Stadol: a painkiller with punch
Analgesia without addiction

If Bristol Laboratories have it their way, morphine's day as medicine's most popular painkiller may be over.

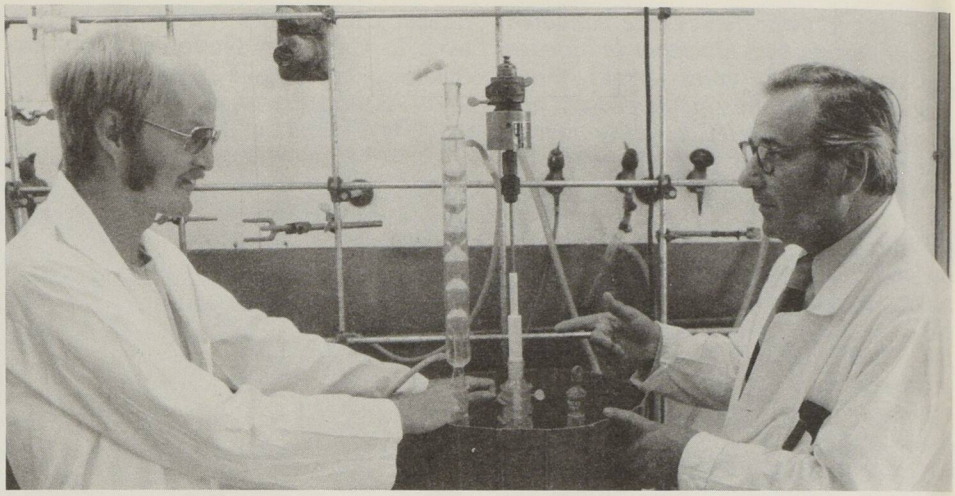
Last year, Bristol Laboratories of Candiac, Quebec, announced the introduction of a new analgesic (painkiller) onto the pharmaceutical market. Stadol, the result of eight years of concerted effort by a team of company chemists, is not only a much stronger analgesic than morphine (medicine's drug of choice) but it does not have the latter's undesirable quality of addiction. Like many of modern medicine's other painkillers, the new drug has a molecular structure very similar to the substances that make up that much-maligned and much-abused "alkaloid mix" opium.

Opium. The very word conjures up a host of other impressions and names — addiction, euphoria, dulled senses, Asian poppies, and for some, Edgar Allen Poe. But, as doctors and other healers have known since antiquity, it is also associated with analgesia, the killing of pain.

In fact, early European chemists working on opium found that the addictive and painkilling properties seemed to go hand in hand. When the active ingredient in opium (morphine) was chemically altered in 1874 to produce heroin, scientists found that their new compound was not only a far better analgesic, but a much more powerful narcotic as well. (Codeine, another opiate derivative, underscores the point; this much weaker analgesic is also much less addictive.) For chemists working with opiate compounds, the trick has been to separate these properties, to create an ideal medical molecule — one that is both a powerful painkiller and non-narcotic. In Stadol, Bristol Laboratories seems to have done the job.

But to better understand the manner of Bristol's achievement, it is necessary to go back to the early seventies and the state of the alkaloid art of the time.

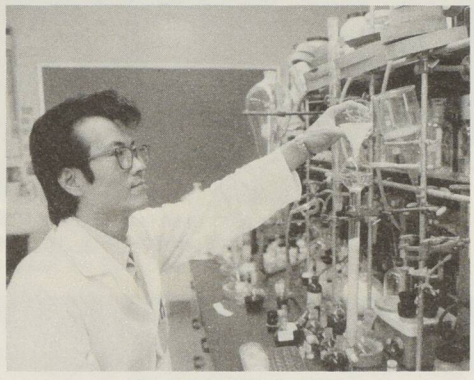
Explains Dr. Yvon Perron, Director of Bristol Laboratories research division at Montreal: "To appreciate what we did, you have to know something more of morphine chemistry. Not only can it be altered to give a more powerful analgesic/narcotic like heroin, it can also be changed into what we call a 'narcotic antagonist', a substance that blocks the action of narcotics. The important point regarding these antagonists is that some, like a substance called nalorphine, are not only non-addictive, but have strong painkilling properties of their own. Unfortunately, nalorphine has other undesirable side effects: besides being short-acting, it causes hallucinations and disorientation. But it tipped us to the fact that analgesia and addiction are not inseparable qualities in opiate substances."



Bruce Kane, NRC/CNRC

Jacques Jérome and Jacques Chapuis, members of the team that developed Stadol, discuss the construction of apparatus for an experiment.

Jacques Jérome et Jacques Chapuis, tous deux membres de l'équipe qui a mis au point le Stadol, discutent de la construction d'un appareil de laboratoire en vue d'une expérience.



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Bristol's Henry Wong carefully fills the head of a separation column. Such laboratory-scale chemistry led to the industrial process for Stadol production.

Henry Wong, chimiste des Laboratoires Bristol, remplit un récipient au sommet d'une colonne de séparation. De telles expériences de chimie à petite échelle ont conduit à la mise au point du procédé industriel de fabrication du Stadol.

Looking over the chemical structures of heroin, nalorphine and another so-called "pure" antagonist called naloxone (used to treat drug overdose victims), Bristol's molecular architects designed on paper a molecule they thought would have the sought-after pharmacological features. Briefly, it had to be, like nalorphine, a strong analgesic, and non-addictive, but without the unpleasant side effects.

"Once we settled on the right structure," continues Perron, "we opted to build the molecule from scratch rather than attempt to modify an alkaloid from opium. To achieve this, Bristol devised a completely new chemical methodology that used as starting materials simple coaltar derivatives. In the commercial process, these abundant petroleum products are first transformed to a certain chemical stage by Raylo Chemicals of Edmonton, Alberta, and the synthesis is then completed by Bristol at Candiac. The use of these chemicals removes the risk of working with imported opium materials."

The end result of this long, often difficult and demanding research project was Stadol (butorphanol tartrate). The test trials of the drug on laboratory animals confirmed the theoretical predictions of the scientists, and were reconfirmed in later trials with human volunteers. Now fully licenced for sale in Canada, the new Bristol analgesic will shortly be granted similar licences in the United States and Europe.

Concludes Yvon Perron: "Eight years ago, the state of the art in this area would not have justified the kind of effort that Bristol put into the Stadol project. With the support provided by NRC's Industrial Research Assistance Program, however, we were able to proceed with what was, at the time, a risk venture." □

Wayne Campbell