transplants at four months subsequently had little evidence of rejection. Eight (32%) had no clinical or biochemical evidence of rejection at any time. Three had rejection crises between four and 12 months after operation which were successfully treated. In most of these the transplant function has slowly improved. The average blood urea level was 60 mg./100 ml., with a range of 27–150 mg./100 ml., serum creatinine 1.8 mg./100 ml., with a range of 0.9–3 mg./100 ml., and creatinine clearance 58 ml./min., with a range of 20–120 ml./100 ml. Twenty-four patients have been restored to normal activity: the majority have returned to their previous jobs; the most active patient operates a bulldozer. One patient lives a restricted life due to steroid arthropathy and probable chronic rejection of the transplant.

As soon as the transplants function adequately the patients develop a sense of well-being which is in excess of the euphoria due to steroids. They develop voracious appetites and often say that they feel “cleaner” than when they were on dialysis.

The complications developing in our patients were numerous and bizarre. They will be the subject of another communication. The correlation of clinical results with tissue typing will also be reported separately. The most obvious difficulty has been the management of rejection. The independent value of actinomycin C, extracorporeal irradiation, and antilymphocyte globulin were impossible to assess, since all rejection crises were also treated with massive doses of steroids. During the course of this series of cases policy has changed. Instead of pursuing immunosuppression to life-threatening toxicity, a kidney with inexorable rejection is now removed and immunosuppression stopped.

Discussion

Though the maximum follow-up period is only two and a half years, the satisfactory quality of life of the majority of our patients has convinced us that cadaveric renal transplantation is valuable therapy. Our patients do not require convincing; most had suffered severe symptoms of uraemia often complicated by hypertension, heart failure, peripheral neuritis, and pericarditis. To be restored from such a moribund condition to a normal life is worth while even if the ultimate prognosis is uncertain. The pressure on dialysis beds and the shortage of cadaver donors caused us to embark on a limited programme of live donor transplants from close blood relatives who insisted on giving a kidney. We feel that it is unjustifiable to refuse to perform a transplant under these circumstances when the alternative is death. There have been 20 deaths on the waiting-list in the past two years due to inadequate facilities for dialysis in the referring hospitals. This figure, however, means little in the context of the 2,000–3,000 deaths per annum from uraemia in the United Kingdom in patients between the ages of 5 and 55. Unfortunately, at present the dialysis and transplant centres in the United Kingdom can treat only a small fraction of these cases.

Summary

Fifty-four consecutive renal transplants in 49 patients were reported. There were 51 cadaver and 3 live donors. At the time of writing 33 (60%) of transplants were functioning and 34 patients (70%) were alive. All transplant failures had occurred within four months of operation. Seventeen of the 29 (59%) transplants were functioning at one year and six of the seven transplants performed more than 22 months ago continued to function. The longest period of survival is two and a half years since operation.

We wish to acknowledge the help we have had from our medical and nursing colleagues and in particular the nursing staff of the renal unit. We are grateful to the John Bonnett Clinical Laboratories for the numerous biochemical, haematological, and bacteriological studies they have performed on our patients. We thank the referring physicians for their collaboration both preoperatively and in the postoperative follow-up period.

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Preliminary Communications

Body Height and Imipramine Side-effects


Genetically determined variations in metabolism are of importance in determining the steady-state blood concentrations of some drugs. Variability in the population depends on polymorphisms of enzymes involved in the metabolism of a drug and may influence both clinical effectiveness and toxicity (Price Evans, 1965; Hamner et al., 1967; Moody et al., 1967).

A genetic polymorphism in drug metabolism may be suspected when blood levels seem to be influenced by sex (Gilllette, 1963; Moody et al., 1967) or racial differences (Motulsky, 1957), or show a discontinuous variability (Price Evans, 1962), or show an association with a genetically determined disorder such as Down's syndrome (Turpin et al., 1967).

A well-known example of genetic polymorphism is that which determines that all persons are either rapid or slow acetylates of the drugs isoniazid, sulphasalazine, hydralazine (Price Evans and White, 1964), and probably phenelzine (Price Evans et al., 1965).

The steady-state plasma levels of depressed patients on a standard dosage of tricyclic antidepressants have been shown to have markedly bimodal frequency distributions (Hammer and Sjovist, 1967); this suggests the existence of a genetic polymorphism for the metabolism of these drugs. Patients complaining of side-effects while on this group of antidepressants are those with high steady-state plasma levels (Hammer et al., 1967).

It seems possible that genes controlling drug plasma levels may also have an influence on physique. In this study a retrospective investigation has been made of the physique of patients who complained of side-effects while on imipramine therapy.

METHOD

Over a period of three years 93 patients with sustained depression in my general practice were considered for admission to a
controlled trial of imipramine. At the same time demographic
and physical data were collected as the basis for a study of the
natural history of the disorder. It is thus possible to relate
various indices of physique to the presence or absence of volun-
teed side-effects.

Of the 93 original patients (14 men and 79 women), 12 were
excluded in accordance with the trial protocol, the escape clause
was invoked for a further two, and 11 defaulted (four on
placebo and seven on imipramine). Thirty-one of the remain-
ing 68 patients had been allotted a placebo by the randomiza-
tion procedure, leaving seven men and 30 women taking imip-
ramine. Since there were so few men attention has been
concentrated on the 30 women; of these, 10 volunteered side-
effects (group 1) and the remaining 20 had no side-effects
(group 2).

The following indices were recorded: age in years; nude
weight in pounds, height in inches, ponderal index (height
divided by cube root of weight), and subcutaneous fat in milli-
metres (measured with Harpenden's skinfold callipers over the
left triceps).

Each patient was included in the trial for three weeks. The
starting dose was one tablet (25 mg.) of imipramine thrice
daily; if there was no response at the end of the first week
the dose was increased to two tablets (50 mg.) thrice daily.
Patients were not questioned about side-effects, but any volun-
teed symptoms were recorded. They were encouraged to
avoid other drugs and sedatives; it is impossible in retrospect
to be quite certain that no patient took a barbiturate, but is
unlikely.

Results and Discussion

Group 1 patients were similar in physique to those in group
2 except that they were significantly taller (see Table).

<table>
<thead>
<tr>
<th>Index</th>
<th>Group</th>
<th>No.</th>
<th>Mean</th>
<th>S.D.</th>
<th>t</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>2</td>
<td>10</td>
<td>37-4</td>
<td>8-0</td>
<td>0-12</td>
<td>N.S.</td>
</tr>
<tr>
<td>Height in inches</td>
<td>1</td>
<td>10</td>
<td>65-4</td>
<td>1-4</td>
<td>2-7</td>
<td>0-01 &lt; P &lt; 0-02</td>
</tr>
<tr>
<td>Weight in pounds</td>
<td>2</td>
<td>20</td>
<td>139-7</td>
<td>19-3</td>
<td>0-37</td>
<td>N.S.</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>1</td>
<td>10</td>
<td>12-7</td>
<td>0-7</td>
<td>7-4</td>
<td>N.S.</td>
</tr>
<tr>
<td>Subcutaneous fat in mm.</td>
<td>2</td>
<td>19</td>
<td>19-8</td>
<td>8-5</td>
<td>4</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

The side-effects might have been a function of varying dosage
alone, but there is no evidence for this; group 1 were taking an
average of 3.3 tablets daily at the time they first volunteered
cide-effects, while group 2 were challenged by a peak average ofour tablets.

As the weights of both groups are similar the factor of
metabolically active mass is not likely to be of importance.
It may be noted that the index of physique, which correlates
significantly with the volunteering of side-effects, is the only
one independent of age.

The main enzymic actions to which imipramine is subjected
are demethylation and hydroxylation (Bickel and Baggiolini,
1966; Moody et al., 1967). Other drugs, in particular barbi-
turates, are able to potentiate these biotransformations (Remmer
and Merker, 1965) and lower the blood level of desmethyl-
imipramine (Hammer et al., 1967); it is fortunate, therefore,
that polypharmacy was avoided during the trial.

A result based on such a small series may be influenced by
chance, and the ideal procedure would be to see if it could be
corroborated by a larger prospective study.

Other explanations may also exist—tall women may, for
example, be more expansive in declaring their symptoms than
short ones. Alternatively, there might be an association be-
tween height, social class, and rhetoric, though the proportion
of women of non-manual class in the two groups was not
greatly different (5 out of 10 and 7 out of 20 respectively).

It remains possible that the same genes may influence both
body height and imipramine metabolism.

Summary

Women who volunteered side-effects while taking imipramine
were found to be significantly taller than those who did not.
This may indicate that both the rate of metabolism of imi-
pramine and body height are influenced by the same genes.

This paper owes much to a lecture given by Dr. D. A. Price
Evans in the "Scientific Basis of Medicine" series, and to his
subsequent advice. I am also indebted to Professor W. W. Holland.

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