Collagen genes and proteins in osteogenesis imperfecta

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SUMMARY Type I collagen is a heteropolymer of α1(I) and α2(I) chains, each of which is a separate product of genes localised to chromosomes 17 and 7 respectively. Molecular defects of type I collagen produce a group of inherited disorders of connective tissue primarily affecting bones, which are easily broken and collagen depleted (osteogenesis imperfecta). Sillence classifies these diseases into four groups, two of which are autosomal dominant and relatively mild, the others being either genetic lethals or responsible for very severe progressive disease. Here we describe two specific molecular abnormalities of type I collagen. One, a cysteine substitution in α1(I) collagen, causes a mild Sillence type I disease, the other, a four base deletion in the C terminal extension of α2(I) collagen, causes progressive Sillence type III disease in the homozygously affected patient and mild premature osteoporosis in his clinically symptomless parents. We have briefly reviewed a variety of other similar mutations causing various OI syndromes, which are tabulated, including various helical and non-helical deletions and a variety of structural protein changes. Several restriction fragment length polymorphisms for α2(I) and α1(II) collagens have also been described, and 5' EcoRI and 3' MspI polymorphisms for α2(I) collagen segregate with Sillence type IV OI.

Modern recombinant DNA technology combined with protein chemistry provides a powerful means of understanding single gene disorders. The best known application of this approach to date has been to the molecular pathology of the haemoglobinopathies. The spectrum of genetic mechanisms responsible for these diseases includes single base mutations, deletions and insertions, fusion genes, chain termination mutations, premature termination, splice mutations, and various regulatory mutations.1-3

Recent spectacular advances in the molecular biology of interstitial collagen genes now allow a similar approach to inherited collagen mutations in a variety of human diseases. Here we describe how this approach has worked in the family of inherited diseases chiefly characterised by a hereditary propensity to fracture bones from minimal injury—osteogenesis imperfecta.

Collagen genes and proteins

At least seven collagen proteins coded by 11 genes are already fully documented but 10 proteins with 16 genes are likely. The genes are non-allelic and some collagens are the product of more than one gene. In general there are classical and atypical collagen proteins. The former, better called the interstitial collagens, include types I, II, III, and V.4,5 These are widely distributed in a variety of scaffolding and supporting tissues including skin, bone, and tendon (type I), cartilage (type II), arteries, veins, pleuroperitoneal linings, and skin (type III) collagens. In addition, type I collagen also occurs in skin and blood vessels and type V is also present in skin, blood vessels, and to a limited extent in bones. The other minor collagen includes type IV,6 specific for basement membranes, possibly with different types in skin, lung, and glomerular basement membranes, other minor types including types VI,7 VII,8 and VIII,9 which are blood vessel associated, and type IX10 which includes the minority cartilage components.

Structural composition of interstitial collagens

The interstitial collagens are the most abundant members of this protein family and are virtually the only collagens contained in bone and therefore relevant to osteogenesis imperfecta.
All have a regular order and gross structural similarities sharing C and N terminal non-helical extensions which have inter- and intra-chain disulphide bonds. These regions are excised by specific N and C terminal peptidases before the head to toe assembly of individual collagen triple helices to form the final mature collagen fibrils. These then pack in a characteristic one-quarter staggered pattern, which appears in longitudinal section as a regular banded cross striation.

Intermolecular cross linking occurs between specific overlapping peptide regions of the interstitial molecules, and mutations of this region could certainly produce significant disease, as could abnormalities within the procollagen extension peptides which contain globular non-helical and helical sequences at the N terminus and non-helical extensions at the C terminus. The C propeptide also contains an asparagine residue which is later mannosylated. The extension peptides are crucial to secretion of the proteins and their correct assembly into the final mature fibrils.

The amino sequence of these proteins is highly conserved and is really a repeating polymer of general formula (Gly XY)$_n$ where X and Y are often proline and lysine respectively. These latter residues are usually hydroxylated by specific proline and lysine hydroxylases and this stabilises the triple helix which would otherwise melt below normal body temperatures. Other modifications include an excess of hydrophobic side chains ($\alpha$2(I), $\alpha$1(IV), and $\alpha$1(V) chains) and cysteine residues which form and stabilise interchain disulphide bands in $\alpha$1(III) and $\alpha$1(IV) chains. Presumably these modifications stabilise and strengthen the collagen triple helix and have been highly conserved in evolution. Conversely, point mutations or other structural alterations produce instability of these regions and also very probably specific human diseases.

Collagen genes

The rapid advances in human recombinant DNA technology in the past five or six years has allowed the cloning and sequencing of numerous collagen and other structural genes. cDNA clones from collagen mRNA enabled $\alpha$1(I) and $\alpha$2(I) collagen genes from sheep and chick to be quickly isolated. As expected, these have non-coding introns separating the coding exons and the chicken $\alpha$2 gene proves to have more than 50 introns with exon sizes which are always multiples of nine base pairs, the most common being 54 base pairs. This reflects a fundamental three amino acid Gly XY unit coded by nine base pairs with an ancestral unit of six such repeats to give a 54 base pair 18 amino acid sequence. Subsequently, various other human and animal interstitial collagen genes have been isolated and sequenced, and usually cDNA clones have been used for screening human or other mammalian libraries for the relevant genomic sequences.

There is always nearly 5 kb of coding sequences in genes ranging from 18 to 35 kb. The organisation of the 3' ends of the various interstitial genes is also highly conserved. Exon 1 codes for the C terminal 48 amino acids (and the 3' untranslated region). Exon 2 contains sequences coding for the carbohydrate attachment site and is closely conserved between particular collagen types like I, II, and III. Specific collagen types are also conserved between various animal species. Similarly, exon 3 codes for the intramolecular cysteines and exon 4 the junction of the C propeptide telopeptide and the beginning of the helix. The chromosomal locations of the various interstitial genes have also been identified. Thus, $\alpha$1(I) is on chromosome 17, pro $\alpha$2(I) is on...

FIG 1 Close up of longitudinal sections of normal (a) and OI (b) bones. The bony trabeculae (arrowed) are reduced in size in OI bones compared with normal.
sometimes minor disturbances at the cartilage-bone interface of the epiphyseal plates, which often show irregularity and relative depletion of the normal cartilage palisades (fig 2). Additionally there are deficiencies of both peripheral cortical bone and the more spongy perimedullary trabecular bone which is sparse and deficient in osteoid matrix, although properly calcified. Since the severer forms of disease affect long bones, lacunar cartilage cells of the epiphyseal plate may also sometimes be faulty as well as the nearby osteoblasts, which are the principal bone forming cells.

Clinically, osteogenesis imperfecta is not a single entity, but is a family of similar disorders sharing a tendency to brittle, easily fractured, collagen depleted bones. Although a disease of considerable antiquity, recognised in Egyptian Mummies and in pre-Norman Scandinavian Britons, the disease has several different clinical patterns. This was recognised early from the descriptions of Looser, who in 1906 described differences in the early onset (congenital) and late onset (tarda) forms. Sillence has established beyond any doubt the clinical and genetic heterogeneity of the disease (table 1). In the main he recognised four types, two of which are relatively mild and autosomal dominant, and two of which are often autosomal recessive and severe or even lethal. Sillence type I disease with at least three subgroups is clearly autosomal dominant with multiple affected generations, blue sclerae, deafness, and short stature. In the main, bones break when the child begins to walk, deafness is common, and there may or may not be dentinogenesis imperfecta which breeds true in any given family. Although the disease does not usually occur at birth there are exceptions. Additionally, although the disease is fairly uniform within families, occasional very much more severely affected persons occur, possibly because of a second (different) mutation. Sillence type IV disease is similar to type I except that the sclerae are white rather than blue. Again, true breeding varieties with and without dentinogenesis occur and, like type I disease, the frequency of fractures drops dramatically at puberty although it may increase again in menopausal women.

Silence type II disease is a lethal, short limbed dwarfism which may be fatal in utero, at birth, or perinatally. The commonest cause of perinatal death is respiratory infection from lung restriction secondary to fractured ribs (fig 3a, b). Even if infancy is survived, it is rare for affected children to live beyond the age of 5 years. Although Sillence recognises several types, a reasonable classification is into broad and thin boned types. Broad boned disease may be confined to the limbs but can also affect the ribs. Different patterns of rib fractures

Clinical classification of osteogenesis imperfecta

Osteogenesis imperfecta is a group of inherited collagen diseases in which bones are abnormally fragile, collagen depleted, and osteoporotic. Van Gieson staining shows a marked depletion of collagenous material which is also distorted and badly organised compared with normal bones (fig 1a, b). In the worst forms of the disease there are

![Figure 2](http://jmg.bmj.com/)

**FIG 2.** Epiphyseal plates of normal (a) and OI (b) long bones. By comparison with normal the OI cartilage cell palisades are sparser and more poorly organised. The accompanying bony trabeculae are less well developed in OI bone.

chromosome 7, types III and V collagens are on chromosome 2, α1(II) collagen is on chromosome 12, and α1(IV) is on chromosome 13. The reason for such dispersion is completely unclear but has precedents in other proteins, such as the globin clusters in which the human α gene cluster consists of embryonic and duplicated α1 and α2 genes on chromosome 16 and the α, α sequence on the short arm of chromosome 11.
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TABLE 1 Osteogenesis imperfecta: classification modified after Sillence.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Inheritance</th>
<th>Type</th>
</tr>
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<tbody>
<tr>
<td>Mild disease: blue sclerae; deafness; improves at adolescence:</td>
<td>Autosomal dominant</td>
<td>I</td>
</tr>
<tr>
<td>short stature; variable penetrance; (a) normal teeth,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) dentinogenesis, (c) scatty fractures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethal short limbed dwarfism; fatal in utero or perinatal life:</td>
<td>Autosomal recessive, may be</td>
<td>II</td>
</tr>
<tr>
<td>several types: (a) broad bones, broad ribs, (b) broad bones,</td>
<td>autosomal dominant; genetic</td>
<td></td>
</tr>
<tr>
<td>thin or beaded ribs, (c) thin or normal bones</td>
<td>compounds with double heterozygosity</td>
<td></td>
</tr>
<tr>
<td>Severe fractures in utero or early childhood; blue sclerae;</td>
<td>Autosomal recessive</td>
<td>III</td>
</tr>
<tr>
<td>normal teeth; progressive course; popcorn deformities of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lower femur and upper tibia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similar to type I except sclerae white; dentinogenesis or</td>
<td>Autosomal dominant</td>
<td>IV</td>
</tr>
<tr>
<td>normal teeth; thin boned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loose jointedness and features of Ehlers-Danlos syndrome</td>
<td>Variable</td>
<td>V</td>
</tr>
<tr>
<td>associated with OI; usually normal stature; minor fractures or</td>
<td></td>
<td></td>
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<tr>
<td>osteoporosis</td>
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distinguish various types (fig 3a, b), but biochemical investigation will ultimately test the validity of this classification.

Silence type III disease is also called the progressively deforming disease; fractures occur at or shortly after birth and continue throughout childhood and adolescence if the child survives. Grossly distorted limbs seem to be the rule and types with normal and distorted facies can be recognised (fig 4a, b). There may be overlap with Silence type II OI and some thin and broad boned survivors look very like Silence type II disease (in early childhood). There is considerable controversy as to the genetics of this variant. Although several sibs in some families and proven heterozygote parents in other families are certain indications of autosomal recessive inheritance in some instances at least, in the main population surveys do not show a sufficient number of affected subjects within the families of proven index patients. Possible explanations include a sizeable proportion of new dominant mutations, a high frequency of (undetected) miscarriages shortly after conception, and the reluctance (conscious or otherwise) of parents with one severely crippled child to run the risk, however small, of another affected child.

Molecular mechanisms of disease in osteogenesis imperfecta

As illustrated above, collagen is very obviously depleted in histological sections of long bones in osteogenesis imperfecta. Since type I collagen (α1(1)2α2) is the predominant protein of bones, it seems a logical conclusion that molecular abnorma-

FIG 3 (a, b, c) Chest x-rays from various Silence type II variants showing thickened, beaded, and normal ribbed patterns. Beaded and thickened ribs can both be accompanied by widened, crumpled upper and lower limb bones.
bies of genes coding for this substance might be faulty in this disease. In this section we illustrate this point by describing two specific abnormalities of type I collagen associated with OI. The first, a mild disease, has an amino acid substitution in the \( \alpha_1(I) \) protein, and the second, a severe form of OI, has completely absent collagen \( \alpha_2 \) chains from OI bones because of a rather subtle mutation in the \( \alpha_2(I) \) procollagen gene.

**FIG 4 (a, b)** Sillence type III OI showing normal and abnormal facies. Both types are associated with severely distorted and progressive limb fractures.

**AN \( \alpha(I) \) SUBSTITUTION CAUSES MILD Autosomal Dominant Sillence Type I OI**

This disease presented as a series of badly healed fractures to the left tibia of a 9 year old male (fig 5). He fractured his right tibia quite justifiably from a fall from a climbing frame but subsequently had broken his left tibia which then repeatedly fractured through the union. Eventually, healing was achieved only by rodding of the affected bone. At this operation the surgeon noted that the abnormal bone was unusually hard but also brittle. We were provided with bone and skin biopsies from which we successfully cultured skin and periosteal fibroblasts. Using radiolabelled \(^{14}\)C glycine and proline we then examined the cultured collagens by column chromatography and polyacrylamide gel electrophoresis (figs 6 and 7a, b). His mother, who had premature lumbar spinal osteoporosis (fig 5c) and a history of childhood fractures of small hand bones, was also studied. Column chromatography of pepsinised radiolabelled collagens showed an unexpected shoulder in the position of \( \alpha_1(I) \) collagen. Polyacrylamide slab gel electrophoresis showed an extra disulphide linked dimer in addition to normal \( \alpha_1(I) \), which could be reduced to monomeric form by mercaptoethanol (fig 7a). This was clearly separate from \( \alpha_1(III) \) collagen, which is normally disulphide linked, in contrast to normal \( \alpha_1(I) \) collagen, which never is. Then we fingerprinted the mutant molecule.

**FIG 5** Clinical features of Sillence type I OI child with collagen \( \alpha(I) \) cysteine substitution. Note (a) normal face and teeth, (b) tibial sclerosis with a nicked fracture through abnormally united callus, and (c) premature lumbar osteoporosis of his clinically affected mother.
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A SMALL MUTATION OF THE α2(I) COLLAGEN GENE CAUSES SILLENCE TYPE III OI

In this example, the disease presented at 5 weeks of age with recurrent fracturing of various long bones. Although at first the child was suspected to have been battered, the fractures continued while in hospital and subsequently fracturing has occurred several times a month. When first examined by us at 21 months of age there was already quite obvious bowing and deformity of the long bones, although the face and skull were relatively normal. The teeth appeared normal at this stage. Subsequently there were persistent and frequent fractures so that by the age of 5 years the upper and lower limbs were severely distorted and deformed. Fracturing has been so frequent that orthopaedic setting and plastering has never been a practical possibility and the fractured regions are merely bandaged firmly. The x-rays exclude the broad boned, lethal form of OI and early ones showed osteoporotic long bones with multiple healed and recent fractures. Subsequent x-rays have shown severe osteoporosis and extreme alteration of the long bones with pseudoarthroses of the humerus and an expanded 'popcorn' deformity of the lower femur and upper tibia (fig 8). The trunk and face are relatively normal, although the skin is soft and hyperextensible and the joints markedly hypermobile (fig 9).

Family history

There is parental consanguinity as the parents, who live in the Hartz mountains of northern Germany, are third cousins. Clinically they look normal but have early premature osteoporosis of the lumbar spine.

Biochemical investigations

Radiolabelled profiles of cultured skin fibroblast using a variety of double two dimensional electrophoresis. Mercaptoethanol reduction in both dimensions showed the new band on a diagonal which was lacking in normal tissues. When the radiolabelled proteins were run in the first dimension by molecular weight after conversion into their constituent cyanogen bromide peptides, and then run in the second dimension, either mercaptoethanol reduced or unreduced (fig 7c), the unreduced disulphide linked dimer in the extra band was converted to a peptide in the position of collagen peptide α1(CB6) in the second dimension. This conclusively localises the mutation to the C terminal end of the collagen helix. Three possible mutations will create a cysteine residue in a collagen gene where none existed before. Glycine, arginine, or serine can all mutate by a single base substitution. For experimental and clinical reasons we do not expect a glycine to cysteine substitution in our patient. Firstly, Steinmann et al have conclusively shown just such a mutation in a patient with classical, lethal, broad boned Sillence type II OI. In this patient the collagen melted abnormally easily and they have shown (in collaboration) a glycine to cysteine substitution by molecular cloning of the mutant gene. In contrast, our patient's melting curves are normal and, unless Steinmann's patient contains a second mutation which alters the melting profile, we do not expect this to be the substitution in our patient who has a mild, non-lethal disease. Cloning and sequencing of the mutant protein should therefore show an arginine or serine substitution in this instance. Presumably, the appearance of cysteine in a protein helix normally lacking it subtly alters the properties of the molecule in such a way as to allow the extra hardness but normal brittleness to recur.
medium showed a surprising finding. Collagen α2 chains were absent from the medium proteins of the affected patient (fig 10). Furthermore, his parents were intermediate in this respect and produced between one-third and one-half of the expected α2 chains. We also proved by cyanogen bromide peptide mapping that the α2(I) collagen product was absent and not migrating anomalously, and showed that tissues from the patient were deficient (depleted) in this substance, so that an artefact of culture could be confidently excluded.

Next we collaborated with Dr Darwin Prockop and Dr Jeanne Myers of the Rutgers University Medical School, New Jersey, to identify the specific
molecular defect responsible for this disease. First, we showed that sufficiently rapid and heavily labelled cells produced small amounts of collagen α2 chains which occurred only within the cell layer and did not become exported into the surrounding medium. This explained why α2 collagen was absent from normal tissues. Secondly, Northern and Southern blotting experiments showed no major deletion of the α2 gene. We then suspected that the C terminal propeptide might be altered so as to inhibit the incorporation of α2 chains with the mature type I collagen triple helix. We already had evidence that instead of the heteropolymeric α1(II)α2 chains, the affected child produced significant quantities of the usually rare α1(II), so called α(I) trimer. To detect a small mutation of the 3' end of the gene coding for this region, Dr Leon Dickson from Dr Prockop's laboratory constructed a 687 base pair gene fragment which he and Dr Myers then used in S1 blotting experiments with cDNA (gene) RNA hybrid experiments. By using S1 nuclease digestion of 3' and 5' labelled RNA/cDNA hybrids, a 12 base deletion was detected in the 3' propeptide coding region (fig 11). Subsequent cloning and sequencing of this mutation have shown a four base pair deletion (fig 12) which completely alters the phase of the last 34 amino acids of the α2 C propeptide region. Because of this, assembly into the normal type I helix is impossible and the α2 gene
FIG 11  
SI nuclease mapping of mRNA from patient (P) and parents (M+F) compared with control (C1) using 3' and 5' labelled cDNA to 687 base pair C terminal fragment. Here the affected child shows only a 480 base pair protected fragment when labelled 3' and a 195 base pair fragment when labelled 5' (not shown). Overall the child's mRNA is protected by 675 base pairs instead of 687 (12 bases short). The parents are heterozygous for 480 and 687 base pair protected fragments.

product is intracellularly degraded (and never appears extracellularly). Prenatal diagnosis of this disease would be possible by fibroblast culture of a fetoscopic biopsy and examination for α2 protein chains. Better would be Southern blotting of polyacrylamide Southern blots using the 687 bp fragment as a probe.

Other type I collagen mutations

Comparatively rapid progress has been made in other forms of osteogenesis imperfecta and a variety of type I collagen mutations has been identified by several different workers. We have correlated the clinical pattern of disease (Sillence type) with the biochemical and genetic abnormalities in table 2. In general, specific abnormalities include small deletions, amino acid substitutions, an apparent amino acid insertion, protein over-hydroxylation of lysyl residues, and a variety of slowly migrating α1(I) and α2(I) collagen chains. Other defects are certain and will probably include many of the full range of mutations already mentioned earlier as applying to the haemoglobinopathies1-3 (table 2).

Alternative (complementary) approaches

The evidence so far available (and summarised above) suggests that the causes of the different types of OI form no coherent pattern but are a series of individual mutations. As such they do not have general applications to the disease as a whole,
although of course they are highly relevant to the individual families concerned. The alternative method of identifying causes of mutated collagen genes is to search for random restriction fragment length polymorphisms near or within the gene, which can then be shown to be in marked linkage disequilibrium with the relevant collagen gene. This approach has been very successful in globin gene pathology, especially in the β globin gene related cluster on chromosome 11, of which the HpaI 13 kb associated sickle gene polymorphism is an excellent example. Another good example is the polymorphism at the haemophilia B locus. As far as OI is concerned, α1(I), α2(I), and α1(II) linked RFLPs would all be useful for the diagnosis of autosomal dominant disease. In principle, a similar approach could be used (in much smaller pedigrees and therefore with lesser accuracy) for autosomal recessive families.

**COLLAGEN α2(I) RFLP**

Two intragenic RFLPs have been identified for the human collagen α2 gene by Tsipouras and his colleagues. One is an EcoRI fragment in the middle of the 5' end of the gene and the other is an MspI polymorphism localised to intron 6 at the opposite 3' end. The EcoRI polymorphism generates an extra site in a fragment which is normally 13 kb which, with an added site, generates 9-5 and 3-5 kb fragments (fig 13a, b). The MspI polymorphism at the opposite end of the gene normally generates a 2-1 kb fragment, which in the presence of an added site becomes 1-6 and 0-5, giving 2-1, 1-6, and 0-5 kb fragments in heterozygotes; this has also been described by others. The allelic frequencies are EcoRI (no site) 68%, MspI (no site) 14%. Both

![Fig 13](http://jmg.bmj.com/ on July 13, 2023 by guest. Protected by copyright.)
these polymorphisms have proved informative in Sillence type IV OI. A typical example of the segregation of the EcoRI site is shown in fig 12, in which the presence of the extra restriction site segregates with the gene for type IV OI. Two new polymorphic markers using EcoRI and BglII with this gene have also just been published.56 No examples of linkage to Sillence type I OI have so far been established. suggesting that perhaps non-α2 chain mutations are responsible for this disease and implicating the α2 chain in the white eyed Sillence type IV variant.

**Collagen α1(I) polymorphisms**

Cartilage collagen is an interstitial collagen closely related to types I and III collagens. Although it has never previously been implicated in OI, recent evidence suggests that it might be. We recently described a 300 bp deletion in a type I like gene in two Caucasian and two Asian patients with lethal OI congenita (fig 13a).57 Subsequently, Cheah et al localised the deletion to the 3' non-coding region of the gene and also recognised that the gene is localised to chromosome 1258 and is the gene for α1(II)59 (in contrast to the α1(I) and α2(I) genes on chromosomes 17 and 7 respectively). Gene sequencing and Northern hybridisation confirmed the gene to be α1(II) collagen which was simultaneously confirmed by Sangiorgi et al.59 Since then, we have observed several variations of this deletion with small and large deletions and also probably insertions in this region (fig 13b).60 Sykes and his colleagues61 62 in studies following our original observations have shown a frequency of these deletions close to 20% in certain Asian and African populations but have observed it in very few Caucasians (none in our case). The presence of the deletion in broad boned lethal OI Caucasian families is unexplained but reliably detects the OI gene if present in this racial group. In Asian or West Indian families the deletion does in any case have a 20% frequency. Time will prove whether this deletion segregates with OI in that population and also whether the increased frequency of the deletion is accompanied by a markedly increased frequency of lethal congenital OI in that population. (These data are not at present available.) Alternatively, only some of this family of deletions are associated with disease states or the deletions may in all cases be irrelevant to the disease. Cloning, sequencing, and transient expression experiments will ultimately resolve these speculations but there is a strong implication that cartilage collagen genes and proteins may have a significant role in the generation of the more severe and lethal forms of hereditary brittle bone disease.

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