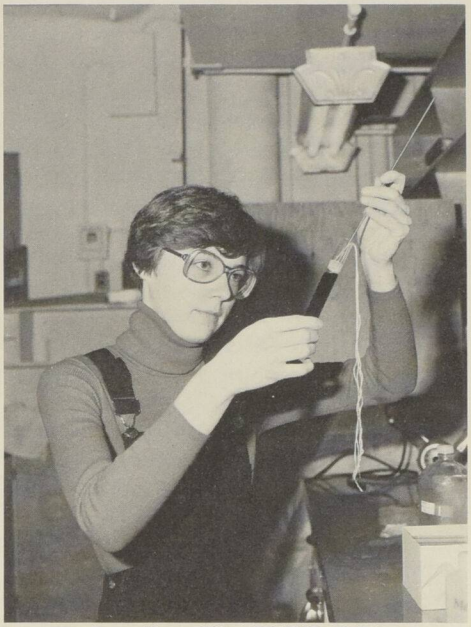
models. According to Dr. Smith, a nerve signal can be considered a "ripple" that travels down the long membrane sheath of a nerve cell. (More specifically, the precise biological instruction that keeps sodium and potassium ions on opposite sides of the membrane — thereby generating nerve voltage — is relaxed; this "relaxation" or momentary loss of what biologists call "selective permeability," travels down the membrane as a nerve signal.) "It appears that anesthetics like alcohol kill the ability of the nerve to ripple by relaxing the entire membrane — by making it more fluid," explains Smith. "On the other hand, local dental anesthetics like Tetracaine and Lidocaine operate by making the membrane too stiff to conduct the ripple."

The NRC scientists have strengthened their hypothesis by showing that there is an excellent correlation between the effect of an anesthetic on a membrane, and its changes in both fluidity and permeability to sodium and potassium ions.

Other work concerns antibiotic resistance in microorganisms. "Some antibiotics may work by changing the membrane fluidity of bacterial cells," explains Smith. "This would eliminate its selectivity to compounds moving in and out — the cell would begin to leak, destroying the complex chemical balance required for survival."

The process of developing resistance to antibiotics, therefore, may involve the bug changing the chemistry of its membrane components to stop this fluidity increase. "In certain yeasts for example," says Dr. Smith, "the development of antibiotic resistance coincides with chemical modifications in the membrane cholesterol."

But understanding the chemistry of these processes is one thing; putting the knowledge to work is quite another. The real vindication of this "atomistic" approach to medicine will come in purposive drug design. "What we want to do," states Dr. Smith, "is build a drug based on what we know about cellular chemistry. For example, studies are now under way in a number of laboratories aimed at producing better contraceptives. Our approach has been to synthesize molecules that have structures very similar to those of the peptide hormones that control ovulation. Such analogues, according to current thinking, block ovulation by attaching to receptors in the cell membrane that are targets for the natural hormones. This kind of contraceptive would have none of the side-effects of many of the birth control drugs in use today.



Bruce Kane, PIB, NRC/DIP, CNRC

Dr. Roxanne Deslauriers prepares a sample for analysis in an NMR machine. The analytical technique has been particularly useful in the study of hormone-like chemicals (notably those with contraceptive properties) and certain peptides from the pituitary gland that mimic the opiates morphone and heroin.

Le Dr Roxanne Deslauriers prépare un échantillon en vue d'une analyse à l'aide d'un spectromètre de RMN. Cette technique analytique s'est révélée particulièrement utile dans l'étude des produits chimiques ressemblant à des hormones (notamment ceux qui ont des propriétés contraceptives) et de certains peptides hypophysaires qui imitent des narcotiques comme la morphine et l'héroïne.

"Among the other substances the group looks at," continues Smith, "perhaps the most intriguing are two groups of naturally-occurring peptides that target on the membrane receptors for opiates like morphine and heroin. Called the endorphins and enkephalins, these analogues bind specifically to the heroin-morphine membrane sites, raising the interesting question of what it is about these structures that enables them to mimic non-peptides like the opiates.

To create effective analogues, one must know something of the relationship between a drug's chemical structure and its biological activity. With C-13 NMR, the NRC biophysicists are studying the structures of a number of these peptides with special attention given to the conformational changes that occur when they are chemically modified. The insight gained into the nature of these structure-function relationships is a valuable guide to the design of new drugs. □

Wayne Campbell

Acupuncture — the opiate of the masses?

It would be difficult to imagine a more unusual crossing of disciplines — the research of a University of Toronto zoology professor on acupuncture and Ian Smith's study of chemicals that mimic heroin and morphine. But both programs, starting from opposite ends of the scientific spectrum, have touched on one of medicine's most intriguing postulates — that the body produces natural pain-suppressing substances.

The first hint for Dr. Bruce Pomeranz that these internal analgesics exist came from tests with anesthetized mice which involved the monitoring of brain cells that transmit pain messages. Pomeranz found that acupuncture caused these cells to lose their capacity to transmit signals, and that the speed of the effect (about one half hour) pointed to mediation by a hormone. Aware of recent findings that the pituitary gland produces powerful pain-suppressing substances called endorphins (200 times more potent than morphine), he repeated the tests on animals where the gland had been removed. This time, acupuncture did not stop the nerve cells from transmitting signals, and further, the drug naloxone, known to block the effects of endorphin, also neutralized acupuncture's effectiveness. Pomeranz's conclusion: acupuncture stimulates the pituitary to release endorphin, which in turn blocks the neural system involved in pain transmission.

For Smith's biophysics group, working with endorphin break-down products called enkephalins, these results were not all that surprising. Enkephalin and its synthetic analogues had already been shown to key onto the same receptor sites on the cell membrane as the opiates heroin and morphine, both strong pain suppressors. More important, analysis with NMR spectrometry showed that the three-dimensional structure of enkephalin — the way the individual atoms are arranged in space — is very similar to that of the two opiates. The significance of this finding lies in the intimate relationship that exists between a molecule's shape, and the activity it performs in a living system.

It seems, therefore, that the body may have what Smith calls a 'built-in aspirin' and that acupuncture, far from being a hoax out of Chinese mythology, has a sound physiological explanation. □