Synthesis and Conservation of Ribosomal Proteins during Compensatory Renal Hypertrophy

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The rate of synthesis of ribosomal proteins was investigated as an index of the rate of production of ribosomes in mouse kidney during the first few days after contralateral nephrectomy. Compensatory renal hypertrophy was not associated with a major increase in the synthetic rate of ribosomal proteins and rRNA. Instead, the ratio of the rate of ribosomal-protein synthesis to that of total protein synthesis remained nearly constant. The conformation of glutaraldehyde-fixed ribosomes and ribosomal subunits was unchanged. During the early stages of compensatory renal hypertrophy the accretion of rRNA is due largely to conservation of ribosomes that would otherwise have been degraded.

Three proposals (Hill, 1975; Melvin et al., 1976; Cortes et al., 1976) have been advanced to account for the 20–40% increment in average cellular content of rRNA in the rodent kidney remaining in situ 2–28 days after contralateral nephrectomy (Halliburton & Thomson, 1965; Threlfall et al., 1967; Malt & Lemaitre, 1968; Bucher & Malt, 1971; Dicker & Shirley, 1971; Shirley, 1976). Our view is that a decreased rate of degradation (conservation) of mature rRNA is sufficient to account for most of the increment during the first 2 days and that an increased rate of synthesis becomes progressively more important thereafter (Hill et al., 1974; Melvin et al., 1976). These processes lead to the new steady state with both increased rates of rRNA synthesis and degradation and an expanded pool of ribosomes, restoring the rate of turnover to that of normal kidneys (Malt & Lemaitre, 1968). Hill (1975) states that conservation of rRNA occurs by diminishing the wastage of precursor rRNA. To the contrary, Cortes et al. (1976) describe an increased rate of renal synthesis beginning shortly after contralateral nephrectomy sufficient to account for the increment in rRNA.

Since both we (Melvin et al., 1976) and Cortes et al. (1976) derived opposite conclusions about the rates of rRNA synthesis from measurements of the rates at which radiolabelled UTP enters RNA, correction for possible changes in the nucleotide precursor pool must be more complex than would appear. We have therefore investigated the rate of synthesis of ribosomal proteins as an index of the rate of production of ribosomes during compensatory renal hypertrophy. We find that an increased rate of synthesis of ribosomal proteins is not a major contributor to the initial rate of accumulation of ribosomes.

Materials and Methods

Animals

Male Charles River mice (40 days old) were subjected to unilateral nephrectomy (Malt & Lemaitre, 1969). To avoid artifact in uptake of precursor produced by trauma, kidneys were not touched during sham nephrectomy (Malamud et al., 1972). Radiochemicals were given by intraperitoneal injection.

Specific radioactivity of the leucine pool

Kidneys were frozen in liquid nitrogen after removal and were later analysed in batches after storage at −20°C. Leucine pools were not changed by these conditions. Each kidney was thawed and homogenized in 3 ml of ice-cold water. Protein from a 1 ml sample of homogenate containing about 35 mg of protein was precipitated by addition of 1 ml of cold 10% (w/w) trichloroacetic acid and from another 1 ml sample by 4 ml of 1.2% (w/v) picric acid.

The trichloroacetic acid mixture was heated at 90°C for 20 min to solubilize radioactive aminocacyl-tRNA, and the precipitate was washed twice with
5% trichloroacetic acid before being dissolved in 6 ml of 1 M NaOH at 60°C for 60 min. Protein content was measured by the method of Lowry et al. (1951), with bovine serum albumin as standard, and radioactivity of the basic solution was counted at 30% efficiency in Omnifluor (New England Nuclear Corp.).

The picric acid supernatant (27000 g for 15 min) was washed twice with 2 ml of 0.1 M HCl. After passage of the combined supernatant through a column (1 cm x 2 cm) of Dowex 2 (X8), the eluate was freeze-dried and redissolved in 2.5 ml of 0.2 M sodium citrate buffer (pH 2.2). This solution was used for amino acid analysis of a Beckman 120C analyser; the leucine peak was split for determinations of leucine content and radioactivity. Fresh L-[4,5-3H]leucine added to the solution was recovered with 98% efficiency.

**Specific radioactivity of proteins**

Ribosomal subunits were isolated from a post-mitochondrial supernatant of four kidneys homogenized in 2 ml of cold RSB buffer (0.01 M-Tris/HCl, pH 7.4 at 20°C, 0.01 M-NaCl, 0.0015 M-MgCl₂). The supernatant after centrifugation at 15000 g for 10 min and adjustment to 10 mM-EDTA was layered on a linear gradient of 15–30% sucrose in NEB-0.25 buffer (0.01 M-Tris/HCl, pH 7.4 at 20°C, 0.25 M-NaCl, 0.01 M-EDTA), centrifuged, and fractionated as described in Fig. 1. Fractions representing the peaks of the large and small ribosomal subunits were separately pooled.

Alternatively, ribosomal subunits were isolated from a polyribosomal pellet. Post-mitochondrial supernatant was prepared from four kidneys homogenized in 6 ml of cold RSB buffer with a Dounce homogenizer. The entire supernatant was layered over a discontinuous gradient of 1.5 ml of 1.5 M-sucrose over 2.5 ml of 2.5 M-sucrose (each in 0.01 M-Tris/HCl, pH 7.4 at 20°C, 0.25 M-NaCl, 0.05 M-MgCl₂); polyribosomes were deposited by centrifugation (50000 rev./min, Beckman type 65 rotor, 4 h). The pellet was dissolved in 1 ml of NEB buffer (0.01 M-Tris/HCl, pH 7.4 at 20°C, 0.01 M-NaCl, 0.01 M-EDTA) for layering on 36 ml 15–30% linear sucrose gradients in NEB buffer. Approx. 30 fractions were collected after centrifugation at 25000 rev./min for 16 h in a Beckman type SW27 rotor and scanned at 260 nm. Centrifugation under the same conditions through 0.5 M-NaCl was also employed on occasion.

Pooled ribosomal subunits from either means of preparation were further purified by precipitation with 2 vol. of cold ethanol and were stored at −20°C overnight. Precipitates collected at 15000 g for 15 min were dissolved in 4 ml of 0.3 M NaOH for digestion at 37°C for 1 h. Protein was precipitated after cooling by addition of 0.75 ml of cold 2.4 M-

\[ \text{HClO}_4, \text{and protein content and radioactivity were measured. The A}_{260} \text{ of RNA in the supernatant and its radioactivity were assayed.} \]

**Isopycnic banding of ribosomal subunits**

A modification (Pederson & Kumar, 1971) of the method of Baltimore & Huang (1968) was used.

**Radiochemicals**

All products were from New England Nuclear Corp., Boston, MA, U.S.A. Specific radioactivities were: L-[4,5-3H]leucine, 33 Ci/mmol; L-[methyl-3H]methionine, 4 Ci/mmol; [5-3H]orotic acid, 11.1 Ci/mmol; [14C]orotic acid, 55.2 mCi/mmol.

**Results**

**Labelling of proteins**

Because amino acids in general are rapidly transferred from peritubular plasma into tubular cells, uptake of leucine was prompt (Fig. 2). In three experiments the half-life of the rapid-decay phase of the disappearance of leucine was 4.5 min, and protein was rapidly labelled. Therefore pulse-chase conditions prevailed, permitting the progress of ribosomal subunits, assembled in the nucleus, to be traced into the cytoplasm. We obtained similar
results using arginine and methionine as precursors, and they have been reported by others using lysine (Ausiello et al., 1972). Neither we nor Ausiello et al. (1972) were able to correct for amino acids present in collecting ducts, in molecular species other than proteins and in incomplete proteins.

From about 1 to 10h, incorporation of leucine into protein was equivalent in the nephrectomized and the sham-nephrectomized mice, but was about 30% greater than in normal mice at 4h ($P<0.05$) and 12h ($P<0.01$) (Fig. 3). After 12h, incorporation was greater into protein of kidneys of mice with unilateral nephrectomies. Table 1 suggests that increases in the specific radioactivities of the leucine pool could account for enhanced labelling of protein in the nephrectomized and sham-nephrectomized groups, in keeping with the increased specific radioactivity found for the pool of a non-metabolized amino acid ($\alpha$-aminobutyric acid) in similar circumstances (Ross et al., 1973).

Assays of 26 free amino acids in kidneys harvested 1, 2, 4, 7 and 24 days after contralateral nephrectomy showed no change in amino acid composition as compared with kidneys from sham-nephrectomized and normal mice. These data have been deposited with the National Auxiliary Publication Service (obtainable by requesting Document No. 03619 from the National Auxiliary Publication Service, c/o Microfiche Publications, Grand Central Station, New York, NY 10017, U.S.A., and remitting $5.00; outside U.S.A. add postage of $3.00 for photocopy or $1.00 for microfiche).

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**Table 1. Leucine pools in kidney**

Specific radioactivities were determined 5min after injection of 5$\mu$Ci of L-[4,5-$^{3}$H]-leucine, as described in the Materials and Methods section.

<table>
<thead>
<tr>
<th>Time after operation (h)</th>
<th>Leucine pool (d.p.m./$\mu$g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17800</td>
</tr>
<tr>
<td></td>
<td>16600</td>
</tr>
<tr>
<td></td>
<td>19800</td>
</tr>
<tr>
<td>12</td>
<td>21500</td>
</tr>
<tr>
<td>32</td>
<td>26400</td>
</tr>
<tr>
<td>48</td>
<td>33000</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Unilateral nephrectomy</td>
<td></td>
</tr>
<tr>
<td>Sham operation</td>
<td></td>
</tr>
</tbody>
</table>
Labelling of ribosomal proteins

Unilateral nephrectomy and sham nephrectomy each increased the labelling of ribosomal proteins as compared with labelling in normal mice, but not when results were corrected for labelling of total renal protein (Table 2). Mixing experiments involving a $^3$H-labelled post-ribosomal supernatant and unlabelled post-mitochondrial supernatant showed no detectable adventitial contamination of ribosomal subunits.

Appearance of ribosomal subunits in polyribosomes

To check on possible cross-contamination and to confirm that only structural proteins were being examined, ribosomal subunits from purified polyribosomes were analysed. As expected, the 30S subunit became associated with polyribosomes before the 50S subunit (Warner, 1966; Malt & Miller, 1967; Warner et al., 1973). (Fig. 4). The time required for all labelled subunits to be associated with polyribosomes was 2 h; this delay before appearance of labelled proteins in polyribosomes assured freedom from appreciable contamination by proteins of the supernatant.

Labelling with methionine

Methionine labelled the renal protein faster and

<table>
<thead>
<tr>
<th>Time after operation (h)</th>
<th>4</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>50S subunit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral nephrectomy</td>
<td>11.7 ± 1.0 (8)</td>
<td>12.8 ± 0.13 (2)</td>
<td>15.3</td>
</tr>
<tr>
<td>Sham operation</td>
<td>12.0 ± 1.1 (8)</td>
<td>10.6 ± 0.2 (2)</td>
<td>9.3</td>
</tr>
<tr>
<td>Normal</td>
<td>9.3 ± 0.7 (6)</td>
<td>8.2 ± 0.2 (2)</td>
<td>6.1</td>
</tr>
<tr>
<td>30S subunit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral nephrectomy</td>
<td>11.0 ± 1.2 (8)</td>
<td>11.0 ± 0.1 (2)</td>
<td>13.1</td>
</tr>
<tr>
<td>Sham operation</td>
<td>11.1 ± 1.1 (8)</td>
<td>10.1 ± 0.1 (2)</td>
<td>7.8</td>
</tr>
<tr>
<td>Normal</td>
<td>8.4 ± 1.0 (6)</td>
<td>7.3 ± 0.2 (2)</td>
<td>5.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time after operation (h)</th>
<th>4</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>50S subunit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral nephrectomy</td>
<td>156 ± 9 (8)</td>
<td>132 ± 0 (2)</td>
<td>148</td>
</tr>
<tr>
<td>Sham operation</td>
<td>150 ± 8 (8)</td>
<td>120 ± 4 (2)</td>
<td>137</td>
</tr>
<tr>
<td>Normal</td>
<td>135 ± 9 (6)</td>
<td>135 ± 3 (2)</td>
<td>136</td>
</tr>
<tr>
<td>30S subunit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral nephrectomy</td>
<td>141 ± 5 (8)</td>
<td>114 ± 2 (2)</td>
<td>128</td>
</tr>
<tr>
<td>Sham operation</td>
<td>136 ± 5 (8)</td>
<td>114 ± 1 (2)</td>
<td>116</td>
</tr>
<tr>
<td>Normal</td>
<td>135 ± 3 (6)</td>
<td>120 ± 3 (2)</td>
<td>117</td>
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</tbody>
</table>
more intensely than did leucine. In addition, methionine labelled both ribosomal proteins and rRNA. When ribosomal subunits from polyribosomes were examined on sucrose gradients after having been labelled with methionine for 2h, much radioactivity appeared at the top of the gradients, even after purification through 0.25 M-NaCl. However, there was no change in labelling of ribosomal proteins or of rRNA with methionine for 2h at times between 1 and 6 days after unilateral nephrectomy or sham-nephrectomy (Table 3). The material at the tops of the gradients probably represented nascent protein chains or proteins with a high rate of turnover.

**Physical characteristics of ribosomes**

Velocity-sedimentation characteristics of mixed ribosomal subunits from kidneys labelled in vivo with [3H]orotic acid or [14C]orotic acid were unchanged 24h after contralateral nephrectomy, when accumulation of ribosomes was well under way. Isopycnic banding of polyribosomes and of ribosomal subunits at the same time were likewise unchanged (Fig. 5), whether polyribosomes were prepared in 0.5 M-NaCl or in 0.25 M-NaCl. Fixation and analysis of subunits individually instead of mixed gave identical results. Densities of 1.57 g/ml for the large subunit prepared in 0.25 M-NaCl and of 1.53 g/ml for the small subunit agree broadly with values for subunits in liver (Henshaw et al., 1973). Some breakdown of the small subunit appeared after treatment with 0.5 M-NaCl, even after the subunit was fixed in glutaraldehyde.

**Discussion**

These experiments confirm previous data (Melvin et al., 1976) that an increase of the rate at which some ribosomes are produced cannot explain the accumulation of ribosomes in the remaining kidney for the first few days after unilateral nephrectomy in the mouse. At that time, the number of ribosomes per cell in the remaining kidney is increased about 10%. Since the fractional synthetic rate is about 15% per day (Melvin et al., 1976), an average increase of 60% in the rate of ribosome synthesis would be required to account for the observed accumulation of ribosomes in the first 4 days. Nonetheless, there is no change in the rate of incorporation of leucine into total protein or in the rate of incorporation of methionine into ribosomal protein or rRNA. Moreover, as corrections were made for nominal changes in the specific radioactivity of the

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**Table 3. Labelling of ribosomal subunits with methionine**

<table>
<thead>
<tr>
<th></th>
<th>10⁻¹ × Specific radioactivity of subunits</th>
<th>Specific radioactivity of subunits</th>
<th>Specific radioactivity of total protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(c.p.m./µg)</td>
<td>Protein</td>
<td>RNA</td>
</tr>
<tr>
<td><strong>Subunit</strong></td>
<td><strong>30S</strong></td>
<td><strong>50S</strong></td>
<td><strong>30S</strong></td>
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<tr>
<td>Expt. I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>101</td>
<td>72</td>
<td>55</td>
</tr>
<tr>
<td>Normal</td>
<td>102</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>Unilateral nephrectomy, 1 day</td>
<td>111</td>
<td>65</td>
<td>41</td>
</tr>
<tr>
<td>Sham operation, 1 day</td>
<td>93</td>
<td>71</td>
<td>34</td>
</tr>
<tr>
<td>Unilateral nephrectomy, 2 days</td>
<td>96</td>
<td>74</td>
<td>35</td>
</tr>
<tr>
<td>Sham operation, 2 days</td>
<td>96</td>
<td>76</td>
<td>34</td>
</tr>
<tr>
<td>Unilateral nephrectomy, 3 days</td>
<td>100</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>Sham operation, 3 days</td>
<td>87</td>
<td>59</td>
<td>32</td>
</tr>
<tr>
<td>Expt. II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>46</td>
<td>42</td>
<td>22</td>
</tr>
<tr>
<td>Normal</td>
<td>74</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>Unilateral nephrectomy, 4 days</td>
<td>85</td>
<td>65</td>
<td>32</td>
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<td>Sham operation, 4 days</td>
<td>66</td>
<td>50</td>
<td>24</td>
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<td>Unilateral nephrectomy, 6 days</td>
<td>74</td>
<td>50</td>
<td>38</td>
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<tr>
<td>Sham operation, 6 days</td>
<td>52</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>Expt. III</td>
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<tr>
<td>Unilateral nephrectomy, 12 h</td>
<td>81</td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td>Sham operation, 12 h</td>
<td>73</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>Unilateral nephrectomy, 1 day</td>
<td>109</td>
<td>78</td>
<td>44</td>
</tr>
<tr>
<td>Sham operation, 1 day</td>
<td>91</td>
<td>68</td>
<td>35</td>
</tr>
</tbody>
</table>
Polyribosomes and ribosomal subunits from mice labelled for 24 h were prepared as described in the legend to Fig. 4. After being fixed in glutaraldehyde, 0.5 ml samples were centrifuged through 5 ml CsCl gradients (p1.45–1.65) in a Beckman SW41 rotor for 24 h at 30000 rev./min at 0°C. Fractions (ten drops) were collected. (a), Polyribosomes; (b), large subunit; (c), small subunit. ○, Unilateral nephrectomy ([14C]orotic acid, 12.5 μCi/mouse); ▲, normal ([3H]orotic acid, 125 μCi/mouse). ●, Density of fractions measured by refractive index.

If the rate of protein synthesis is not accelerated, if ribosomes cannot be assembled until appropriate molar ratios of protein and RNA are available, and if there is no pool of preformed protein available for incorporation into ribosomes, the findings parallel results of our investigation of the mechanism by which the amount of renal rRNA increases after contralateral nephrectomy (Melvin et al., 1976). We recognize that in HeLa cells ribosomal proteins can be synthesized in the absence of rRNA synthesis (Warner et al., 1973; Warner, 1977).

Lessened degradation of rRNA is sufficient to account for the post-nephrectomy increment. Degradation of rRNA is slower in exponentially growing BHK cells than in growth-arrested cells (Melvin & Keir, 1978), and slower degradation of protein accounts for appreciable accumulation of proteins in other cells at low rates of division (Baxter & Stanners, 1978). Moreover, the rate of degradation of total renal proteins is also decreased after unilateral nephrectomy in the mouse (Hill & Malamud, 1974). Lessened degradation is also a mechanism by which rat liver increases its content of protein during a phase of rapid anabolism (Amlis et al., 1977) and preserves membranes during liver regeneration and neoplasia (Tauber & Reutter, 1978). It is the major mechanism by which the breast muscle of growing chicks accumulates its protein (Maruyama et al., 1978). Decreased rates of enzyme degradation accompany increased rates of enzyme synthesis in developing chick and rat liver (Paskin & Mayer, 1977).

In compensatory renal hypertrophy in the mouse, conservation of RNA at the outset does not seem to be a consequence of a detectable conformational change from additional protecting proteins, as shown in the present experiments, nor is it correlated with a decrease in the number of monomeric ribosomes (Priestley & Malt, 1969), as has been proposed for contact-inhibited chick-embryo fibroblasts (Weber, 1972). There may, however, be subtler changes in the chemistry of ribosomes during compensatory renal growth. Ribosomes from hypertrophying

leucine pool, and as the rate at which ribosomes and their subunits was unchanged, the inference is that the rate of protein synthesis itself is unchanged in the earliest phase of compensatory renal hypertrophy. Although there is evidence in the liver that the valine pools are compartmented (Mortimore et al., 1972), and in intestine that a small amount of protein can be synthesized from amino acids that have not passed through the pool (Alpers & Thier, 1972), similar phenomena were unlikely to have influenced our results appreciably.

Fig. 5. Isopycnic banding 24 h after unilateral nephrectomy

Polyribosomes and ribosomal subunits from mice labeled for 24 h were prepared as described in the legend to Fig. 4. After being fixed in glutaraldehyde, 0.5 ml samples were centrifuged through 5 ml CsCl gradients (p1.45–1.65) in a Beckman SW41 rotor for 24 h at 30000 rev./min at 0°C. Fractions (ten drops) were collected. (a), Polyribosomes; (b), large subunit; (c), small subunit. ○, Unilateral nephrectomy ([14C]orotic acid, 12.5 μCi/mouse); ▲, normal ([3H]orotic acid, 125 μCi/mouse). ●, Density of fractions measured by refractive index.

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kidneys preserve their capacity for protein synthesis on cold storage for several weeks better than do ribosomes from normal rat kidneys (Sendecki et al., 1973).

Indeed, an increase in protein synthesis should not have been expected. A maximal estimate of 10% increase in wet mass of the mouse kidney undergoing compensatory hypertrophy for 24 h corresponds to a 2.5% increase in dry weight (protein content) at that time (Malt & Lemaitre, 1968). In rats the increment in dry mass is about 3% (Halliburton & Thomson, 1965; Janicki & Argyris, 1969). A reported increase of 20–30% in labelling of rat renal protein 1 day after contralateral nephrectomy (Tomashesky & Tannebaum, 1969) may be discounted when corrected for the increase in the amino acid pool and for the assumption that non-precipitable radioactivity in plasma was equivalent to amino acid productivity. Studies in vitro, which minimize problems of precursor pools, show an 11% decrease in leucine incorporation after 24 h of compensatory hypertrophy and an 18% increase after 48 h (Coe & Korty, 1967).

The increase in renal amino acid pool has its counterpart in the concentrations of free amino acids in rat liver 4 h after partial hepatectomy (Ferris & Clark, 1972). Although a compensation was introduced for interstitial, tubular and vascular amino acid when renal uptake of α-aminoisobutyric acid was measured after contralateral nephrectomy (Ross et al., 1973), similar compensations in other experiments were not practical. The possibility of compartmented intracellular amino acid pools, as in liver (Mortimore et al., 1972), could also not be assessed. The rise in amino acid concentration in the remaining kidney is likely to be a specific consequence of contralateral nephrectomy rather than of a non-specific hypermetabolic state, since 15 min of swimming lowers amino acid concentrations in rat kidney (Christophe et al., 1971).

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Pederson, T. & Kumar, A. (1971) J. Mol. Biol. 61, 655–668