Scientifically Speaking

Symposium on genetics

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Bar Harbor, Maine—Zoologist Clarence Cook Little founded a small laboratory here fifty years ago to study cancer through the idiosyncrasies of inbred mice. Before air conditioning, the foggy and relatively cool days of this coastal island setting provided a comfortable summer environment for scientist and mouse, and 1929 heating devices were sufficient to offset even Maine winters. Thus began the Roscoe B Jackson Memorial Laboratory, named for one of its initial benefactors, the president of the Hudson Motorcar Company.

Twenty years ago the Jackson Laboratory, Johns Hopkins University, and the National Foundation-March of Dimes joined talents and money to initiate the first short course in medical genetics, designed principally for faculty and staff of schools for the health professions and teaching hospitals. The short-course lecturers annually supersaturate 150 or more registrants with the laboratory and arithmetic techniques of the study of genetics, and, at the same time, bring their students up to date with findings that have barely been published.

The double anniversary of these enterprises was celebrated here in July with a symposium of internationally known workers in mammalian genetics, followed by a short course with many of the same scientists as lecturers and an abundance of new insights into old human disease problems whose genetic components are becoming clear only now.

Chromosomal links

Until very recently a disease could be tied to a chromosomal abnormality only if it was a rather gross abnormality. Customary karyotypes readily disclose extra chromosomes or missing ones, and, stained to bring out banding patterns, can reveal duplication or deletion of a chromosomal arm. These, however, are chromosomes seen well along in mitosis, each with its DNA tightly bunched—"shrunken," as Park S Gerald described them. Dr Gerald, a paediatrician and chief of clinical genetics at Harvard's Children's Hospital in Boston, said that a sharpening of techniques into "high resolution cytogenetics" over the past year or so has enabled identification of the smallest chromosomal abnormality yet found to have clinical meaning. The technical improvements, reported by several authors,[1 2] hinge on cell preparations made earlier in metaphase, when the DNA is less closely packed and can furnish a larger-scale chart of the chromosomal layout.

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This kind of fine-grain view has led to the discovery, reported last December,[3] that a minuscule deletion on the short arm of chromosome 11 is associated with the so-called AGR triad (aniridia, genitourinary abnormalities, and mental retardation) and, in almost half of the instances, with Wilms's tumour. The linkage of Wilms and lessened or missing iris had been made in 1964,[4] but identification of a discernible genetic flaw awaited more deft laboratory work.

Now that the abnormality is recognised, Dr Gerald said, he and his associates have examined nine patients with Wilms's tumour and aniridia, and have found the abnormality in every one of them. In karyotype, it shows up as a deleted or lessened band on the chromosome arm, and is probably approaching the lower limit of visible aberrations that can be limned by Giemsa staining.

In terms of possible numbers of genes, however, the barely discernible alteration on the short arm of chromosome 11 is huge —"the segment is perhaps the equivalent of a couple of hundred genes," Dr Gerald said. The entire chromosome 11 contains about 4·6% of the haploid gene complement; the short arms (p) make up about 40% of the chromosome, accounting for about 1800 genes; the missing part must contain 90 or more genes at the very least.

"If we can only barely detect this big deletion," Dr Gerald mused, "then it is very difficult to say, from karyotyping, that someone is not missing some chromosomal material." That degree of diagnostic certainty will await the ultimate step in gene identification: the determination of sequences in DNA as it is teased out of the chromosome—introns, exons, and all.

A possible line-up of genes on the 11p deletion is becoming established as more cases come to light, Dr Gerald said. The incidences of linkage indicate that Wilms's tumour, which is hypothesised as a single-gene defect, has a locus fairly close to the aniridia locus. In a registry of patients with Wilms's tumour aniridia occurred about once in every 70 people, compared with once in perhaps 50 000 to 100 000 people in the general population.

The locus for the genitourinary abnormalities would appear to be on the other side of the Wilms's locus from the aniridia, and probably somewhat more distant. The locus for the mental retardation seems likely to be beyond the GU locus. But if that is the correct order, then how does one explain the clinical existence of the AGR triad without Wilms's tumour? "Having 11p- poses only a 50% chance for having the tumor," Dr Gerald said. "The chromosome is step 1; then you need an unknown step 2 to produce the actual tumour."

Mental retardation

Another chromosomal abnormality brought to the students' attention here by Dr Gerald is being reported in detail only this year, largely by Australian investigators, to help explain a genetic reason for a greater incidence of mental retardation among men than women. The reason is a form of retardation that

probably is X-linked. In affected males—and at least one female checked by Dr Gerald's group—the marker is a tiny projection at the end of the X long arm, or sometimes even a completely detached piece of the long-arm end. Grant Sutherland, at the Adelaide Children's Hospital in Australia, calls it a "fragile site" on the X in his publications this year.[5 6] The entity and the condition rapidly became dubbed the "fragile X" syndrome in discussions here at Bar Harbor.

Gillian and Brian Turner and their associates in Melbourne suggested in the mid-1970s that some mental retardation could be X-linked.[7] They and others had found brothers of retarded males who were also found to be retarded, but seldom could find an affected sister. In most industrialised countries men in institutions with mental retardation outnumber women by 10% to as much as 40%, according to Dr Gerald, but there is no discernible social or custodial reason for the discrepancy.

Over the years there have been sporadic reports of an odd-looking X accompanying some mental difficulties, Dr Gerald said, but it was Dr Sutherland who discovered a reproducible way to find the fragile X: culture blood cells in a medium deficient in thymidine and folic acid. Well-supplemented medium prevents the defect from appearing.

In a private communication, according to Dr Gerald, Dr Sutherland said he had found the fragile X in five of 205 men institutionalised with mental retardation. The Australian suggests that the condition is identical with the form of retardation earlier associated with macro-orchidism.

If the fragile X turns out to be more than a marker—to be, indeed, an X-linked cause of mental retardation—then the Sutherland figures for its occurrence in institutionalised males—2 or 3%—would put it in second rank as a source of mental deficiency. Down's syndrome is generally regarded as the largest cause of retardation, accounting for about 5% of the mental institution population in the United States.

Gene-related diseases

The endless difficulties for doctors attempting to treat diabetes mellitus are becoming more understandable as the heterogeneity of diabetes-like diseases becomes more appreciated. David L Rimoin, professor of pediatrics and medicine at the University of California in Los Angeles, noted that it was not too long ago that diabetes was regarded as a single disease. Then distinctions were discovered between a juvenile-onset diabetes that was insulin dependent and a maturity-onset condition that wasn't. Further distinctions arose to blur the concept of age of onset.

Nowadays, said Dr Rimoin, "diabetes is a symptom complex whose many manifestations share glucose intolerance." There are more than 30 genetic diseases in man, plus a range of other ailments, such as pancreatitis, all of which are associated with abnormal glucose tolerance. Drs Rimoin and Jerome Rotter, who combed published work in search of evidence for genetic links with diabetes,[8] found the strongest hints in the association of insulin-dependent diabetes with some HLA types. HLA B8 and BW15, for instance, each pose an increased diabetes risk of twofold or threefold compared with persons lacking those alleles. Further, a person having both of those alleles has a compounded risk of the disease. That observation is partly explained, perhaps, by a difference in effect between the alleles; B8 is accompanied by a persistence of antibody to islet cells, which does not show up in BW15, but the latter develops antibodies to exogenous insulin. Most recently, Dr Rimoin noted, Boston workers have identified a rare inherited trait that is found in 20% of insulin-dependent diabetics but less than 2% of the general population.[9]

Among some 25 recognised mutations that alter the human handling of vitamins is one that shows up as a late complication of alcoholism, the Wernicke-Korsakoff syndrome. Charles R Scriver, director of biochemical genetics at McGill University in Montreal, touched on the condition in his review here of vitamin-responsive inborn errors of metabolism.

Wernicke-Korsakoff causes a loss of short-term memory, progresses to complete psychosis, and is responsible for as many as 5% of institutionalised psychotics in countries where alcohol is drunk. The defect is a deficiency of transketolase, whose normal binding of thiamine is interfered with by alcohol. Pharmacological doses of B_1 could prevent development of the syndrome among drinkers screened for the mutation, Dr Scriver said, but he doubted the worth of a recent suggestion to add thiamine to liquor: "It tastes terrible." He noted that B_1 is ingested by some outdoorsmen to repel blackflies and mosquitoes by setting up an unsavoury body odour.

References

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The anaesthetic department of this hospital will not allow midwives to "top-up" epidurals because although the primary dose down the catheter may have caused no untoward effects, the catheter may then erode its way through the dura so that a subsequent dose of local anaesthetic would enter the cerebrospinal fluid. This risk must be infinitesimally small; could you please tell me how often it might occur?

This is currently the focus of considerable dissent in informed circles. There have been very few reported occasions when a top-up dose subsequent to the initial dose has apparently been injected directly into the cerebrospinal fluid via the cannula in the absence of prior evidence that the dura had been breached. One explanation proffered runs as follows: if the epidural cannula has two apertures near its tip, and only the distal one is passed into the cerebrospinal fluid at initiation of the epidural, local anaesthetic slowly injected will pass mainly out of the proximal hole and hence into the extradural space, whereas a rapidly injected bolus will mainly be directed intrathecally, and the latter circumstance might apply to second or subsequent injections rather than to the initial one. It has also been postulated that erosion of the dura by the cannula tip—possibly at the site at which the dura had been superficially damaged during the initiation of the epidural—could occur during labour. These are both somewhat tenuous arguments. Scrutiny of the reports of the occurrences under review leaves room to suspect that the dura was punctured at the time of insertion of needle or cannula but the occurrence was not recognised—injection of the local anaesthetic directly into the cerebrospinal fluid will result in the clinical appearance of motor and sensory nerve block slightly more rapidly than would have been the case had the drug entered the extradural space, but possibly not so rapidly as to arouse suspicion, and the extent of spread of nerve block will certainly not be untoward if the patient is in the appropriate position. The policy of perfection would be to attempt to aspirate immediately before administering a top-up dose, but this entails difficulties of identification of any fluid that might appear in the cannula. I agree that the risk of this complication is infinitesimally small, but most importantly, if it does occur it should occasion no danger to the mother if the standards of observation and care—obstetric, anaesthetic, and midwifery—are compatible with those required in any delivery suite where epidural analgesia is available.