iCONTACT

for pensioners of the Reckitt Benckiser (formerly Reckitt & Colman) Pension Fund

No. 65, April 2016

In this issue

In the Reckitt's and Colman's societies it's not only former directors (right) but workers too (below) whose names go down to posterity P2.

Another 99.9% killer

A whiff and a puff of new for our 84-year brand – Dettol. The All in One Disinfectant Spray, was rolled out across all major retailers last month. It comes in three floral scents: Spring Waterfall, Crisp Linen and Orchard Blossom. See also new product news on P6.

Also on that page...

...that's our society

RB PENSIONER OPENS THE BUILDING NAMED AFTER HIM

John Lewis names the Lewis Building, watched by Mark Hulme, Indivior Global Quality Director.

An informal but historically significant and symbolic event saw RB pensioner Dr. John Lewis, former research and development director at Dansom Lane, unveil the plaque on a building named after him.

The event was an international recognition of buprenorphine as one of the most important scientific discoveries and, taking place literally in the shadow of one of the city's biggest new building projects, underlines Hull's role as a centre of scientific excellence.

The Lewis Building, the former Mount Pleasant police station, featured in our last issue (No.65, December 2015) when its purchase had been reported but purpose unknown.

That became clear last month when the naming was announced with the current Indivior team on the site and former colleagues of John being invited to attend.

Two floors of offices

The two floors of the building, which is conveniently sited by the fine chemicals plant, have been made into offices and it was made clear that this indicated the intention to remain in Hull.

To what extent future plans include Dansom Lane is not clear in what is a very volatile and fast-moving industry, but Indivior also has a site in west Hull which can be developed.

RB's increasing international marketing success, reported on P6, lends credence to the company's decision to exit drug abuse research with the setting up of Indivior, but drug-fuelled terrorism is increasing the political pressures.

RBPA Committee

The next meeting of the Reckitt Benckiser Pensioners' Association Committee will be held in June, when preliminary consideration will be given to the Committee elections for 2017.

Trevor Clark, Chris Eagleton and **Alistair Stewart** must offer themselves for re-election in 2017 and must decide whether they are willing and able to stand again. We shall report their intentions in our August issue.

Any member of the Association may stand for election to the Committee. Our August issue will also provide details of the nomination and election procedures.

DIARY DATES 2016

Forthcoming get-togethers:

HIGH WYCOMBE
Wednesday, October 19, 2016
12pm, Brewers Fayre, Loudwater, High Wycombe
Contact Paul Gilliam
Tel: 01494 562843

LEICESTER
Tuesday, May 3, 2016
11 am, Oadby Owl, 7 Glen Road, Oadby, Leics

DERBY
Tuesday, September 13, 2016
10.30 am at Bryers Farm Cafe, Markeaton Lane, Derby
Contact Brian Bradley
Tel: 01526 321575
for Leicester and Derby

NORWICH
Tuesday, July 12, 2016
Tuesday, October 11, 2016
10.30am at the White Horse, Trowse
Contact Ken Herbert
01379 852854

HULL
Wednesday, April 27, 2016
11am at Cafe Chocolat, Newbegin, Hornsea
Wednesday, June 22, 2016
Barges *Syntan/Sun*, Beverley Beck
Wednesdays, September 7, October 26, December 7, 2016
Cheval Cafe, Willerby
Contact Phil Shearsmith
Tel: 07858 137178
alloa@alloa.karoo.co.uk

CHISWICK/LONDON (W)
Thursday, October 20, 2016
12 noon at The Wheatsheaf Hotel, Virginia Water
Contact Peter Moores
Tel: 01276 34778
petermoores@ntlworld.com

If you go down to the woods today...

...it's probably best not to link it to a Norwich get-together. The picture, right, of the Ray Gray memorial bench in Trowse wood was produced at the January meeting but, on a freezing extremely bitter day, none of the 18 pensioners opted to go to look at it and torrential rain put a dampener on any ideas the 22 present might have had to go after this month's (April 12) meeting.

So the visit is now planned for the July meeting. The picture shows Ray's son John seated at the bench. The memorial plaque features on our front page.

This is the wood where Ray, former Colman's timekeeper, sourced the wood for the walking sticks he made for country lovers. As a skilled and experienced beater, Ray joined the Colman family shooting parties at local events and had a similar role at Sandringham with parties including Royalty.

The wood is a good walk from the White Horse at Trowse where Pamela, the landlady, soon put a smile on cold faces with her blazing open coal fire and hot sausage rolls at the first two meetings of the year. At the first Ken Herbert presented her with a bouquet of flowers. It was 25 years ago that Colmans asked Ken to become their pensions adviser.

Derby is Lorraine's

Become a pensioner visitor and you might also get to organise the get-togethers, as Lorraine Mugleston, whose appointment for Derby we reported last August, has discovered.

Brian Bradley was happy to hand over as it has been taking him two hours to get there and he is busy planning a Nottingham get-together now that there are quite a number of ex-Boots employees there.

Late breaking news has been a feature of this issue, not least three get-togethers coming just days before press day. So there are more pictures at
www.icontactnewsletter.co.uk

Lorraine found this month's meeting at Bryers Farm, Markeaton a lively affair, with two new pensioners, Ray Cowen and Avril Record, among the 25 in attendance.

Before moving to Hull, Dr Cowen, beaming under the beams, right, was head of the Derby Laboratory. Following his retirement he returned to the Derby area to be near family.

Avril was a hairdresser in the salon situated within the laboratory. Her appointments were very popular with the Derby workforce! It was also nice to see Sue Palmer again after being unable to attend for while.

Hull had a good response again (more that 20) for the Christmas extra with free coffee and mince pies.

ANY RECORDS SET HERE?

Reckitt Benckiser Hull sites' annual reunion dinner was held at the Staff House, University of Hull, on Friday March 11 and, in sending this report, organiser Brian Huggett asks: Have any records been set here?

He reports: "Sixty guests attending—probably the 113th function—and probably the 35th one organised by Brian Huggett."

Editor's note: That first "probably" is understandable, Brian, as our previous reports have highlighted the long-running uncertainty about the exact number – but that second "probably" looks like the sort of memory lapse familiar to many of us pensioners!

Attending were: Bob Allison; Kate Ansell; Karen Bateman; Mike Bowsher; Karen Beach; John Benstead; Richard Bays; Alan Brooke; Trevor Busby; Alan Clarke; Dave Copeman; Martin Craven; Tony Dale; John Dunlin; Roy Farnhill; Bill Foreman; Carl Filby; Andrew Forster; Phil Gibson; Janet Gibson; Brian Huggett; Mark Hulme; Alan Hitchcock; John Howden; Peter Hessel; Ken Houghton; Ken Johnson; Ian Jolliffe; Kevin Kilvington; Fiona Houghton; Angie Lamb; John Laydon; Bill Maxwell; Ian Mackechnie; Gill Morrell; Hazel Mee; David Nellist; Neil Muir; Sid Newman; Tony Payne; Dave Price; David Parker; Ted Parker; Tony Pawson; Lilian Pooley; Pat Quarterman; Malcolm Ruddiforth; Bridget Rimmington; Steve Rial; Michael Spence; Phil Slater; Jon Sewell; Pauline Settle; Joy Sutton; Andi Wright; John Smallwood; Charles Trafford; Ron Watson; Jackie Whitham; Barbara Worrell.

Alan Hitchcock was guest speaker this year.

This is an advertisement...

Twenty years after the third issue of *Contact* recorded the sale of Colmans to Unilever, more than 50 of the Norwich sales staff attended the 2015 reunion, pictured above, at The Park Farm Hotel at Hethersett.

An announcement in the December 2014 issue *(No.61)* of *Contact* possibly helped to swell the attendance and organiser Robert Thurston said it was gratifying to see some former staff attending for the first time. Unilever made a welcome donation to the event.

So Robert sent us the photograph to accompany the announcement that initial arrangements have been made for a further get-together in May 2016 (details will be circulated shortly to previous participants) and anybody who would like to attend will be most welcome. He can be can contacted by e.mail (robert.thurston12@btinternet.com) or by telephoning 01405 785201.

...and so is this

The Southern Region's get-together attendances are heading upwards with the March meeting in Virginia Water only a couple short of the 40 mark. Organiser Peter Moores told us: "It's developed into a very friendly and varied group, joined on this occasion by no less than three former Group directors." The next meeting is on October 20 at the same venue, The Wheatsheaf Hotel.

It's people's names not brandnames that make history

Royal approval, top left above, in 1985 when John Lewis received the Queen's Award for Technology symbol and managing director Mark Foster the Grant of Appointment from the Lord Lieutenant of Humberside Tony Bethell. Less formality at Dansom Lane last month with (l to r) Dr. John Doxey, Jo and John Lewis, Dr. Ted Parker, John Davis of Contact *and Alf Davis. NB - the "black sheep" (that's JD) normally scribbbles away in the background but became part of the story this time because he and John Lewis were at the same school together (Sir Thomas Rich's in Gloucester) 70 years ago. John D produced a copy of the school magazine,* The Richian, *lauding JL's academic acheivements while labelling JD as an underperforming "black sheep".*

Buprenorphine, the focus of our front page lead story in this issue, marks the spectacular success of a consumer products company's comparatively shortlived venture into discovery research, while echoing the enterprise driving the founding family business nearly 180 years ago.

In our potted R&D history over the last three issues we have recounted how Frederic Reckitt (son of founder Isaac Reckitt) invented soluble starch in the 1840s. He was followed in the 1920s by Harold Scruton (Disprin) and bacteriologist Dr. William Colebrook Evans (Dettol) and, as highlighted in this issue, by Dr. John Lewis in the second half the 20th century.

Complexity and legislation

The complex nature of scientific research, together with the commercial secrecy surrounding inventive product developments, means stories such as buprenorphine tend to be restricted to scientific papers or lectures.

It took several issues of *Contact* in 2003, for example, to unearth the full story of Dettol.

One reason is a natural reticence and aversion to publicity among highly intellectual people like William Colebrook Evans, but also because the success of such ventures is invariably a team effort – in Dettol's case as much that of a marketing team as that of a laboratory team.

With buprenorphine we have been able to take advantage of the extra space which our digital edition affords us (www.icontactnewsletter.co.uk) to publish two papers by RB pensioners which give the full story to date. The first by **Gordon Stephenson** of the Dansom Lane Heritage Centre and the other by **John Lewis**.

Gordon's story (P9) can be described as a layman's account which, as head of the Dansom Lane Business Intelligence Unit until his retirement in 1995, he was well-qualified to write.

After the hiving off the pharmaceutical division to form the new Indivior business in 2014 Gordon wrote the account for the Heritage Centre archive.

A golden heritage

John's (P10) might be hard going for some of our pensioner readers *(not a criticism – count your editor among the occasionally uncomprehending).*

It is a golden heritage and John has the medal to prove it! Its great merit is that it emphasises the team effort and mentions the colleagues involved.

At the same time it describes not only the complexity of the science but the legislative hurdles that have to be faced.

Dansom Lane is now, through the new CSE venture, a centre for health and hygiene product development and production plus an equally leading role, through the neighbouring Indivior, in opioids (the name comes from opium, one of the oldest known drugs, derived from poppies).

Many other people have played and will play their part but John Lewis, as he says in his award-winning lecture, had a particularly high regard for Ken Bentley, right, who maintained a low profile in the company while making a considerable impact outside it.

A rare reference in the *Link* magazine in 1972 reports that The Chemical Society Award for Medicinal Chemistry, which was being made for the first time that year, was being awarded to Dr K. W. Bentley.

The award, which was sponsored by Boots Pure Drug Co. Ltd., was being made on the basis of published work over the previous seven years including the structure, synthesis and mode of action of materials used in medicine and veterinary science.

Dr Bentley joined Reckitts in 1963 as Head of Organic Chemistry Research. He became Research Manager and then Assistant Research Director in November 1970. In October 1972 he became Honorary Professor of Organic Chemistry at the University of Hull.

Don Wilson, right, was Reckitt's expert on the use of the drugs Immobilon and Revivon. Ex-RAF PoW Don joined Reckitts in 1946 and became the company's first full-time veterinary representative, selling Dettol products to vets. When Immobilon was launched, Recktttt's set up an emergency service, so that veterinary surgeons who had problems with an animal could call in marksman and anaesthetising expert Don to immobilise. Don died in 2003 at 93.

HOW THE CSE TEAM WILL CONTAIN THEMSELVES

...but this is what you call a Stop Press

Neale Harrison sent us the picture on the left with his progress report earlier in April and we pressed on towards our press date of April 18 – then we heard that the new temporary office was to be opened on April 19 by SVP R&D Sharon James! We sent the finished Contact to the prInter with a request to stand by for a page change. Neale took the pictures above and e-mailed them to us direct from his smartphone at 12.11 and we sent the page off at 13.15.

Neale Harrison, *RB Pension Fund Trustee and CSE Project Director, reports:*

There has been a lot of visible activity taking place on the Dansom Lane site over the past couple of months. We have erected a new temporary building (named the 'Wren Incubator') to house the 300 staff who will vacate the KWN building for its 18 month complete refurbishment from May.

This was made from 117 individual 'portakabin' units (supplied from a local company in Brough) which were lifted into place by a giant crane.

Whilst it may have been constructed as a temporary building, it will not feel that way inside as it will have high quality fittings, meeting rooms and kitchen areas, making it feel like a modern office.

We are in the final stages of selection of the main contractor who will start building the new laboratory building from the end of May and hope to make an announcement about this shortly.

The plan is for the external structure of the building to be completed by the end of this year, leading to the long and complex job of the creation of the individual laboratories and pilot plants throughout 2017.

Work has also recently started on the Chapman Street roundabout to create a new spur which will ultimately allow deliveries to the new R&D site from this direction rather than via Dansom Lane.

It's now a bigger community

Community support, a tradition of both the Reckitt and Colman family companies, is now a global responsibility for RB – which is now Save the Children Fund's biggest international fmcg sponsor.

The company has launched a $1 million Zika Relief Package consisting of both cash and product donations that will be made available to health authorities and international NGOs battling the outbreak. The Zika outbreak is having a profound impact on many communities in the Americas and RB shares the concern that is being felt around the world.

As a global leader in consumer health and hygiene, RB has provided support to communities during previous outbreaks such as H5N1 avian influenza, SARS and more recently Ebola. Last year Save the Children launched a ground-breaking partnership with RB to work with the governments of India, Nigeria and Pakistan – countries where death and prevalence rates of diarrhoea are among the highest in the world – and other partners to launch a unique and sustainable Stop Diarrhoea programme.

A unique opportunity to help in the UK comes on August Bank Holiday when RB sponsors camel racing at Beverley in aid of Save the Children.

THAT SOCIETY OF OURS...

The news that cheers RBPA members as stakeholders came in the February press release on the annual results, showing that earnings rose to £8.9 billion with profits up from £2.1bn to £2.2bn with the share price rising accordingly.

As the 2015 Annual Report, published at the beginning of this month makes clear, RB's culture is critical to its success.

The culture, it says, makes RB a dynamic and exciting business, which rewards outperformance and is constantly looking to do better for our customers, consumers and shareholders.

During the year, RB's share price rose by 20.6% to 6281p, well ahead of the 4.9% change in the FTSE 100. A final dividend of 88.7p per share, up 12%, is proposed – giving a total dividend for the year of 139p to be paid at the end of May.

Filling the gaps

Contact is very conscious that its readers cannot access all the information they would like about the fascinating global business of which they are still part; so some of the newsletter's service must be to fill perceived gaps.

Products will always be a major source of interest so we have reproduced at the top this page the illustration issued in February showing 2015's product launches. There is as much pleasure for pensioners in recognising the "old" brands as the new.

At 172 pages, profusely illustrated and crammed full of information, the latest annual report must be the best yet. There is so much in it, covering such a wide range of activities around the world that we could not hope to cover more that a small part of it in these pages - but what we can do is reflect a familiar and heartwarming philosophy that shines through.

This is encompassed in the corporate strategy encapsulated in the "betterbusness" artwork reproduced left and on our front page.

The "how we do its" of better financials, better society and better environment are certainly echoes of the fondly-remembered past for our readers.

The "How we support our communities and develop our people" core of the better society strategy has been a theme in *Contact* for the past five years as we have recorded the company welfare policies introduced more than century ago, while the present government still tries to define its "Big Society" idea.

The three pages in the RB Annual Report devoted to Better Society set out the objective of attracting great people to an achievement-focussed culture and community initiatives to support the vision of a world where people are healthier and live better.

FOOTNOTE: *The Annual Report describes RB as A connected company: "The digital revolution is transforming the business world, so the need to be where our consumers are, means we are increasingly moving online."* Contact *cannot but agree - we have been digitally composed since our launch in 1994 and went on-line in 2008.*

Community restores heritage

This was the run-down and overgrown appearance of the Quaker Burial Ground in Chanterlands Avenue, Hull before the Avenues and Pearson Park Residents' Association started restoration work.

APPRA "exists to help retain the unique character of the Avenues and Pearson Park conservation area and to support the neighbourhood's strong community spirit."

The ground contains the Reckitt family graves and the restoration was supported by the James Reckitt Charity. See the story by Chris Coulson on P17 of the Digital Supplement.

LETTERS

E-mail: contact@nilspin.com

An inch of difference mattered – Joan Wills at her retirement

From Mrs Kathleen Cusworth, 45 Sextant Road, Hull HU6 7BA

On October 7th 2015 my sister Joan Alice Wills died aged 90 years. Her obituary was in the December issue of Contact. *As she had had a long association with Reckitts, 39 years and was known by many, I wondered if it would be possible to have a short obituary notice in the magazine at some future date?*

"Joan Wills [nee Cooper] died at the age of 90. Joan had a long career with Reckitt & Colman, Dansom Lane.

She left Mersey Street School at the age of 14 and wanted to be a Reckitts girl. Unfortunately she was only 4' 11" tall and the minimum height was 5', so for one year Joan worked at Metal Box before going back to Reckitts having grown that one inch.

Joan worked on Bag Blue and at 17 years of age during the war she volunteered for the WRNS. Her call-up papers arrived on her 18th birthday and she duly travelled by train to Inveraray in Scotland where, after training, she was put to work repairing Landing Craft.

On her return to Reckitts in 1945 Joan worked her way up from Helper on Steradent to a forewoman on Codis.

In 1962 Joan married Frank Wills and moved to the Production Planning Department in Packing Room, where she became a valued member of the team.

Joan saw many changes during her years at Reckitts and retired in 1981 after a varied and rewarding 39 year career."

Ed's note – It is certainly possible as you can see, Kathleen, and more than welcome from you and the others on this page by renewing warm memories of friends and colleagues.

From Alan Gorwood, 17 Av Estienne d'Orves 64500, St Jean de Luz, France

I read of Tony Bartholomew's death in your December issue. *(Heritage Centre archives show that he was appointed General Manager in Bilbao in 1980, having first joined R&C in 1951. He joined Brasso in 1960 became Assistant Manager in 1977- Ed.)*

I knew Tony well as a colleague at Brasso SAE in Bilbao, Spain. He was a powerful Sales Manager (his physical build was appropriate), who followed each of his salesmen closely.

Telephoning in Spain then was a problem, via operators, and Tony's frustration with them was legendary. His bellowing of "oiga" (hello or listen in Spanish) used to ring down the corridor. Tony made sure our main products were referenced at Spain's first hypermarket, Pryca in Madrid – he knew where the future lay.

Other colleagues were the great Stan Holland, factory manager at Deusto, very close to John, and Sid Brooks, responsible for the ultramarine factory at Limpias. Brasso powder and liquid blue (Azul) were still important products then.

We worked for John Cowl, who used Tony as a sounding board for important letters. John was the son of Richard Cowl, for whom I worked in France (Choisy-le-Roi) as a management trainee fresh from Hull. In his team were some illustrious future Reckitt names : John St Lawrence (Advertising Manager) and Peter Knee (Business Development).

Tony had a fine son, who had a close resemblance to his father. Tony's first wife died of a serious illness in Bilbao, and I believe Tony later moved back to the UK.

From Carolyn Simes, 127 Harbour Road, Bradford BD6 3QX

I am writing following the death of my father Eric Glew earlier this year. He was the manager at Colmans printing works Norwich from the early 1960s until its close.

He enjoyed his time with Colmans and made good friends there. He is pictured above with one of the works football teams. He had previously worked in a paper mill in Cardiff and for the Metal Box in Liverpool.

His primary interest was printing and he had started as an apprentice printer for the Ordnance Survey in Southampton, which was his home town. In Liverpool he had a little printing press in the attic and with a friend made wedding invitation cards etc. in his spare time.

After his redundancy when the works closed he remained in Norwich for another 20 years but following his wife Kathleen's death relocated to Luton and then more recently came to live near me in Bradford.

Memories of Phil Allen from the words spoken by his two sons and grandson at his funeral in Croydon on March 11 attended by Paul Gilliam:

Phil Allen, pension visitor for Kent, a jet fighter pilot in the RAF until invalided out in 1944, was a pilot at heart his whole life.

Phil was employed by Reckitt & Colman Ltd for more than 30 years. His friends and family recall him enthusiastically talking about the tennis at Wimbledon where he diligently ensured the Robinsons Barley Water was always to hand for the umpires and players.

They also remember his professionalism when representing the company. Sometimes his enthusiasm for Colman's mustard, Gales Honey and many other famous brands caused some slight irritation with the family. His family recall suggesting that he should himself perhaps be visited but he embraced the role of pension visitor and his loss will come with sadness to all those he visited.

MEMORIES FROM BINNS ROAD, CHISWICK TO BUCKINGHAM PALACE

Sharing the obituaries page with the preceding letters page in this issue of *Contact* has enabled relatives and friends to meet our requests for pictures and histories that overcome the legal restrictions that inhibit the use of personal company records.

The photographs above are of pensioners who have appeared in *Contact* in the past. Southern Region centenarian **Ivy Parker**, left, had a memorable 100th birthday *(Issue No.61, December 2014)* when Binns Road in Chiswick, where she had lived all her life, was closed for a giant street party.

Eastern Region's **Ken Woolcott**, right, made more appearances (usually with leggy beauties to promote Robinsons products) but this Buckingham Palace shot was a very special occasion when he received his MBE.

Carol and Paul Gilliam attended Ken's funeral at Garston, Watford at the end of December. The service was conducted by the Reverend Geoffrey Whitfied MBE and was attended by more than 150 people.

In addition to the many tributes from family and church members, there were detailed accounts of his contributions to sports coaching. The nationwide scope of 'PopMobility', his still very active fitness programme, was evidenced by attendance of 'dance partners'.

Ken became familiar to Wimbledon TV audiences as the person who made sure the Robinsons squashes were clearly visible to TV audiences.

Former R&C director **David Totton,** who has died at 90, retired in 1987 as group director Australasia.

Peter Averill, has died at 89, he was a well-known member of the Household sales team. **James Allen** and **Eric Glew,** pictured top right, are remembered in letters (P7).

We regret to record the deaths of the following Reckitt Benckiser pensioners:

NORTHERN REGION

(Hull, unless otherwise stated)

Gillian Scott, aged 67, 19 years' service; Maureen Allenby (81), 12; Joan Leary (86), 18; Joyce Pearson (85), 16; Leah Ramsdale (89), 8; Betty Lee (90), 20; Janet Hargreaves (58), 18; Raymond Pedelty (86), 44; Alexander Macfarlane (85), 12; Stanley Cooper (87), 24; James Hendry (88), 31; Jack Parker (94), 46; Edith Butler (92), 17; Peter Averill (89), 28; Harry Boland (91), 45.

Derby **– Colin Mather (56), 2; Frederick Watson (85), 11;**
Grp Dist, Newbury **– Richard Taylor (86), 23.**

EASTERN REGION

(Norwich, unless otherwise stated)

Beryl Burrows (88), 38; Maureen Kemp (79), 16; Gillian Arthurton (76), 9; Vera Billin (95), 10; Beryl Howard (87), 16; Joyce Lacey (88), 15; Kenneth Woolcott (99), 34; Eric Glew (92), 21; James Allen (85), 32; Charles Ratcliffe (82), 7; Annie Williams (86), 40; Dora Feavyer (88), 45; Winifred Goodbody (93), 18; Lily Bush (90),18;

James Allen

Eric Glew

David Parkinson (70), 5; Roy Adams (91), 9; Jack Thompson (92), 27; Roy Hamilton (80), 21.

SOUTHERN REGION

(Chiswick, unless otherwise stated)

Ivy Parker (101), 23; Joyce Woodhams (85), 17; Lilian Flynn (92), 13.
HQ, London House **– Joan Fox (91), 20.**
HQ, Chiswick (director) **– David Totton (90), 29; Violet Lawrence (88), 27.**
High Wycombe **– Irene Bedford(91), 13; Peter Swain (77), 15.**
Jeyes **– Keith Wingrove (82), 11; Betty Dimmock (83), 8.**
Industrial Division **– June Stephenson (88), 13; Terence Thorne (71), 6.**
pmuk **– Maurice Jenkins (87), 7.**
Nottingham **– Jefferson Brown (67), 2; James Heathcote (61), 3.**

NB: What may appear in some cases to have been very short service may be the result of employees transferring pensions from a company with whom they had many years' service e.g. RB's acquisition of the Boots operations at Nottingham.

Buprenorphine

Compiled by: Gordon E Stephenson, RB Heritage, Hull. October 2014

Temgesic (buprenorphine) is a potent analgesic first introduced to the medical world for hospital use in injectable form in 1978 by Reckitt & Colman.

The company's involvement in healthcare products began in 1933 with the launch of Dettol antiseptic and continued during and after WW2 towards an interest in pain relief culminating in the introduction of the aspirin-based pain killer Disprin in 1948 and codeine-based Codis in 1952.

A natural progression of the company's pharmaceutical interest led towards the treatment of more severe pain and resulted in the formation of a joint research association in 1958 with J F Macfarlan & Co of Edinburgh, a company which had pioneered the industrial production of morphine in the nineteenth century.

In 1960 a medicinal chemical research programme was set up and, led by Dr K W Bentley, it began exploring the possibility of preparing compounds substantially more complex than morphine which would meet or surpass its pain-relieving properties and yet reduce its unwanted side effects.

Potent etorphine

Coming out of this research was a very potent analgesic, etorphine, which was chosen for further study. Displaying the whole range of morphine-like effects, etorphine is very much safer and has a greater margin between an effective dose and a lethal dose.

These were the properties which made this compound (combined with the tranquiliser acepromazine snd given the name Immobilon) ideal for use on animals when, for example, the capture and complete immobilization of wild animals in Africa was called for during the clearance of large areas of ground for major land-use redevelopment. A specific antagonist from this so-called oripavine series, diprenorphine (branded Revivon) was developed which would revive the animal as and when it was safe for it to be released into the wild again.

These two products were prepared for use on large and small animals and were contained in vials packed in polystyrene, crush-proof containers. Together they were made available to the veterinary profession in 1970 and were subsequently sold by Reckitt & Colman to the veterinary products manufacturer C-Vet.

Product for humans

The knowledge gained in the production of these successful brands was followed up by further investigations in this field. These were aimed at eventually creating a product that would be suitable for the treatment of post-operative and other moderate-to-severe pain in humans which would be not only effective and safe to use but would greatly reduce the dependency characteristics which are associated with morphine.

This research was conducted in the newly extended pharmaceutical facilities at Reckitt & Colman's site in Hull and involved dependence testing in clinical trials conducted in USA by the University of Michigan and The Addiction Research Centre at Lexington, Kentucky.

A compound of high promise was finally identified and was given the non-proprietary name buprenorphine.

It was on 6th February 1978 that buprenorphine (then to be named Temgesic) was first introduced to UK hospitals on a monitored release programme. It was presented to the medical profession as a potent analgesic with opioid partial agonist properties. It has a lower intrinsic activity than morphine at the mu opioid receptor.

However, buprenorphine has an affinity for the mu opioid receptor several orders of magnitude greater than that of morphine. Thus comparable analgesia is provided by buprenorphine at much lower doses than are required with morphine. This property, along with others which were observed, combined to produce an effective analgesic with a long duration of action.

Temgesic was the first compound to pass through the rigorous animal screening procedures required by the CSM before launch which was eventually shown to be free from unwanted psychotomimetic effects in humans.

Temgesic was initially presented in injection format. Each dose contained 0.3 mg/ml buprenorphine as a hydrochloride, in a 5% dextrose solution. It is a colourless liquid supplied in clear glass snap-ampoules of 1 ml (0.3mg) or 2 ml (0.6 mg). Recommended dosage is 0.3 – 0.6 mg by intramuscular or slow intravenous injection.

The sublingual "first"

In 1981 researchers in Hull notched up a 'first' for Britain by winning the race to produce a prescription-only strong analgesic in tablet form.

Temgesic Injection had been in clinical use for more than three years and its effectiveness, long duration of action and lack of cardiovascular effects had resulted in its wide use post-operatively and in the treatment of severe pain. Yet there had become

...continued from P9

a need for an additional less invasive form of drug-Temgesic.

Sublingual fulfilled this requirement. A tablet (0.2mg) is placed under the tongue and allowed to dissolve for a few minutes. Within sixty minutes good pain relief lasting at least six hours is obtained in most patients. Temgesic Sublingual was first supplied to UK hospitals in 1981 and made available to GPs in 1982.

The research which had gone into the development of Temgesic received formal recognition in 1985 when Reckitt & Colman was awarded the Queen's Award for Technology.

By 1986, the year in which the original patent expired, buprenorphine had launched in 28 countries (Injection) and 19 countries (Sublingual) mostly under the Temgesic name but in some countries registered as Buprenex, Buprex or Lepetan.

The key markets

The key markets at that time, besides UK and Eire, were Germany (launched through Boehringer Mannheim) in 1981; Italy (launched also through Boehringer Mannheim) in 1984; Japan (launched through Otsuka) in 1984; Spain (launched through Esteve) in 1985; USA (launched through Norwich-Eaton in 1985) and Scandinavian countries. The product was launched through Schering-Plough in France in 1988 and has since become represented in all continents of the world.

By the 1990's however heroin dependence and heroin addiction,had become a significant global public health problem. The use of illicit drugs by injection, in addition to posing the dangers of toxicity, had added risks of infection with AIDS and Hepatitis being the most notable.

Faced with this situation and recognising the changing market scene looming with oncoming patent expirations, attention was paid towards the creation of strongly branded and unique buprenorphine variants which would enable healthcare professionals on the one hand to improve the quality of life of opiate addicts whilst still providing for patients in need of relief from severe pain.

Subutex serves the former whilst Temgesic continues to provide for the latter. Subutex had first been launched in France (only) as a new addiction treatment through Reckitt & Colman's partner Schering-Plough in February 1996.

In October 2002 the then recently-merged company Reckitt Benckiser received approval by the Food and Drug Administration (FDA) for the treatment of heroin dependence in the USA.

Almost immediately Reckitt Benckiser (RB) announced that it had purchased the licence to distribute Subutex and Suboxone in the USA. Suboxone had been submitted for approval to the US FDA in 1999.

This product Suboxone differs from Subutex in that it is the preferred medication for maintenance treatment due to the presence of naloxone in the formulation, which is intended to deter intravenous abuse by persons dependent on other opiates.

Subutex on the other hand does not contain naloxone and may be better tolerated by patients in the first several days of treatment and is therefore generally preferred for 'induction' of the patient.

Many patients who suffer from addictive disease, particularly those who are addicted to drugs such as heroin, have been reluctant to enter treatment because of the stigma associated with the disease and its treatment.

Subutex and Suboxone have become major additions to the available range of drugs that can help heroin addicts overcome their dependence. The major benefit of these two products is the relative safety of the compound, allowing patients to be treated for addiction by qualified physicians in the privacy of the doctor's office rather than only from the limited number of existing drug treatment programmes.

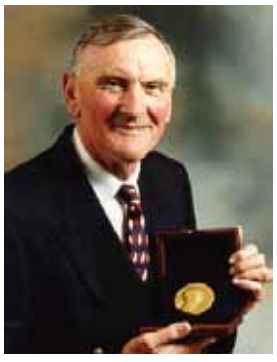
"In Pursuit of the Holy Grail"

The 1998 NATHAN B. EDDY AWARD LECTURE by Dr. John Lewis

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 honoured 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& Colman paid my salary and gave me the opportunity to develop a career among the opioids.



John Lewis, left, with the Award Lecture gold medal.

My Reckitt&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 to be too bored with these personalized reminiscences particularly of the early days of the odyssey which has ☛

The College on Problems of Drug Dependence (CPDD), formerly the Committee on Problems of Drug Dependence, has been in existence since 1929 and is the longest standing group in the United States addressing problems of drug dependence and abuse.

Since 1976, the organization has functioned as an independent body affiliated with other scientific and professional societies representing various disciplines concerned with problems of drug dependence and abuse. In 1991, the CPDD evolved into a membership organization with the new name of College on Problems of Drug Dependence. Currently, CPDD has over 1,000 members.

The Nathan B. Eddy Memorial Award was established in memory of one of the pioneers in the field of drug dependence following his death in 1973. The award acknowledges outstanding research efforts that have advanced our knowledge of drug dependence. Nominees may be citizens of any country and are selected by the Awards committee.

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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.

Designated tutor

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&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 Dansom Lane laboratories, completely destroyed by bombing in 1941, were on the site of the Middleton Mill where the Reckitt&Sons business started in 1834. The new laboratories, right, built on the same site in 1956, incorporated a synthetic organic chemistry laboratory - the forerunner of the adjoining new Biological Research Laboratories, completed in 1962 and opened by Reckitt&Colman chairman J.B.Upton in 1963. This was where buprenorphine was developed.

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&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.

Opium alkaloids

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.

Etorphine too early

At about that time, fentanyl, a synthetic opiate of not dissimilar potency to etorphine was being developed by Paul Jannsen as an intravenous anaesthetic 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 anaesthetic, has had very modest sales as a veterinary anaesthetic.

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 ☛

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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.

Molecular aerobatics

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 times 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.

No need for our *iContact* readers to feel overwhelmed by the science! Here's the introductory note the CPPD used to preface its publication of John's lecture: "It is rather a lot to read but there is a large number of interesting details and insights into the design and selection of a totally new opioid. Here are a few definitions to make it a little more rewarding:

M99 - Etorphine
M5050 - Diprenorphine
M6029 - Buprenorphine
CPM - Cyclopropylmethyl
ED60 - Value for lowest dose active in 50% of trial subjects
LD50 - Value for lowest dose fatal in 50% of trial subjects"

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.

A bright young Ph.D

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 morphine morphine antagonist activity ☛

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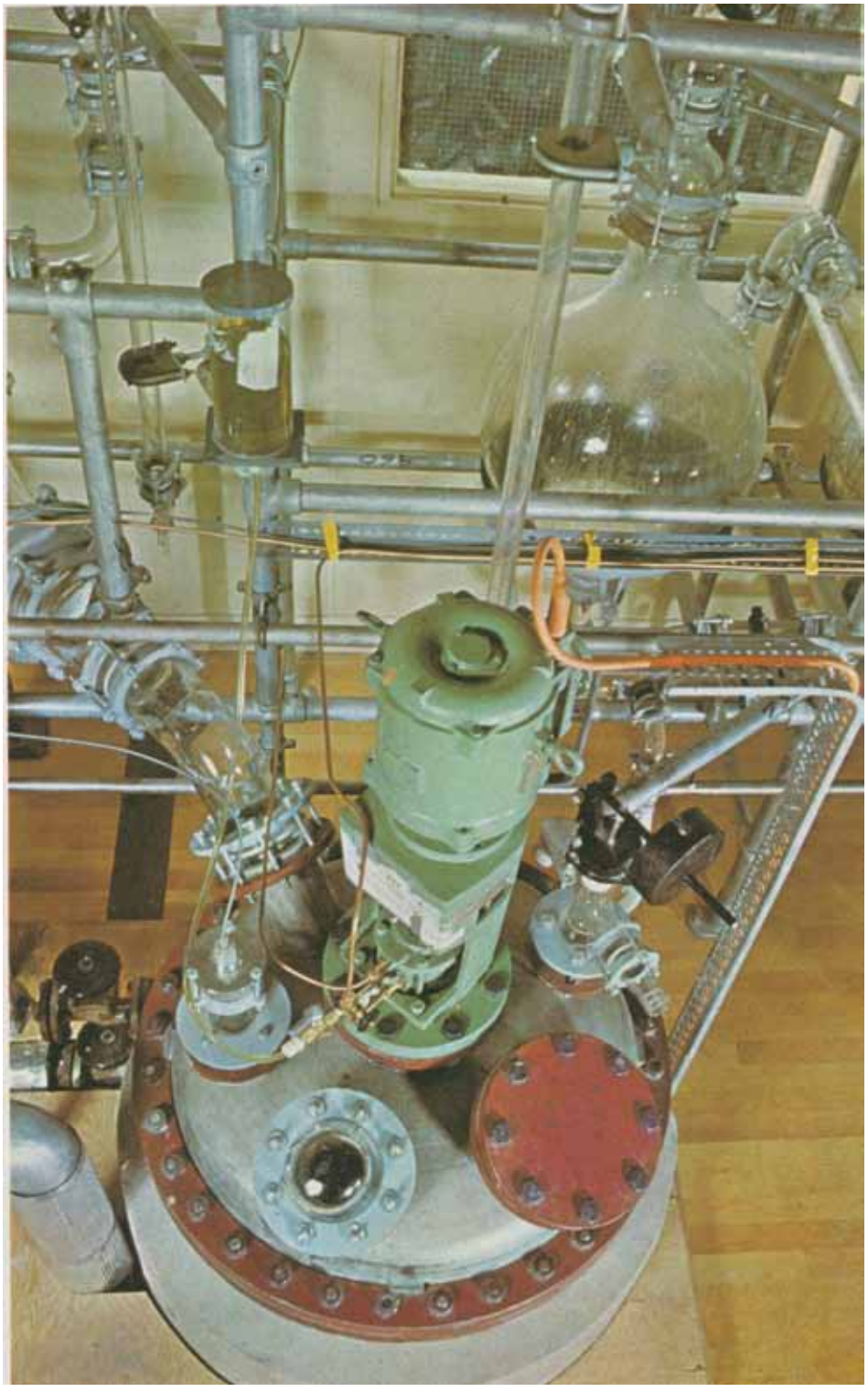
than tail pressure. This proved to be the case and we showed that this group of orvinols indeed were antagonists of morphine in the tail withdrawal test.

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.

It would be M6029

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 that 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.

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When production of the new Reckitt medical compounds fenclofenac and buprenorphine started at Dansom Lane the R&C 1976 Annual Report published this picture of the new fine chemicals line.

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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 mg, 100 mg and 200 mg 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.

Achilles heel

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.

R&D director

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&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.

French's Mustard

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& 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 can be prepared from opiates.

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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.

Control status scheduling

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 started 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.

Cross examinations

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 lead 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 the

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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.

Very attractive profile

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&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.

LOOKING AHEAD

At the unveiling of the Lewis Building a thank you from John Lewis to Indivior's Graham Cairns and Mark Hulme, left, with a typically optimistic message of encouragement for the discoveries to come for the watching staff (reflected on the right).

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 lead 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.

Reckitt's Bristol sponsorship

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.

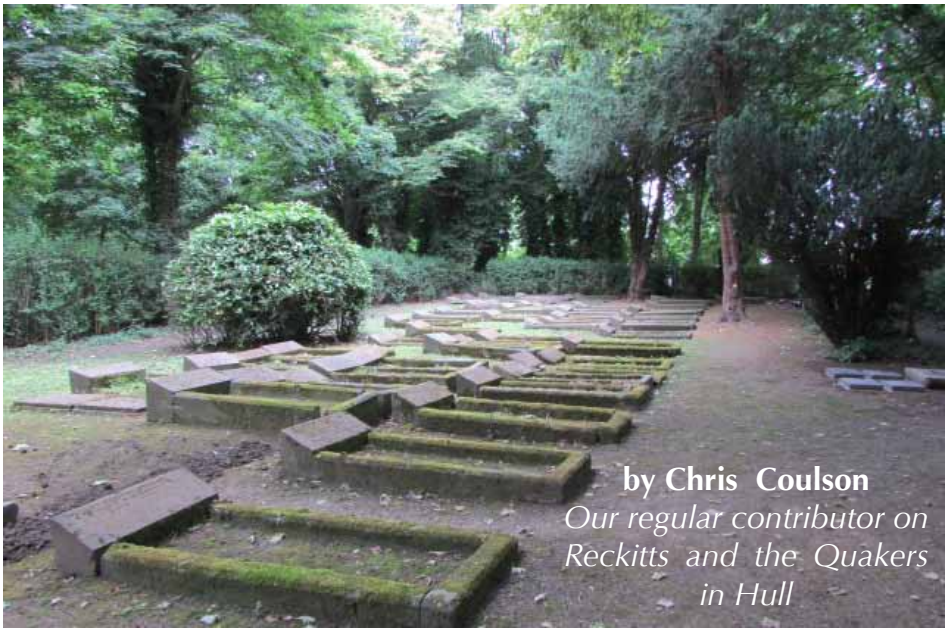
As my retirement approached, I decided I wanted to go back to my medicinal chemistry roots. I was too old a dog to learn new tricks so I looked to NIDA for support in the exploration of the orvinol series for alternatives to buprenorphine. NIDA succumbed and in 1991, I set up a small group in the School 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&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 lead 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.

NOT CONSECRATED, BUT CONSERVATED FOR THE NEXT 834 YEARS



by Chris Coulson
Our regular contributor on Reckitts and the Quakers in Hull

Up to the late 1700s, when Hull was a walled town, there were several Quaker burial grounds outside its walls.

One was initially outside the town in the parish of Sutton. It now lies within the city limits between Spyvee Street and Hodgson Street (53°44'58.00''N/0°19'36.70W).This site has been grassed over and nothing remains of the grave tablets.

The 0.2 acres of land were previously owned by Anthony Wells, Hull merchant, in the 1600s and by 1659 it was in use for Quaker burials.

It is likely that George Fox, the founder of the Quaker movement, met Anthony Wells in 1652, when Fox visited Hull. This burial ground was closed in 1858.

Following the building of The Town Dock (Queen's Dock, now Queen's Gardens) the city suddenly expanded and much land was bought and sold for building.

The 'Avenues' developed

A large area (320 acres) of land eventually ended up in the hands of David Garbutt who sold some but kept 270 acres which he developed into the 'Avenues'.

The sold southern part became the 'Dukeries', and the remaining 20 acres became the Old General Cemetery between Princes Avenue and Spring Bank West. The original gates and chapel were on this corner.

The cemetery was initiated by the Hull General Cemetery Company in 1846 by selling 1000 £10 shares.

Its opening in 1847 was fortuitous for Hull as, from July to Sept 1849, one thousand eight hundred and sixty people of Hull's population died of cholera.

The General Cemetery provided a mass grave for them as the church-yards were now full. A monument stands at the plot.

In 1855 the Quakers took a 999 year lease for £100 on a 0.23 acre plot in the centre of the General Cemetery.

This plot is slightly smaller now as the Quakers donated some land for the path that runs from Thoresby Street to Spring Bank West.

Quaker burial grounds are not consecrated and the grave furniture is simple. The direction of the grave is not necessarily east-west but dictated by what is practicable. The information about the deceased is simple with usually no more than basic information.

Burials in the Spring Bank West Quaker Burial Ground commenced in 1855, starting at the southern end of the eastern-most row.

In the first year of the plot's being opened there were three burials—the first being Mary Ann Heward who on died on 23 June 1855 and was buried on 28 June.

Although the General Cemetery was closed in 1971 burials in the Quaker plot continued until 1974, the last burial being of Philip Dent Priestman.

The Burial Ground contains 81 marked graves in which there are 146 burials as well as some unmarked graves, represented by gaps in the rows. The alignment of the graves are not quite east-west.

Five tablets from Sutton

There are also five tablets recently set by the entrance. These are of interest since they were moved to this burial ground from the Sutton burial ground (1669-1858) which remains as a grassed-over area in Spyvee Street off New Cleveland Street.

The largest of the tablets has some historical significance. Its inscription says, 'Here lies the body of Eliza the wife of Anto Wells Kingston upon Hull (Merch) who departed this life 28th day of the 6th month 1676'.

Many of Hull's benefactors are buried here: Isaac and James Reckitt, Priestmans, Thorps, Kitchens—to name a few, and because of this there is an ongoing restoration plan taking place.

Much work has been done in terms of tree pruning, weeding, hedge trimming etc. A notice board is being prepared to inform the public of Quaker history and the significance of the burial ground.

This historically important plot can be found on the right of the path walking from Thoresby Street through the cemetery or at the north end of the pedestrian crossing at Brandesburton Street, Spring Bank West.If you visit the burial ground please treat it with respect.

Contact *printed a comprehensive Reckitt/Quaker history by Chris Coulson in January 2009. He sent us this picture in 2012 of the grave in Ackworth of Constance (12), the youngest daughter of Issac Reckitt and younger sister of James Reckitt, who died while at school there. The only family grave not in Hull.*

BEST CONTACT

The group photograph of the annual Gaffers' Get-together on P3 gives many of our readers the warming "I remember him/her" opportunity. For those fortunate to make the highly popular event the personal encounters are always the best and most rewarding contact. If we could record all the news, views and memories exchanged round these dinner tables we could fill dozens of Contacts. *But we're not into eavesdropping - so just enjoy the pictures and let memories and imagination run.*

At Derby, above, it's wine and chocolates (left) as raffle prizes; a wine raffle too at High Wycombe, next page, also the flower table decorations, right; and free coffee at the requested Christmas extra at The Cheval, near Hull, below left.

But at all of our meetings the one essential is the companionship, chat and warm memories implied by the very words "get-together".

NB: Pictures right and left, above, taken at Northern Region's meeting at Beverley's East Riding Theatre, where all agreed they had enjoyed meeting each other so much that they should slip another in before Christmas.

High Wycombe's warm weather blessng

Top table at Brewers Fayre (l to r): Chris Mann, Tony Swell, Peter Moores, Patsy Swell, Arthur Tolson and David Saltmarsh

The latest pensioners' event in High Wycombe was just three days before our delayed press deadline but organiser Paul Gilliam reports: "Ignoring any superstitions about the 13th April, the date the event took place, we were blessed with surprisingly warm weather."

The get-together at Brewers Fayre in Loudwater attracted 27 guests – 32 were scheduled to come but illness and misfortune struck in the days leading up to the lunch

"Our visitors included David Saltmarsh and Tony Swell," said Paul, "but we were disappointed to have received apologies from Peter Knee, Bill Roberts, Meg Lambert, George Waddington, David Carter and several others. Next time hopefully they will be able to make it."

Toni Citroni won one of the major prizes in the raffle, a bottle of Prosecco (from Lidl - just in case you think HW are spending their funds unwisely). Of course Paul and Carol Gilliam had to test the vintage before deciding on this as a prize.

Table flowers were eagerly snapped up by the guests.

Table flowers that were "snapped up"

A selection of floor machines in a box like this?

Photographs from the past

There were special thanks also to Bert Childs (those who know him will appreciate why) for coming to every event Paul has hosted and sharing so many photographs from the past – very happy days.

Thanks also to Margaret Wiggins and colleagues representing Winsor and Newton.

The photograph, left, shows an original cardboard box proclaiming that Reckitt-Colman were now the owners of Progress Floor Treatments Ltd.

All wondered why the incorrect nomenclature of Reckitt and Colman was not picked up.

The box will be sent to the Heritage Centre in Hull in due course.

Produced for the Reckitt Benckiser Pensioners' Association by John M. Davis, Beverley.
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