

the time that we must make a choice among the various alternatives.

Palmer, I, and the rest of the Muon Collider Collaboration, which now consists of 100 working physicists, agree in thinking that R&D money should be spent on muon colliders; in particular, both the production of muons and the cooling of the muon beam need experimental demonstration. This is the only way to find out if this exciting possibility is "real" or not. Still to be seen is whether the funding agencies agree with us.

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Insulin/IGF Signaling and HNF-3/*forkhead* Proteins

A report by Kui Lin *et al.* (14 Nov., p. 1319) and a paper by S. Ogg *et al.* (1) demonstrate that *daf-16*, a member of the HNF-3/*forkhead* protein family, contributes to the longevity of *Caenorhabditis elegans* when the activity of *daf-2*, a homolog of the insulin and IGF-I receptor, is compromised. These interesting studies provide strong genetic evidence that signaling by the insulin/IGF-I receptor and

HNF-3/*forkhead* transcription factor homologs may exert opposing biological effects.

Both papers note that HNF-3 proteins have been found to interact with cis-acting DNA sequences that mediate inhibitory effects of insulin on the expression of multiple genes in the liver, including phosphoenolpyruvate carboxykinase (PEPCK) and insulin-like growth factor binding protein-1 (IGFBP-1), yet neither cites the first papers regarding this potentially seminal observation (2, 3). In those studies, we reported that HNF-3 proteins bind to highly related insulin response sequences in both the IGFBP-1 and PEPCK promoters. We also found that HNF-3 binding at this site may enhance the ability of glucocorticoids to stimulate IGFBP-1 promoter activity and demonstrated that overexpression of HNF-3 β stimulates IGFBP-1 promoter activity in NIH 3T3 cells in a sequence-dependent fashion (3). To our knowledge, this report remains the only published data directly demonstrating that HNF-3 proteins and insulin can exert antagonistic effects on gene expression through identical or overlapping cis-acting DNA sequences.

In their report, Lin *et al.* suggest that signaling from insulin and/or IGF-I receptors may directly disrupt effects of HNF-3/*forkhead* proteins on gene expression, perhaps

by reducing the binding of HNF-3/*forkhead* proteins to their target sequence. Although this may be the case, subsequent studies in this and other laboratories indicate that HNF-3 binding does not correlate with the ability of insulin to suppress either IGFBP-1 or PEPCK promoter activity, but relates more directly to the ability of glucocorticoids to transactivate both of these promoters (4). Also, we are not aware of any data indicating that insulin disrupts the binding of HNF-3 proteins to insulin response sequences in either the IGFBP-1 or PEPCK gene. Indeed, both HNF-3 proteins and insulin have been found to contribute positively to hepatic expression of IGF-I (5).

In view of these findings, it may well be that the functional antagonism between the effects of the insulin/IGF-1 receptor signaling system and members of the HNF-3/*forkhead* family on longevity in *C. elegans* may reflect molecular mechanisms that are neither simple nor direct.

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Response: We appreciate the comment by Unterman about our recent report and apologize for not having cited papers by his group (1). We note that the model we cited (2) also considered the possibility that glucocorticoid-stimulated potential, rather than binding of HNF-3, may be influenced by insulin signaling. In our discussion about the possible mechanisms for the antagonism between the insulin/IGF signaling and HNF-3/forkhead proteins, we did not mean to imply that the effects were "direct" or "simple."

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Ending Polio Immunization

In back-to-back Policy Forums on 8 August, A. W. Dove and V. R. Racaniello (p. 779) and H. F. Hull and R. B. Aylward (p. 780) discuss various strategies for the "eventual cessation" of immunization of children against polio, now that the worldwide eradication of the disease is within sight. We, however, would like to add a cautionary point.

If, say, after 5 years of inactivated polio vaccine (IPV) immunization and five further years of nonimmunization, no virus can be detected (even in the susceptible cohorts of nonvaccinated newborns), then intense surveillance might gradually be ended. It is only at this stage (not likely before the year 2010) that the world could be declared free of poliovirus.

To help this approach, priorities on the

research agenda should be (i) to gain insight in enterovirus RNA sequences that determine transmissibility, as well as the possibility that such sequences are obtained by polioviruses, in particular oral polio vaccine (OPV) Sabin strains, through genetic drift or recombination; (ii) to develop serological tests that are able to detect infected persons in populations vaccinated with inactivated polio vaccine; and (iii) to optimize surveillance strategies, sampling theory, and formulation of criteria for certifying countries as poliovirus-free.

We cannot get absolute proof of the absence of "the needle in the haystack" (poliovirus in the world) before we should want to ban immunization. Thus, immediately after ending immunization, a population of susceptible children will develop who necessarily, but much to our unease, will prove the correctness of the assumptions made. Sad disappointments may therefore follow the ban on polio immunization, and we should be prepared to respond rapidly to unpredicted outbreaks with at-the-ready high-quality diagnostics and, above all, large quantities of vaccine (both OPV and IPV).

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MAMMALIAN GENOTYPING SERVICE

Sponsored by the
National Heart, Lung, and Blood Institute
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The Mammalian Genotyping Service is funded by the National Institutes of Health to assist in linkage mapping of genes which cause or influence disease. Genotyping is carried out using short tandem repeat polymorphisms at Marshfield, Wisconsin under the direction of Dr. James Weber. Capacity of the Service is currently about 3,000,000 genotypes (DNA samples times polymorphic markers) per year and growing. Although the Service was initially established for genetic projects dealing with heart, lung, and blood diseases, the Mammalian Genotyping Service will now consider all meritorious applications.

To ensure that the most promising projects are undertaken, investigators must submit brief applications that are evaluated by a scientific advisory panel. At this time, only projects involving humans, mice or rats and only projects with $\geq 10,000$ genotypes will be considered. There are no genotyping fees for approved projects. Application deadlines are every six months.

Upcoming Application Deadlines

March 31, 1998
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For Application Instructions and additional information see:

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