascular gastrointestinal and behavioral tests. In addition, we reported acute toxicity data; the LD50 values in mice and rats are many thousand times higher than the ED50 values in the antinociceptive tests showing how incredibly safe buprenorphine is in acute overdosage. This continues to be one of its most important benefits.

The preclinical safety studies with buprenorphine caused no particular problems and so in 1971 came the next moment of truth - the first administration of buprenorphine to humans. It was quite customary at that time for the people involved in the discovery of a drug to be the first volunteers and so Alan and myself together with Peter Crocker, our development chemist, went to the Western Royal Infirmary in Glasgow to receive buprenorphine administered intravenously by the senior Consultant Anesthetist Donal Campbell. The chosen doses were 50 µg, 100 µg and 200 µg in ascending order. Peter and Alan received the lower doses and experienced no very marked effects either subjective or on any of the vital signs that were measured. When my turn came, things were a little different - after a few minutes, not immediately; I was very aware of a drug effect. I had previously never received morphine so I couldn't describe it as morphine-like but it obviously was. There were no dramatic changes in vital signs and no signs of dysphoria. This was encouraging because we knew that nalorphine, cyclazocine and pentazocine all showed some level of dysphoric effects in patients. But we were still at a relatively low dose equivalent to about 10 mg morphine and higher doses might show these effects. My problems started when the test was thought to be over and I got up to join the others for lunch. I felt dizzy and over the next several hours felt very nauseated and vomited several times. It quite took the edge off our stay in a splendid hotel on the banks of Loch Lomond. After a good night's sleep, I felt fine the next morning but we had had the first glimpse of buprenorphine's Achilles heel as an analgesic - the rather high incidence of nausea and vomiting.

Though our scientific objective was to find a replacement for morphine, the market we were primarily aiming at was the oral opiate market held by codeine and its derivatives. So we needed an oral preparation of buprenorphine. Unfortunately, our volunteer studies of oral buprenorphine did not look promising. We estimated that at least ten times as much drug needed to be administered orally to achieve the effect of an intravenous dose. The problem associated with this low oral bioavailability would be variability of effect and in particular potential overdosage in patients with compromised metabolism. So, we looked for alternatives and turned to the sublingual route because a few years earlier a study of sublingual etorphine in cancer patients had given very encouraging results. Since I was regarded as susceptible to the nausea and vomiting effects, I was required to take part in the trials of all the formulations of buprenorphine; though I never experienced anything quite like that first intravenous dose, our commitment to the cause was certainly put to the test.

The clinical testing program was conducted in patients with post-operative pain or in chronic pain from cancer. Both the injection and the sublingual preparation showed good efficacy with a relatively low incidence of morphine-like side effects in the post-operative pain group. The side effects were somewhat more pronounced in ambulatory patients treated with the sublingual preparation which gave 50-60% bioavailability and was otherwise well tolerated.

By the time buprenorphine reached the market first in the UK in 1978 in injection form, I had been elevated to the post of Research and Development Director. One of the advantages of working in a small pharmaceutical company like Reckitt and Colman was that I could continue to take a direct part in the key activities involving the development of buprenorphine. These increasingly became the issues of abuse liability and national and international controls.

Buprenorphine's launch in the UK was at about the same time as the arrival in the US market of butorphanol and nalbuphine. The evaluation of the abuse potential of these mixed agonist-antagonists and pentazocine occupied the attentions of drug abuse researchers as the WHO and national control authorities tried to decide whether or not they should be controlled and if so, whether the level of control should be like morphine and the other opiates, or at some lower level.

Among the many people who studied the abuse potential of buprenorphine and provided perspective for the control authorities, two were of crucial importance - Bill Martin and Don Jasinski, who at that time were at the Addiction Research Center in Lexington.

I realized that studies in prisoner post-addicts at Lexington would provide the most relevant data in the evaluation of the abuse potential of buprenorphine. When the drug was sent to Lexington in 1974, Bill Martin was using his chronic spinal dog assays to characterize opioids in his two receptor model - which he designated mu and kappa in 1975. At that time, I believed or maybe just hoped that buprenorphine was only quantitatively different from the other mixed agonist / antagonists. In a brilliant study of buprenorphine he showed that it was qualitatively different, a mu partial agonist without significant kappa agonist properties.

The studies in the prisoner post addicts were delayed for two reasons. One was relatively trivial - the sponsors of the study were to be French's Mustard - the Reckitt and Colman US subsidiary. The other which was much more serious, was the increasing opposition to the use of prisoners as subjects for drug evaluations. This had an important consequence for the future of buprenorphine. Don Jasinski responded to the pressure on the use of prisoners by pointing out that the pharmacology of buprenorphine made it an attractive candidate as a treatment for opiate dependence which had been a major factor leading to the incarceration of the volunteers. Thus, Don's studies aimed not only to determine the human abuse potential of buprenorphine but also to investigate its possible use as a treatment drug. The story of the development of buprenorphine as an addict treatment thus started in 1975. Even by the prolonged time scales of drug development, this one is really long, but I am pleased that buprenorphine is now marketed in Europe for this indication and the NDA in this country is, we hope, not far off.

The problems of international control of the mixed agonist-antagonists ran in parallel with the issue of the status of buprenorphine in this Country under the Controlled Substance Act. In the control of opiates, the Act uses the term derivative of an opiate in order to cover substances of similar pharmacological profile which can be prepared from opiates. Thebaine, which is a constituent of opium and therefore defined as an opiate in the Act, is the starting point for a great number of opioid drugs including oxycodone and oxymorphone, which are opiates, but also naloxone and naltrexone which plainly aren't opiates. Because they are prepared from thebaine, they were controlled in Schedule 2 and subject to all the restrictions of the act covering their use, handling, distribution and export. These restrictions applied for several years until their formal exemption from the Act was secured.

This interpretation of the word derivative as "anything prepared from" is unique to the Controlled Substances Act. It meant that every compound we synthesized in our program because thebaine was the starting material, was automatically in Schedule 2 and when we wanted to send them to this country, an Import Permit had to be raised which would usually take about three months. Since we sent more than a dozen compounds for abuse liability testing at the University of Michigan and Medical College of Virginia and many batches of buprenorphine both as drug substance and as formulations, the burden of this control was considerable.

When the NDA for buprenorphine injection was approved at the very end of 1982, the issue of its control status had to be resolved before it could be marketed. In the scheduling process, FDA are required to make a recommendation to DEA on the basis of their assessment of the scientific evidence. We were informed of their provisional decision, fortunately before it was sent to DEA. It was that buprenorphine should be rescheduled to Schedule 3 and classified as a "narcotic drug." This label had previously only been applied to Schedule 2 opiates like codeine and hydrocodone in certain oral preparations which are exempt from Schedule 2 and controlled in Schedule 3-5 with the "narcotic drug" label. With pentazocine in Schedule 4 and without the narcotic drug classification and nalbuphine and butorphanol uncontrolled, buprenorphine appeared to have been harshly treated particularly with respect to the narcotic drug issue. A hastily arranged meeting at FDA with Frank Vocci and others allowed me to convince them that Schedule 3 was unjustified by the comparative abuse liability data. But they felt they could not remove the narcotic drug label and this led to the

formal proposal by DEA to reclassify buprenorphine to Schedule 5 - narcotic. We were invited to seek a review of the decision before an Administrative Law Judge. After discussion within the company and with our US attorneys we decided that the potential damage to the international status of buprenorphine was sufficient to justify the cost of delaying the US marketing of buprenorphine. Since the narcotic drug designation would have no relevance if buprenorphine was exempt from control, we decided to appeal against any control of buprenorphine though our primary motivation was to avoid narcotic drug status.

The process starting in mid 1983 and lasted a year during which period I spent a great deal of time with our attorneys Tom Henteleff and Peter Mathers. We became quite close and I believe were a pretty formidable team. The review was based on written testimony by nearly thirty expert witnesses called by us, DEA, or a third party Johnson and Johnson who decided to try to muddy the waters; they certainly did not intervene to lend us their support! The DEA's case was that there had been reported abuse of buprenorphine particularly in Germany and New Zealand so that this proved that it was a narcotic like morphine. They produced local witnesses to corroborate these reports, so that when it came to the cross examination the Judge decided that it was unfair to require these witnesses to come to Washington. Thus, two of the cross examination sessions took place outside Washington - one in Hawaii for the New Zealand witnesses and one in London for those from Europe; the opening and closing sessions were in Washington for a total of about twelve days of court room activity. This sort of hearing is not exactly Perry Mason, but there were some almost dramatic moments. These moments seemed to come when a witness had been backed into a corner by skillful questioning and then would come the one question too many, perhaps the one to which the attorney did not know the answer, and the witness would be off the hook. But I have to say that our witnesses were superb - we had lined up some of the real heavy weights of this field, among them several past winners of this award.

The definition of a derivative was of course, a central issue in the hearing. As organic chemists, we understand that a derivative is a product prepared from a compound by essentially a single simple chemical step. Moreover, since the Controlled Substances Act also controls the immediate precursors of synthetic opiates, it seems logical that for the purpose of control, the normal organic chemists' definition of derivative should apply. The alternative "prepared from" definition which had been used to control every compound prepared from thebaine, however many and however complex were the chemical steps involved, seemed totally unjustified. It led me to think how we might be able to illustrate just how inappropriate was this definition. I recalled that thebaine had been degraded to a single ring aromatic compound and when I looked this up, I realized that this degradation product could fairly easily be converted to aspirin which we then proceeded to do in the lab. Thus, aspirin could be prepared from thebaine and therefore fulfilled the derivative criterion of a narcotic drug. Of course, no one believes that aspirin is a narcotic but the point was made. To complete the picture, I discussed with Kenner Rice whether his total synthesis of morphine could be modified to allow the synthesis of buprenorphine without involving an opiate intermediate. He assured me that this was the case so that we could justifiably claim that the synthesis of buprenorphine from thebaine was a matter of convenience and cost effectiveness, not necessity.

Our efforts were rewarded when the Administrative Law Judge ruled that buprenorphine should not be controlled under the Controlled Substances Act. It was remarkable that the Judge whom I believe had his salary paid by DEA ruled against the Agency but we soon found out that we had won a battle not the war because the Administrator of DEA proceeded to ignore the Judge's recommendation and after our appeal was rejected, issued the rescheduling of buprenorphine to Schedule 5 narcotic. Out of this frustrating experience came some good - the notice of rescheduling stated that buprenorphine is a narcotic drug because it is a derivative of an opiate and has proven abuse potential. This means that those research products for which abuse potential has not been proved should not be automatically controlled. Interestingly, the WHO control process a few years later resulted in control of buprenorphine in Schedule 3 of the Psychotropic Convention. The narcotic drug classification in this country did not trigger international control under the Single Convention for which we were relieved and control of buprenorphine has not in itself been a deterrent to its further development.

The narcotic drug classification does become a problem when it comes to the marketing of buprenorphine in this country for the treatment of opiate addicts. As a designated narcotic drug there is a requirement for new regulations covering the use of buprenorphine in addicts, as there are for methadone. It is to be hoped that the formulation of buprenorphine with naloxone to prevent diversion will be made exempt from such regulations. When Don Jasinski described the clinical pharmacology of buprenorphine after his study in Lexington in 1975 he concluded it had a very

attractive profile for a treatment for opiate abuse. Why has it taken so long to convert this potential into a marketed treatment? I suppose there are several reasons but they are largely commercial and financial. Reckitt and Colman was naturally reluctant to get involved in addict treatment while the market for sublingual buprenorphine as an analgesic was being developed. The other major problem was the attitude of Reckitt's US licensees who were fundamentally opposed to the prospect of buprenorphine being used in addicts. In 1986, the situation changed when Bob Schuster was appointed Director of NIDA. Bob had a good understanding of the pharmacology of buprenorphine from his membership of WHO Expert Committees which several times in the preceding years had considered the control of the mixed agonist-antagonists. He was largely responsible for ensuring that pentazocine and buprenorphine were controlled under the Psychotropic Convention and not the Single Convention. One of the goals Bob set for NIDA was to provide new pharmacotherapies for opiate abuse and he identified buprenorphine as the prime development candidate. I managed to convince my commercial colleagues that this was now in Reckitt's best interest. There were still licensee problems but these were finally resolved not long before I retired when the US license expired and Reckitt decided to go it alone. That turned out to be a very beneficial decision for buprenorphine because it led to the appointment of Charles O'Keefe to run the operation and he has proved the ideal person to ensure the Reckitt-NIDA partnership achieves a successful NDA.

I am pleased to report that there has been life for me after buprenorphine. Quite some time before I retired, it became clear that Reckitt was going to abandon discovery research. That finally happened when I retired. I was fortunate to be allowed to spend my pre-retirement years with a small CNS research group I set up with Reckitt sponsorship in the Bristol University Medical School under David Nutt. David's scientific skills and qualifications range from basic pharmacology to psychiatry so we had both preclinical and clinical groups. Our program included some opioid work but was largely based on the alpha-2 / imidazoline receptor ligands which had been discovered by the last generation of Reckitt medicinal chemists led by Chris Chapleo.

As my retirement approached, I decided I wanted to go back to my medicinal chemistry roots. I was too old a dog to learn new tricks so I looked to NIDA for support in the exploration of the orvinol series for alternatives to buprenorphine. NIDA succumbed and in 1991, I set up a small group in the School of Chemistry. My first graduate student was Andy Coop who taught me some of the organic chemistry that had been going on during my twenty years of doing other things. I am pleased that Andy is still in the field working with Kenner's group in NIDDK. Having got started, it was not long before I was talking to Jim Woods about collaboration in the field of irreversible antagonists into which we had an entrée with clocinnamox and methoclocinnamox which we had discovered at Reckitt and Colman in the late 1980's and Jim had evaluated as part of the CPDD program. So, Jim and I got together and landed a second grant in 1992; I then recruited a fresh post-doc, Steve Husbands, who has also remained in the field. After three years with me and a successful spell with Amy Newman, he is now a confirmed drug abuse researcher back with me in Bristol. It has given me great pleasure to see Andy and Steve grow in this field.

I very much enjoy collaborating with Jim Woods and John Traynor. It has led to the discovery of a very interesting possible candidate as a successor to methadone. BU72, which we are talking about at this meeting, is a high efficacy mu agonist of long duration and potency about 1000 times morphine. Yet after 18 hours when its agonist effect has subsided, it becomes a profound non-competitive antagonist lasting up to a week. This kind of discovery ensures that there is continued excitement in my involvement in this field.

My response to the tremendous honor the College has bestowed on me is to dedicate it to buprenorphine, and to all those who have contributed to its development and to my career in opioid research which has given me so much pleasure and enjoyment. And finally to my family and particularly my wife Joy, who has experienced the emotional highs and lows of my career and given me unwavering support.

Thank you.