Experimental, theoretical, psychological, and economic barriers have caused physicians to rely on biomedical treatments for infertility at the exclusion of more environmentally oriented ones (e.g., psychosocial stress therapy). An evolutionary model is described for the origin of reproductive failure, suggesting why mammals evolved to be reproductively responsive to the environment and why psychosocial stress should have an especially strong impact on fertility problems. A study of the causal role of psychosocial stress in infertility is then summarized. The paper concludes with implications for future directions for the treatment of infertility and related human reproductive problems.

KEY WORDS: Infertility; Psychosocial stress; Reproductive Filtering Model; Reproductive failure.

Understanding the natural history of an organism can potentially improve treatment of its diseased states. This point is well appreciated in comparative medicine; particular organisms are used as models for a given disease because their adaptations make them either more or less
vulnerable to the problem under study. Yet biomedicine often proceeds without consideration of our own natural history. Lewin (1993) recently described how such neglect limits our understanding of biomedical problems. Failure to understand particular adaptations can even make them appear erroneously pathological, resulting in improper treatments. For example, symptoms such as fever can result from an adaptive response of the host, making the body less hospitable to invading pathogens (Ewald 1980, 1991). Suppressing fever in such cases actually could lead to proliferation of the pathogen.

Natural history should be especially relevant to diagnosis and treatment of reproductive problems because successful reproduction is fundamental to evolutionary success. This paper addresses how evolutionary explanations for the occurrence of reproductive failure in humans can improve diagnosis and treatment of infertility.

Fifteen percent of all couples are infertile (Berkowitz 1986), more than 50% of all conceptions spontaneously abort (Shepard and Fantel 1979), and 7% of all live births are premature or low birth weight (many of which probably have resulted in neonatal death [reproductive failure] prior to the advent of modern medicine). These rates of reproductive failure in humans may seem high, yet they are comparable to those observed in a wide variety of mammals (Brambell 1948; Bronson 1989; Follett 1985; Short 1985; Wasser and Barash 1983). Several investigators (Bronson 1989; Kozlowski and Sterns 1989; Short 1985; Wasser and Barash 1983) have proposed a theoretical model, termed the Reproductive Filtering Model (RFM; Wasser 1990), to explain these high failure rates. The RFM argues that the large cost of reproduction (time, energy and risk) has resulted in natural selection for physiological mechanisms that temporarily suppress reproductive processes when environmental cues suggest that the likelihood of producing viable offspring is relatively low. Suppression is maintained until conditions improve, enabling reproduction to proceed when the chances of success are greatest (Wasser 1990). According to the RFM, a number of sensitive physiological and behavioral mechanisms have evolved to suppress reproduction (Wasser and Isenberg 1986) because temporal variability in environmental conditions that impact reproductive success has been high throughout mammalian evolution. Examples of environmental cues commonly associated with reproductive failure include changes in photoperiod among temperate-living birds and mammals (reflecting poor hatching or birthing conditions; Follett 1985; Sadleir 1969); change in energy balance (reflecting maternal nutritional status; Frisch 1982); perceived stress resulting from social ostracism or other life pressures (DeSouza and Metzger 1991; Edelmann and Golombok 1989; Harris 1989; Wasser 1990; Wasser and Barash 1983; Yen 1991), and embryonic
Psychosocial Stress and Infertility

or fetal malformations (Roberts and Lowe 1975; Shepard and Fantel 1979).

The extent to which the RFM applies to humans reflects the likely effectiveness of acute and/or long-term environmental therapy (e.g., diet, stress reduction, or psychosocial therapies) as a treatment for some forms of reproductive failure. However, of greater concern is the possibility that treating only the psychological and/or physiological symptoms that are suppressing a person’s fertility, without eliminating the causes (e.g. stressors) that triggered them, could lead to reproductive problems of significantly greater magnitude. Such patients may experience elevated risk later on in the reproductive event, for example, from mid- to late-term spontaneous abortion, premature birth (Jansen 1982), or production of infants with birth defects (Beer et al. 1987; Berkowitz 1986; Stott 1958). Demands of infant care on an already distressed parent could also increase the probability of providing an emotionally and physically unhealthy postnatal environment for the offspring (Daly and Wilson 1988; Munro et al. 1992; Osofsky 1985). On the other hand, diagnosis and treatment of environmental mediators in infertility, in conjunction with biomedical treatment, could markedly improve overall reproductive outcomes (e.g., fertility, term gestation, and nurturing) in some cases. This paper focuses on the stress response as a potential reproductive filtering mechanism leading to some forms of infertility.

FACTORS LIMITING ACCEPTANCE OF PSYCHOSOCIAL STRESS THERAPY AS A TREATMENT FOR INFERTILITY

Several factors have limited the acceptance of psychosocial or other stress reduction therapies compared to a rapidly expanding biomedical technology (e.g., in vitro fertilization [IVF], gamete intrafallopian transfer [GIFT], zygote intrafallopian transfer [ZIFT], tubal embryo transfer [TET], GnRH analogs, laser surgery, embryo cryopreservation, intrauterine insemination, zona tearing) as a treatment for infertility.

1. Problems of Experimental Design. Because of the lack of well-controlled studies on the contribution of psychosocial stress to reproductive failure (Istvan 1986; Wright et al. 1989), there are few data to challenge the general belief of infertility M.D.s that stress is not causally linked to reproductive failure, making psychological treatment unproven and unattractive. Two design problems have been particularly prevalent: (a) Investigators have tended to lump together all infertility disorders when looking for an association with psychosocial stress. However, some forms of
infertility may be more likely than others to be stress-induced (see below). (b) Most studies have been retrospective; this makes it difficult to separate stress as a cause versus an effect of infertility since infertility itself is stressful for most couples.

2. Psychological Barriers. (a) Psychological problems tend to be more difficult than biomedical ones for patients to acknowledge. (b) Psychosocial therapy is relatively time consuming and requires considerably more personal effort on the part of the patient than do most biomedical treatments. Biomedical technology, on the other hand, is painted by the media as a relatively rapid treatment for infertility to a comparatively anxious clinical population. (c) Gynecologists and obstetricians are not trained to diagnose psychological problems or to provide psychological therapies.

3. Economic Factors. Biomedical treatments for infertility can be quite lucrative for physicians.

A PILOT STUDY ON THE CAUSAL ROLE OF PSYCHOSOCIAL STRESS IN INFERTILITY

My colleagues and I recently completed a pilot study (Wasser et al. 1993) developed to overcome the design problems mentioned above. The study was based on the argument that neuroendocrine fertility disorders are more likely to be caused by stress than are anatomic ones.

Some Disorders Are More Likely Than Others To Be Caused by Stress

A primary function of the hypothalamus is to maintain homeostasis in response to an inherently changing environment. Thus, the hypothalamus is involved in regulation of body temperature, hunger, thirst, metabolism, blood pressure, heart rate, the stress response, and the timing and maintenance of reproduction (Morgane and Panksepp 1979). Given the primary role of the hypothalamus in maintaining physiological homeostasis in response to environmental change, we hypothesized that environmental stress–related infertility disorders were most likely to be mediated by the hypothalamus via the hypothalamic-pituitary-ovarian (HPO) axis. Indeed, most known forms of reproductive failure in response to the environment appear to be mediated through the neuroendocrine system, involving the HPO axis (Austin and Short 1985; Bronson 1989; Giles and Berga 1993; Wasser et al. 1993; Yen 1991). By contrast, infertility disorders of more anatomic origin (e.g., tubal dis-
Psychosocial Stress and Infertility

ease) are unlikely to be part of this dynamic responsiveness to the environment; anatomic disorders tend to be irreversible without surgical intervention.

Using This Argument to Separate Cause and Effect

We compared levels of psychological distress in infertile women experiencing neuroendocrine disorders with levels among infertile women experiencing anatomic disorders. Controls in this study consisted of women who did not wish to become pregnant, but who had neuroendocrine disorders analogous to those in the neuroendocrine infertility group (e.g., amenorrhea). Since the controls lacked the stress of being infertile, the latter comparison enabled us to distinguish the specific neuroendocrine changes that may have been responsible for the infertile condition. The three hypotheses tested in this study are outlined below. Their predictions are summarized in Table 1.

Hypothesis 1: The Psychosocial Stress Causality Hypothesis. Infertility disorders mediated by the neuroendocrine system are those most likely to result from psychosocial stress, compared with more anatomic fertility disorders.

We assumed that all infertile women were experiencing distress resulting from their infertile condition. However, if the causality hypothesis is correct, infertile women diagnosed with neuroendocrine disorders were expected to report higher levels of psychosocial distress (i.e., distress beyond that induced by their infertile condition) compared with infertile women who have anatomic disorders. Moreover, controls—women with neuroendocrine disorders who do not wish to become pregnant (and therefore lacked the stress of being infertile)—were also expected to experience higher levels of psychosocial distress than infertile women with anatomic disorders.

Table 1. Hypothesis-Generated Predictions of Group Differences in the Magnitude of Psychosocial Distress Self-Reports

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Psychosocial Stress Causality Hypothesis</td>
<td>C = F &gt; I &gt; A</td>
</tr>
<tr>
<td>2. Infertility Stress Effect Hypothesis</td>
<td>C &lt; F = I = A</td>
</tr>
<tr>
<td>Null Stress Is Causally Irrelevant to Infertility</td>
<td>C = F = I = A</td>
</tr>
</tbody>
</table>

C = controls; F = functional infertility group; I = intermediate group; A = anatomic group
Hypothesis 2: The Infertility Stress Effect Hypothesis. The stress resulting from being infertile, independent of the particular fertility disorder, is the only stress that is directly associated with infertility.

This hypothesis predicted that the neuroendocrine and anatomic infertility groups would not differ in the degree to which they were associated with emotional distress, and both of these groups would report more stress than controls.

Null Hypothesis: Stress is causally irrelevant to infertility.

The null hypothesis predicted that emotional distress should be randomly distributed across all infertility groups and the controls.

Methods

Prior to their first clinic visit, all new patients attending the University of Washington Fertility and Endocrine Center were mailed a consent form along with a battery of questionnaires that required approximately 1.5–2 hours to complete (465 questions). These questionnaires provided quantitative measures of social support, the quality of relations with family members and closest friends, self-esteem, and traditional psychological measures, such as anxiety, depression, hostility, and obsessive-compulsive behavior. The scores derived from these questionnaires were used to differentiate statistically between diagnostic infertility and control groups as described below. Following completion of the questionnaires, all patients underwent a thorough infertility evaluation, consisting of a series of tests applied over a period of approximately six months (see Wasser et al. 1993 for details). These tests were followed by a formal chart review by a single reproductive endocrinologist to reach a final diagnosis for each patient. At no time did the physician see or discuss the patient’s completed questionnaires.

In an objective manner prior to study onset, possible diagnoses were preclassified as predominantly the result of anatomic factors (e.g., tubal disease, pelvic adhesions, uterine anomalies, severe endometriosis), termed anatomic group; intermediate in anatomic contributions (e.g., mild endometriosis; polycystic ovary syndrome), termed intermediate group; or nonanatomic factors (i.e., HPO axis disorders, such as amenorrhea, luteal phase defect, anovulation, hyperprolactinemia, idiopathic infertility), termed functional abnormality group. Cases in which women had multiple diagnoses distributed among at least two different groups were also classified as intermediate. For purposes of this study, male factors were classified as anatomic in our analyses (group 3) since, like anatomic factors, these forms of infertility could not have resulted directly from
stress experienced by the woman. A fourth classification (controls) was composed of women with neuroendocrine disorders analogous to those in the functional group but included only those patients who were not attempting to become pregnant. Each patient was assigned to one of the four groups as a result of the diagnosis based on the medical evaluation and chart review.

Results

Compliance with this study was quite high. Sixty-nine out of 72 women (96%) agreed to participate in the study. Fifty-four women (75%) returned questionnaires; however, 16 were removed from the study (11 never completed their biomedical diagnostics; 3 became pregnant before completing the questionnaires; and 2 potential controls were visiting the clinic for consultation before attempting to conceive). Of the remaining 38 women, 7 were categorized as functionally abnormal, 10 as intermediate, 15 as anatomic, and 6 as controls. All six controls had functional abnormalities of the HPO axis.

Wilcoxin's matched pairs signed-rank test using standardized t-scores from all 37 constructs (measured by the nine questionnaires) revealed a highly significant trend: the functional infertility group showed greater psychosocial distress than the intermediate (z = -2.65; P < 0.008) or anatomic (z = -4.58; P < 0.0005) groups. Compared with infertile women with anatomic defects, those with functional abnormalities of the HPO axis reported the following: (a) fewer sources of social support (t = -2.16; P < 0.022); (b) less satisfaction with the quality of social supports (t = -2.14; P < 0.023); (c) lower reliance upon best friend for support (t = -1.84; P < 0.04); and more (d) conflict with their father (t = 3.59; P < 0.001); (e) hostility (t = 2.27; P < 0.017); (f) anxiety (t = 2.3; P < 0.016); (g) phobic anxiety (t = 2.48; P < 0.011); (h) likely to evidence a somatic complaint (t = 1.41; P < 0.051); and (i) likely to feel effects of infertility on their personal life (t = 1.83; P < 0.04). The intermediate group fell between the functional and anatomic groups on all measures, showing only four significant differences. The intermediate group reported significantly less anxiety (t = 1.83; P < 0.045) and phobic anxiety (t = 1.85; P < 0.043) than did the functional group. Intermediates also reported more conflict with father (t = 1.86; P < 0.039) and less support from spouse (t = 1.72; P < 0.033) than did the anatomic group.

Wilcoxin's signed-rank test comparing controls with the functional group across all standardized measures was not significant. In fact, controls only differed from the functional abnormality group in reporting more self-esteem (t = -2.35; P < 0.04). By contrast, the Wilcoxin's signed-rank test revealed significantly more overall distress in the control
group than in the anatomic group \((z = -3.55; P < 0.0002)\). Compared with the anatomic group, controls reported significantly (a) fewer sources of social support \((t = -2.1; P = 0.025)\); (b) less reliance on best friend for support \((t = -2.23; P < 0.02)\); (c) more conflict with father \((t = 1.7; P < 0.054)\); (d) greater conflict with their second-closest friend \((t = 2.3; P < 0.02)\); (e) less depth in their relation with spouse \((t = -2.85; P < 0.005)\); and (f) less support from spouse \((t = -2.57; P < 0.01)\).

A stepwise multiple regression was used to partial out shared variance between the correlated independent variables described above. Comparison between the functional abnormality and anatomic groups (dummy coded: 1,0) revealed significance in the expected direction for the number and quality of social support \((t = -2.23; P < 0.05\) and \(t = -3.35; P < 0.006\), respectively), reliance on support of best friend \((t = -3.35; P < 0.006)\), conflict with father \((t = 7.1; P < 0.0001)\) and the tendency to evidence a somatic complaint \((t = 3.98; P < 0.002)\), with an overall \(r^2 = 0.86\ (P < 0.0001)\). Comparison between the anatomic group and controls revealed significance in the expected direction for reliance on support of best friend \((t = -2.51; P < 0.025)\) and conflict with father \((t = 2.33; P < 0.035)\), with an overall \(r^2 = 0.39\ (P < 0.02)\).

PSYCHOSOCIAL STRESS AND INFERTILITY

Because of its small sample size, the results of the Wasser et al. (1993) study must be interpreted with caution until they have been replicated. [My colleagues and I are in the process of replicating this study with a substantially larger sample size.] Nevertheless, the findings of this study were consistent with the hypothesis that psychosocial distress contributed significantly to the etiology of some forms of infertility. The group differences we found were not expected if stress associated with infertility was primarily caused by the inability of couples to fulfill their desire to conceive because all three groups seeking infertility treatment were presumed to have been experiencing such stress equally.

The similarity between controls and the functional abnormality versus anatomic infertility groups further supported the psychosocial stress hypothesis, while being inconsistent with the hypothesis that psychosocial distress is merely an effect of infertility.

It was noteworthy that the majority of significant psychosocial distress scores that distinguished groups 1-3 were social measures (i.e., number of sources of social support, satisfaction with social support, reliance upon best friend, and conflict with father). All measures distinguishing the anatomic and control groups were also social ones. These results strongly suggest that social factors, in general, are a major component of the overall psychological distress syndrome that appears to be a causal
part of infertility. This finding of the general importance of social stress is highly consistent with comparative findings across species.

Competition motivated social stress, ranging from low social status to peripheralization from the group, physical aggression, and social ostracism, is one of the most frequently observed negative environmental conditions (i.e., stressors) associated with reproductive failure in mammals (Wasser and Barash 1983). The stressfulness of these social pressures appears to stem from the threat to survival from loss of social support in socially living mammals. Stated in comparative terms, social support facilitates access to critical resources through both competitive and noncompetitive means, as well as provides protection from harm (e.g., predation or aggression). Socioecological conditions have been argued to have promoted such sensitivity to social conditions throughout human evolutionary history as well (Wasser and Isenberg 1986; Wasser 1990). Humans have historically been resource-limited, and individuals appear to have regulated their reproduction, and hence population growth, in response to resource limitation (Cohen et al. 1980; Lee 1980; Schrimshaw 1984; Wagley 1977; Wood and Smouse 1982). Such regulation also appears to occur in contemporary societies, and one’s relative social status still appears to be of critical importance under such circumstances (Easterlin 1980; Kasarda et al. 1986). Given the above, psychosocial stress in humans may best be defined as distress resulting from psychological or social pressures, including concerns over inadequate (personal, social, or environmental) resources for self or family (e.g., lack of social support). Thus, although the presence of social support may serve to buffer the impact of stressors on the body (House et al. 1988), our definition of psychosocial stress implies that lack of social support or aversive social relations may themselves be stressors. The results of the Wasser et al. (1993) study support this view.

Other findings in the clinical literature appear to be consistent with ours (Wasser et al. 1993). Giles and Berga (1993) found that women with functional hypothalamic amenorrhea reported more dysfunctional attitudes, poorer coping, and greater interpersonal dependence than eumenorrheic women. Women with organic disorders were intermediate in these measures. Harris (1989) found that women with secondary amenorrhea reported significantly more nonsevere life events than did women with organic disorders, whereas women with menorrhagia (hypermenorrhea) reported significantly more severe life events than did women with organic disorders. Morse and Dennerstein (1985) compared in vitro fertilization/embryo transfer (IVF/ET) patients suffering from idiopathic infertility with those whose infertility had a clear anatomic cause. The idiopathic group had higher neuroticism scores on the Eysenck Personality Inventory than the group with the anatomic etiology. Moreover, although infertile women generally tended to be anx-
ious, women with idiopathic infertility tended to be more anxious during IVF/ET treatment than did women with anatomic etiologies. Morse and Dennerstein (1985) reported few sources of social support in the majority of infertility subjects in their studies. Mazure et al. (1987) similarly found that a larger portion of IVF/ET patients who eventually became pregnant in their study reported looking to others for support compared with the nonpregnant group.

Success rates of biomedical procedures remain quite low for most infertility disorders (Collins et al. 1983). Greater appreciation of the biological bases of reproductive failure, as well as the psychological and economic issues surrounding infertility, could change this trend. Most mammals, including humans, experience high rates of reproductive failure, particularly early in the reproductive event (Shepard and Fantel 1979). Most mammals, including humans, also invest heavily in reproduction and experience considerable temporal variation in conditions favoring offspring survival. A large portion of the reproductive failure can be explained in terms of conserving this investment by adjusting the timing of reproduction to optimize offspring survival. Nutrition and other potentially seasonal conditions, such as weather (Bronson 1989; Follett 1985), are among those to which the timing of reproduction is adjusted to optimize offspring survival. Social conditions greatly impact offspring survivals, and reproductive failure appears to occur in a large number of social birds and mammals in response to such conditions (Wasser and Barash 1983). The research by Wasser et al. (1993) and others summarized here also points to the importance of social factors in human reproductive failure, simultaneously suggesting that psychosocial therapies may provide a valuable complement or alternative to biomedical therapies for certain forms of infertility.

Generic stress-reduction or relaxation therapies, and particularly therapies to help cope with infertility and its treatment, should also be an important component of the treatment of infertility. To the extent that the reproductive system has evolved to be responsive to psychological stress in general, the stressfulness of infertility and/or its treatment is a likely cause of secondary fertility disorders. Basic stress-reduction or relaxation therapies could enhance overall treatment success by helping to resolve such secondary problems. At least one study has already shown tremendous success in this area (Domar et al. 1992). Perhaps not surprisingly, success rates of all treatments in that study were highest when delivered as group, rather than individual, therapy.

This work would not have been possible without the collaboration of Gretchen Sewall and Michael Soules. Don Moore provided valuable discussion of the issues addressed in this manuscript.
Samuel Wasser is Assistant Professor in the Division of Reproductive Endocrinology at the University of Washington School of Medicine as well as Scientific Director of the Center for Wildlife Conservation in Seattle. His interests include the behavioral ecology and endocrinology of reproductive control, and conservation biology.

REFERENCES

Austin, C. R., and R. V. Short, eds.

Beer, A. E., and J. F. Quebbeman

Beer, A. E., J. S. Quebbeman, Y. Hamazaki, and A. E. Sempini

Berkowitz, G. S.

Brambell, F. W. R.

Bronson, F. A.

Cohen, M. N., R. S. Malpas, H. G. Klein, eds.


Daly, M., and M. Wilson

DeSouza, M. J., and D. A. Metzger

Domar, A. D., P. C. Zuttermeister, M. Seibel, and H. Benson

Easterlin, R. A.

Edelmann R. J., and S. Golombok
Ewald, P. W.

Follett, B. K.

Frisch, R.

Giles, D. E., and S. L. Berga

Harris, T. O.

House, J. S., K. R. Landis, and D. Umberson

Istvan, J.

Jansen, R. P. S.

Kasarda, J. D., J. O. G. Billy, and K. West

Kozlowski, J., and S. C. Sterns

Lee, R. B.

Lewin, R.

Mazure, C., D. A. Greenfeld, W. DeL’Aune, M. P. Diamond, and A. H. DeCherney

Morgane, P. J., and J. Panskepp
Morse, C., and L. Dennerstein
1985 Infertile Couples Entering an in vitro Fertilization Programme: A Prelim-

Munro, J. M., W. Ironside, G. C. Smith
1992 Successful Parents of in vitro Fertilization (IVF): The Social Repercu-

Osofsky, H.
1985 Transition to Parenthood—Risk Factors for Mothers and Infants. Paper
presented at the International Society for Psychosomatic Obstetrics and

Roberts, C. J., and C. R. Lowe

Sadleir, R. M. F. S.
Methuen.

Scrimshaw, S. C. M.
1984 Infanticide in Human Populations: Social and Individual Concerns. In
*Infanticide: Comparative and Evolutionary Perspectives*, G. Hausfater and S. B.

Shepard, T. H., and A. G. Fantel

Short, R. V.
1985 Species Differences in Reproductive Mechanisms. In *Reproduction in
Cambridge University Press.

Stott, D. H.
1958 Some Psychosomatic Aspects of Causality in Reproduction. *Journal of
Psychosomatic Research* 3:42-55.

Wagley, C.
University Press.

Wasser, S. K.
1990 Infertility, Abortion and Biotechnology: When It’s Not Nice to Fool

Wasser, S. K., and D. P. Barash
1983 Reproductive Suppression among Female Mammals: Implication for Bio-

Wasser, S. K., and D. Y. Isenberg
1986 Reproductive Suppression: Pathology or Adaptation? *Journal of Psychoso-
matic Obstetrics and Gynecology* 5:153-175.

Wasser, S. K., G. Sewall, and M. R. Soules
1993 Psychosocial Stress as a Cause of Infertility. *Fertility and Sterility*
59:685-689.

Wood, J. W., and P. E. Smouse
1982 A Method of Analyzing Density-dependent Vital Rates with an Applica-

Wright, J., M. Allard, A. Lecours, and S. Sabourin

Yen, S. S. C.