Biochemistry

Getting from the egg to the chicken

Every chicken, toad or person starts as a single cell that multiplies and differentiates into spatially organized structures such as digits on a limb. This developmental process remains one of the great unsolved mysteries of biology. Scientists have conjectured that chemicals called morphogens may help orchestrate embryonic development by turning on or off genes in specific sets of cells at different times.

That conjecture got an experimental thumbs-up several years ago when Christina Thaller and Gregor Eichele of the Harvard Medical School found that retinoic acid—a member of the "retinoid" class of chemicals, which also includes vitamin A—induces the finger-like projections, or digits, to sprout from the wing buds of chick embryos. They measured higher amounts of retinoic acid in the posterior portion of the wing, where digits normally develop, than in the anterior part. But they found that a dab of retinoic acid on the front part of the wing bud leads to the growth of an additional, though misplaced, set of well-formed digits there (SN: 6/27/87, p.406).

In the June 28 NATURE, the Boston researchers report evidence for another potential morphogen. They found that the retinoid 3,4-didehydroretinoic acid (ddRA) also induces digit duplication on the wing bud. Moreover, they measured five to six times more ddRA than retinoic acid in the wing buds—a hint that ddRA may be even more important in development.

In a companion paper, Michael Wagner and Thomas Jessell of the Howard Hughes Medical Institute in New York City join Thaller and Eichele in reporting that tissue grafted to the wing bud from the floor plate—a region of the chick embryo's developing nervous system—also induces digit development. Test-tube evidence indicates that floor plate tissue can make retinoic acid and a chemical precursor to ddRA.

An accompanying commentary notes that "ddRA is clearly a player of potential significance." But according to the author, Jeremy Brockes of the Middlesex Hospital in London, the case for ddRA's and retinoic acid's morphogenic role during embryonic development remains open.

If retinoids actually serve as morphogens, they presumably latch on to cellular receptors, which then activate genes that determine the developmental fate of the cell. Researchers have identified several distinct retinoid receptors on cell nuclei membranes that appear related to other receptors known to regulate genes in this way.

Evidence for the developmental role of retinoids such as retinoic acid and ddRA continues to build, Eichele says. Scientists already know that retinoids play a role in skin-cell differentiation, and still other functions may await discovery. Comments Brockes, "The retinoids are likely to have a variety of unsuspected roles in development and adult physiology."

Chemists strive to match plant chemistry

"The goal of current research in organic synthesis is to find ways to approach or surpass the finesse shown by nature in the assembly of complex organic molecules," write Clayton H. Heathcock and Serge Piettre of the University of California, Berkeley, in the June 6 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. These two chemists seem to have neared that goal.

Heathcock and Piettre report synthesizing proto-daphniphylline, a 30-carbon molecule suspected as the chemical parent of a family of chemicals found in the Asian yuzuriha tree (*Dathniphyllum macropodum* Miquel). In a remarkably simple triad of steps involving reagents such as ammonia and vinegar, the researchers coaxed a linear precursor to form six new chemical bonds and twist into proto-daphniphylline's complex structure comprising five rings and a few carbohydrate appendages. It's so simple, they say, that yuzuriha trees probably make the compound in a similar way.

Biomedicine

Kathy A. Fackelmann reports from San Francisco at the Sixth International Conference on AIDS

Some HIV-infected people forgo AZT

About half of all people who have asymptomatic or mildly symptomatic HIV infections, and who qualify for treatment with the antiviral drug AZT, do not take the drug, a new study suggests. Without AZT, they may risk faster progression to full-blown AIDS, many specialists warn.

In March 1987, the Food and Drug Administration approved AZT for people with advanced AIDS and for people infected with the AIDS-causing virus, HIV, who have fewer than 200 CD4 T-lymphocytes per cubic millimeter of blood. People with such low levels of these white blood cells—which play an important role in the body's immune response—become vulnerable to the lethal opportunistic infections associated with AIDS.

An epidemiologist at the Johns Hopkins School of Public Health in Baltimore and his colleagues now say many HIV-infected men apparently didn't get the message about the benefits of early AZT therapy.

Neil M.H. Graham and his team studied 1,195 HIV-infected men, some with AIDS-related complex (ARC) and others with no symptoms of the disease. All volunteers knew they were infected. Among people with CD4 counts below 200, the researchers found that AZT usage rose from 23 percent in April 1987 to 53 percent in September 1989. For people with ARC, usage increased from 20 percent to 54 percent during the same time period.

The good news is that AZT use is more common than before among people with very low CD4 counts, Graham says. But the researchers had expected to see a much larger percentage of such high-risk people taking the antiviral drug.

Graham says he can't explain the finding, but he speculates that AZT's price tag deterred some from taking the drug. Manufacturer Burroughs Wellcome Co. in Research Triangle Park, N.C., has since dropped the price, but during the study period the treatment cost as much as $8,000 per year. In addition, Graham says, infected people may put off taking it because they worry about developing early resistance to the drug. Others may fear discrimination, especially if they use employer-provided health insurance to help cover drug costs.

Graham plans a future study to find out more about AZT usage, especially now that scientists have shown the drug slows the progression to AIDS among asymptomatic HIV-infected people with CD4 counts below 500 (SN: 8/26/89, p.135).

Smoking may hasten AIDS development

Cigarette smoking may speed the progression to AIDS in some people infected with HIV, according to scientists who studied 387 HIV-infected men, including some who were asymptomatic and others who had AIDS-related complex.

The researchers—led by Rachel Royce, now at the Harvard School of Public Health in Boston, and Warren Winkelstein at the University of California, Berkeley—discovered that the cigarette smokers in this group were nearly twice as likely to develop AIDS during the 56-month observation period than were their nonsmoking counterparts.

It's possible that smokers in the study had acquired their HIV infections earlier than nonsmokers, but Winkelstein says the researchers controlled for that factor by looking at the number of CD4 T-lymphocytes in the blood, a sign of how far the infection has advanced.

"We can't be sure, but it looks like the smokers are progressing faster to disease," Royce says. Winkelstein notes that further research must confirm the link between smoking and the development of AIDS.

While chemicals in cigarette smoke initially activate the immune system, this study shows that smokers with HIV infection suffer a more rapid depletion of CD4 cells than do infected nonsmokers, Winkelstein adds.