findings on three deletions involving those exons that have been cloned and sequenced.

One of these is a 6-kb deletion originally detected in a Becker patient by Kevin Hart (Guy's Hospital, London) and which results in the excision of one exon, probably leaving the adjacent exons and their splice junctions intact so that the rest of the coding sequence can be read in frame. The two Duchenne deletions that have been investigated by contrast can be shown to change the reading frame. The more distal end of the gene is so far relatively unexplored and may turn out to encode domains more critical for function than any of the 5′ exons. Monaco and Kunkel are hoping that other researchers will be willing to supply them with further data on specific patients to follow up these analyses.

Although it is possible to see in broad outline how a combination of mapping, cloning and sequencing will eventually show how various different mutations in the gene encoding a muscle protein can give rise to a muscle disease of varying severity, the occasional association of DMD and BMD with mental retardation may prove more problematical.

First, there is no evidence so far that the gene is transcribed in brain. This, as Kunkel was careful to stress, may not mean anything: probes are only available for a quarter of the gene and it is possible that brain tissue expresses only or primarily those exons for which probes do not yet exist. On the other hand, if that is the case it should be possible to link the deletion of particular regions of the gene with the occurrence of mental retardation. No such association emerged from a collation of information at the meeting; but again, a pattern may emerge with data from an increasing number of probes.

In any case, it is perfectly possible for a gene to cause mental retardation without being expressed in brain at all. Such an indirect effect might be very difficult to identify.

Finally, there is the problem of diagnosis. The consensus at the meeting seemed to be that mental retardation associated with DMD is a distinctive phenotype that breeds true within a family. But several participants quoted apparent exceptions to this rule and cogent dissent was voiced by Allen Roses (Duke University) who argued that cognitive function is depressed to some degree in all DMD patients and mental retardation is simply the consequence of depressing an already low intelligence. An additional complicating factor is the effect of neglect of the disabled child by some families, quite possibly most often those of lower intelligence.

But even assuming the majority view is correct and mental retardation is a distinct phenomenon associated with specific mutations, establishing reliable diagnoses of mental retardation or its absence in all 220 deletion cases available (or at any rate those in which affected individuals are still alive) may demand an effort of organization of a different order from that required for the collaborative effort that led to the original compilation of deletion data on the gene by Kunkel and a total of 72 co-authors[5].

The clinician's headache

It is no surprise that in a gene of about 2,000 kb the mutation rate and the rate of intragenic recombination, each a serious handicap to genetic counselling and prenatal diagnosis, are high. Two points of particular relevance for clinicians emerged at the meeting, the first (the bad news) arising from the analysis of new mutations. Several participants reported families in which a mother with two apparently normal X chromosomes produced more than one offspring with an identical *DMD* deletion. This means it cannot be assumed that a DMD boy born to parents of normal genotype must himself be a new mutant, and the chance of an affected sibling thus no higher than in any normal family. There are three possible explanations for the occurrence of identical mutations in the offspring of a mother of normal genotype. The simplest is germline mosaicism: a mutation occurring in a mitosis early in the differentiation of the mother's germ line. A second possibility is a 'pre-mutation' in the mother — a postulate familiar to students of the fragile-X syndrome, in which the mentally retarded phenotype can be silent for a generation or two before reappearing for no apparent reason. More concretely, such a phenomenon could result from a large inversion at the *DMD* locus, which would be undetectable by most probes but could predispose to deletions at chromosome pairing in meiosis (although it is not clear why this should lead to identical deletions). The third possibility (Uta Francke, Yale University) is that in some cases the disease can be autosomally transmitted[6]. Any or all of these mechanisms may account for isolated cases of DMD and each complicates prenatal diagnosis.

The second clinically relevant point to arise at the meeting was the dramatic illustration of the very high proportion of cases that are due to deletions (see ref. 7). Van Ommen's data, which directly test the potential hinted at in three recent papers[8–10] of pulsed-field gel electrophoresis in prenatal diagnosis, imply that there must be a particularly deletion-prone region at the 3′ end of the gene.

Pulsed-field gel electrophoresis (the Leiden group in fact used the field-inversion variant, or FIGE) will separate very large fragments of DNA generated by digestion with rare-cutter enzymes at a resolution of 20–30 kb and can be used for the direct detection of deletions. If, as van Ommen's data suggest, 50 per cent of DMD cases result from deletions detectable by FIGE then half of all prenatal diagnoses should be possible without linkage analysis. Some participants demurred that pulsed-field gel electrophoresis is too sophisticated for routine use, the ideal being an appropriate battery of complementary DNA and flanking probes which would detect small deletions as well as large ones. Others, massively supported by historical precedent, averred that no convenient diagnostic technique was so sophisticated as to escape eventual adoption for clinical use. □

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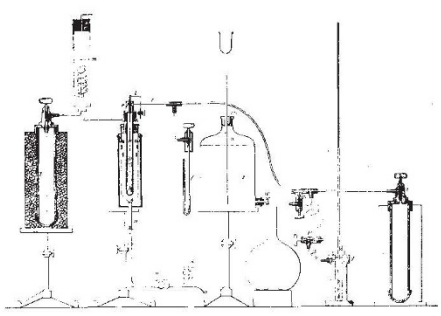
100 years ago

CONDENSATION OF GASES

AMONG the numerous subjects which have engrossed the attention of the knowledge-seekers of the present century, probably none have surpassed in fascination and in the wealth of results which have showed persistent effort the question of the possibility of liquefying those gases which for ages had been considered permanent. On the assumption that the molecule of iodine consists of two atoms, which, according to the view now becoming more and more accepted by thinkers on this subject, may themselves consist of aggregations of a still simpler substance — aggregations which, at temperatures obtainable in the laboratory, we have not been able to break up — the classical experiments of Victor Meyer have shown that at a temperature of about 1500°C the molecules are dissociated into single atoms, that is to say, the intensity of the heat-vibrations is so great that the attraction between the two atoms in the molecule is overcome, and they are torn asunder. At still higher temperatures there is a possibility that the atom itself could be resolved into something simpler still.



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