been observed, namely hysteresis. Hence (and perhaps not surprisingly), the coercive field is tiny, less than 0.1 oersted.

What of the future? The dog having walked on its hind legs, albeit unsteadily, we can confidently expect T_cs of molecular organic magnets to increase further. Sticking my own neck out, though, I shall be surprised if a magnet containing only carbon, hydrogen, nitrogen and oxygen is ever made with T_c above room temperature. My reasons are twofold: first, the nature of organic radicals is that they contain only one unpaired electron per repeat unit, and second, the interaction between the orbitals carrying the unpaired electrons takes place across distances equal to the van der Waals intermolecular distance. Both factors militate against high T_cs. Still, the search is fun, and I shall be pleased to be proved wrong. □

Peter Day is at the Royal Institution, 21 Albemarle Street, London W1X 4BS, UK.

DNA REPAIR

Engagement with transcription

D. Bootsma and J. H. J. Hoeijmakers

ON 18 May 1968 J. E. Cleaver published his discovery that cells of patients suffering from xeroderma pigmentosum carry a DNA-repair deficiency[1]. Two papers in this issue[2,3], which appear 25 years later almost to the day, are part of a stream of findings which show just how far we have come in understanding repair syndromes since then.

On page 182, Scherly and co-workers[2] describe the serendipitous cloning of a frog and subsequently a human homologue of the yeast excision repair gene *RAD2*, and demonstrate that this gene is responsible for one of the severe forms of xeroderma pigmentosum (XP-G). On page 185, using an enzymological approach, O'Donovan and Wood[3] show that the factor capable of correcting XP-G is identical to the protein missing in rodent cells mutated in the DNA-repair gene *ERCC5*. So the RAD2, XP-G correcting protein (XPGC) and ERCC5 proteins are one and the same. When put into the context of other new developments the implications of this work are far reaching, not least because we can begin to discern the details of a connection between the processes of transcription and nucleotide-excision repair in certain rare disorders.

EUKARYOTIC NUCLEOTIDE-EXCISION-REPAIR GENES AND MUTANTS

Human mutant (and gene)*	Rodent mutant†	Yeast gene
XP-A *(XPAC)*	?	*RAD14*
XP-B *(XPBC)*	*ERCC3*	*RAD25 (SSL2)*
XP-C *(XPCC)*	?	*RAD4*?‡
XP-D *(XPDC)*	*ERCC2*	*RAD3*
XP-E	?	?
XP-F	?	?
XP-G *(XPGC)*	*ERCC5*	*RAD2*
CS-A	?	?
CS-B *(CSBC)*	*ERCC6*	?
TTD1BR	?	?
?	*ERCC1*	*RAD10*
?	?	*RAD1*
?	?	*RAD7*
?	?	*RAD16*

**XPAC* (and so on) is the term for the gene encoding a protein that corrects XP-A.
† Rodent complementation groups are numbered. The human genes correcting the defect of rodent mutants are designated *ERCC* (for excision repair cross complementing) genes, the number referring to the number of the corrected group.
‡ Level and type of homology not conclusive.

Nucleotide-excision repair (NER) is a multi-step process that has evolved in all living organisms for the removal of a broad spectrum of DNA lesions. It is central to the prevention of the effects of genotoxic agents, among which is the most ubiquitous environmental threat to DNA, ultraviolet light. The pioneering studies of Hanawalt and his colleagues[4] have revealed that in most — if not all — organisms there are actually two subpathways for NER (see Fig. 1).

Most insights in this field stem from mutants defective in NER. Typically, such mutants display extreme sensitivity to ultraviolet light and to numerous chemicals, as well as elevated levels of induced mutagenesis. The collection of yeast NER mutants currently includes at least 11 members, which make up the *RAD3* epistasis group. Most of the genes involved have been cloned (see ref. 5 for review). Similarly, many mammalian NER mutants have been generated in the laboratory using rodent cell lines. By cell fusion, at least 11 complementation groups have been identified, and by transfection-correction cloning strategies a series of complementing human NER genes has been retrieved (see table).

The phenotypic consequences of an NER defect in humans are apparent from several rare, inborn disorders. Three distinct syndromes are recognized, each characterized by hypersensitivity of the skin to the ultraviolet component of sunlight and by remarkable clinical and genetic heterogeneity[5,6]. These are XP itself (seven genetic complementation groups, designated XP-A to XP-G); Cockayne's syndrome (two groups, CS-A and CS-B); and PIBIDS, which is a peculiar photosensitive form of the brittle-hair disease trichothiodystrophy (at least two groups, TTD1BR and one equivalent to XP-D).

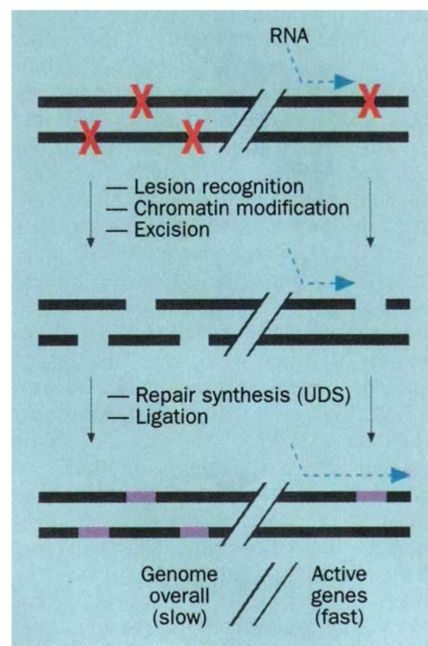

FIG. 1 Steps in nucleotide excision repair. Broadly, the mechanism has five stages: recognition of the lesion; incision of the damaged strand on both sides of the lesion at some distance from it; excision of the injured oligonucleotide; synthesis of new DNA using the intact complementary strand as template; and ligation. Two NER subpathways can be discerned. One is the rapid and efficient repair of the transcribed strand of active genes (transcription-coupled repair). The other is the slower and less efficient repair of the bulk DNA, including the non-transcribed strand (genome overall repair).

As well as sensitivity to sunlight, other manifestations of XP include pigmentation abnormalities and a more than 2,000-fold increased frequency of skin cancer, often accompanied by progressive neurological degeneration. In the case of CS, neurological dysfunction is associated with dysmyelination of neurons, which could be due to poor expression of one of the myelin proteins, and this disease is also characterized by poor physical and sexual development. Patients with PIBIDS manifest all the CS symptoms and, curiously, two hallmarks of trichothiodystrophy: ichthyosis, and brittle hair and nails (the brittleness being due to a reduced content of a cysteine-rich matrix protein). Intriguingly, individuals with CS and PIBIDS do not seem to be unduly prone to cancer. This remarkable clinical heterogeneity associated with NER impairment is even more perplexing because defects in one gene may give rise to symptoms of XP, combined XP/CS or PIBIDS. Notably, this holds for XP-B, XP-D and XP-G[7], and implies that all the syndromes are

© 1993 Nature Publishing Group

manifestations of a much broader clinical entity.

Molecular genetic analysis has revealed striking homology between all eukaryotic NER genes. Indeed, the entire NER system seems to be highly conserved from yeast to man, the gene products in yeast, rodents and humans fitting as pieces of the same puzzle (see table). The cloning of the *XPGC* gene by Scherly *et al.*[2] and the *in vitro* complementation studies of O'Donovan and Wood[3] fill in two of the remaining holes: *XPGC* is the human homologue of *RAD2*, and *ERCC5* is probably *XPGC*. The primary amino-acid sequence does not reveal any secrets, however, so this protein's role remains enigmatic.

Putting the clinical and molecular observations into a broader perspective, a puzzling question is how such features as neurodysmyelination, retarded development and brittle hair can be interpreted in terms of a repair defect. A first hint that other aspects of cell metabolism are also affected in some of these mutants came from the yeast homologues of the XPBC and XPDC proteins. The corresponding genes appeared to have another function in an unknown process essential for yeast viability[8–11], and the nature of that process was uncovered only a few weeks ago in a completely unrelated line of research.

Egly's group in Strasbourg has a long-standing interest in the molecular mechanism of transcription initiation of most of our genes (transcribed by RNA polymerase II). While searching for a transcription factor they stumbled upon a repair gene, and last month reported the identification of the repair protein XPBC/ERCC3 as part of the basal transcription factor TFIIH[12]. In TFIIH, ERCC3 seems to fulfil a DNA-melting function as an obligatory late step in the complex process of transcription initiation. The DNA-unwinding function was already anticipated on the basis of the primary amino-acid sequence[13].

This rediscovery of the same protein in a different context points to several conclusions. First, the CS features of neurodysmyelination and retarded development typical of XP-B, which are reminiscent more of a defect in expression than in NER, may reflect a subtle impairment of general transcription. This proposition also provides an explanation for the curious phenotype of the XP-B equivalent in *Drosophila*, 'haywire', which has defects in the central nervous system and in its sexual development[14]. The same may hold for the symptoms of CS and brittle-hair trichothiodystrophy in XP-D, which in many respects are very similar to XP-B. As such these complex disorders may define a new class of transcription syndromes that may also occur in the absence of an associated repair deficiency (for instance trichothiodystrophy without photosensitivity).

Second, the new findings imply that a subset of proteins is involved in two quite different aspects of DNA metabolism, initiation of transcription and NER.

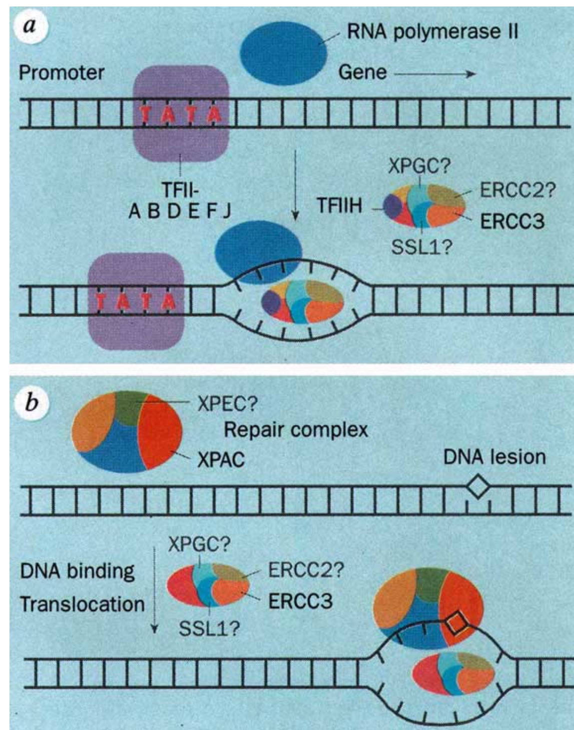

FIG 2. Models for the role of ERCC3 in transcription and nucleotide excision repair. *a*, Possible function of ERCC3 and the TFIIH transcription factor in transcription initation by RNA polymerase II. Various factors including TFIIA, B, D, E, F and J assemble on the promoter (upper part). The local melting activity of the ERCC3 helicase in the TFIIH factor may be required for loading the RNA polymerase onto the template and/or for translocation of the complex along the DNA during the elongation reaction (lower part). *b*, Possible function of ERCC3 in NER. The local DNA-melting activity of ERCC3, perhaps in the context of a TFIIH-like factor, may be required for assembling a DNA-damage-recognition complex onto the DNA, for translocation along the helix, or for both. Alternatively, or in addition, ERCC3 may be involved in inducing a specific, locally denatured conformation in the DNA at the site of the lesion as a prerequisite for the binding and action of the NER-incision complex.

A model for a similar function of the ERCC3 protein in both processes is that it carries out DNA unwinding coupled to translocation of the transcription complex (Fig. 2*a*) and the repair complex (Fig. 2*b*) along the helix. Alternatively (or in addition) it may be involved in inducing a specific DNA conformation for loading RNA polymerase or the NER-incision complex onto the DNA. Because XPBC/ERCC3 is part of the multi-protein TFIIH factor, it would not be a complete surprise if other repair products turn out to be hidden in this or a similar complex. One candidate is XPDC/ERCC2/RAD3, because this protein is also a DNA helicase and the corresponding mutants resemble XPBC/ERCC3/RAD25 mutants in many respects[5,6,13]. Another is the uncloned human homologue of *SSL1* that seems to interact with *RAD25 (SSL2)*[10,15]. XP-G, like XP-B and XP-D, belongs to the exceptional class of groups harbouring patients with combined XP/CS[7], so it may turn out that XPGC is also involved.

The relationship between transcription and repair, as revealed by Hanawalt and colleagues, therefore now reaches the stage of an official engagement. Indeed, it fits nicely into the emerging pattern that the eukaryotic NER system recruits many of its factors from proteins already involved in other basic aspects of DNA metabolism such as replication[16] and recombination[17]. Finally, the concept of 'transcription syndromes' in the human population is remarkable in itself. Not only does it show that extremely rare disorders can still be very revealing, but it will open a new chapter in human genetics as well. □

D. Bootsma and J. H. J. Hoeijmakers are in the Department of Cell Biology and Genetics, Medical Genetics Centre, Erasmus University, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

1. Cleaver, J. E. *Nature* **218**, 652–656 (1968).
2. Scherly, D. *et al. Nature* **363**, 182–185 (1993).
3. O'Donovan, A. & Wood, R. D. *Nature* **363**, 185–188 (1993).
4. Hanawalt, P. & Mellon, I. *Curr. Biol.* **3**, 67–69 (1993).
5. Hoeijmakers, J. H. J. *Trends Genet.* **9**, 173–177 (1993).
6. Hoeijmakers, J. H. J. *Trends Genet.* (in the press).
7. Vermeulen, W., Jaeken, J., Jaspers, N. G. J., Bootsma, D. & Hoeijmakers, J. H. J. *Am. J. hum. Genet.* (in the press).
8. Naumovski, I. & Friedberg, E. C. *Proc. natn. Acad. Sci. U.S.A.* **80**, 4818–4821 (1983).
9. Higgins, D. R. *et al. Proc. natn. Acad. Sci. U.S.A.* **80**, 5680–5684 (1983).
10. Gulyas, K. D. & Donahue, T. F. *Cell* **69**, 1031–1042 (1992).
11. Park, E. *et al. Proc. natn. Acad. Sci. U.S.A.* **89**, 11416–11420 (1992).
12. Schaeffer, L. *et al.* Science **260**, 58–63 (1993).
13. Weeda, G. *et al. Cell* **62**, 777–791 (1990).
14. Mounkes, L. C., Jones, R. S., Liang, B.-C., Gelbart, W. & Fuller, M. T. *Cell* **71**, 925–937 (1992).
15. Yoon, H. *et al. Genes Dev.* **6**, 2463–2477 (1992).
16. Shivji, N. K. K., Kenny, M. K. & Wood, R. D. *Cell* **69**, 367–374 (1992).
17. Schiestl, R. H. & Prakash, S. *Molec. cell. Biol.* **10**, 2485–2491 (1990).

© 1993 Nature Publishing Group