Much of the internal architecture of the nucleus is extremely delicate. Attempts to isolate its components are therefore often snared on troublesome artifacts. Nevertheless, such dissection is essential if the relationship between selection, processing, and transport is to be understood. With luck, Kornberg's new system will help here.

But there are many conundrums. "The fact is that not all RNA's in eukaryotic [higher] organisms are spliced," says Berg. Apart from histone and interferon genes, all genes from the nuclei of higher organisms analyzed so far are interrupted. So, in the normal course of events, the RNA from most genes goes through processing whereas that from histone and interferon does not. As Berg notes, "The curious thing is that, if you take out the intervening sequences from some split genes, the uninterrupted DNA sequence is not always expressed." This is a paradox. "Why are there two kinds of nuclear RNA: some that need a ticket to get through the splicing gate, and others that do not?" he asks. "Nobody has a handle on this."

Splicing puzzles group into three main areas. Mechanisms: How is the process achieved with such precision? Function: Does splicing have a role in normal cell metabolism beyond removing "unwanted" RNA—for instance, in controlling gene expression? Evolutionary significance: Has the fragmented structure of genes permitted great evolutionary flexibility in the past and does it offer future potential?

"We are amazed by the precision of the splicing mechanism," says Berg. And for good reason. There is no regularity apparent in the structure or the spacing of the intervening sequences. No convincing structures have yet been discovered in the nucleus that might serve as a bench on which splicing might be performed. "How does a system recognize a nucleotide at point A and another at point B some five or seven thousand nucleotides away, bring the two together, break the chemical links, and join the adjacent sequences—all with such high precision so that the reading frame is maintained?"

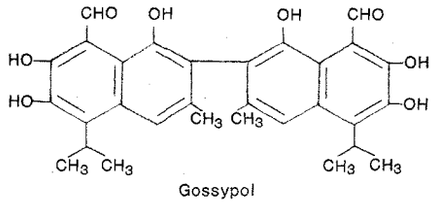
More than that, how in a gene that has multiple intervening sequences does the system avoid skipping from the beginning of one intervening sequence to the end of the next one, thereby losing a whole coding region? If there is even a little play in the mechanism, the chances of producing an intact message from a gene with 20 or so intervening sequences would be very low indeed.

So far the only consistency in the structure of intervening regions is the few nucleotides at either end of the intervening sequence. They begin with the nucleotides containing guanine and thymine and end with adenine and guanine, each dinucleotide being associated with a short stretch of "consensus sequences" first recognized by Pierre Chambon's group in Strasbourg. Different intervening sequences seem to have very similar consensus sequences at their beginnings and ends. It is therefore not surprising, as Berg and his colleague Andrew Buchman and Phillip Sharp and Gilbert Chu at MIT have shown, that a hybrid intervening sequence, made by linking the front section of one intervening sequence with the rear end of anoth-

Male "Pill" Blocks Sperm Enzyme

Gossypol, a potential male contraceptive, apparently works by inhibiting an enzyme that has a crucial role in both aerobic and anaerobic metabolism of sperm and sperm-generating cells. Chi-Yu Lee and Heinrich V. Malling of the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, provided the first clue regarding the mechanism of action of this agent when they showed that its target enzyme is lactate dehydrogenase X. This finding is promising since it indicates that gossypol does not affect either sex hormone levels or libido. It also suggests that the contraceptive effect might be fully reversible.

Gossypol first became identified as an antifertility agent as a result of some studies in China in the 1950's. At the time, investigators were puzzled by the extremely low birth rates in a particular geographic area and eventually related the phenomenon to the residents' exclusive use of crude cottonseed oil for cooking. Further investigation revealed that the active substance was gossypol, which is a phenolic compound found in the seed, stem, and roots of the cotton plant.



Gossypol

Clinical trials of gossypol began in 1972 in China and, to date, more than 10,000 men have been studied. Each received a daily oral dose of 20 milligrams until his sperm count was sufficiently reduced—about 2 months. Subsequent maintenance doses of 75 to 100 milligrams were taken twice monthly. Among the first 4000 men who received the drug for periods ranging from 6 months to 4 years, Malling says, it was found to be 99.89 percent effective. Side effects were minimal; about 13 percent of the men reported transient weakness during the first days of administration, about 3 percent reported a decrease in appetite, and an equal number reported an increased appetite. Sperm levels returned to normal within a few months after use of the agent was discontinued, and several births of apparently healthy babies have been observed among the wives of men who have stopped using it.

Several lactate dehydrogenases occur throughout the body, and gossypol appears to inhibit each of them to some extent. Its greatest inhibitive effect, however, is on lactate dehydrogenase X, which is found only in sperm and testis cells. Gossypol appears to be a competitive inhibitor of a cofactor that is necessary for enzyme activity and thereby inhibits sperm production. The agent also affects some other enzymes. In rodents, it can cause irreversible inactivation of an important enzyme called malate dehydrogenase, but this effect has not been observed in human tissues.

More disturbing, in both rodents and humans, gossypol also inhibits glutathione *S*-transferase, an enzyme that participates in the detoxification of certain organic compounds, including potential carcinogens. At higher doses, some 100 to 700 times the amount required for contraception, the agent has also been shown to cause hair discoloration, diarrhea, malnutrition, circulatory problems, and even heart failure. It is thus clear that a great deal more study will be required before gossypol might be used as a contraceptive agent in this country.—THOMAS H. MAUGH II

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