Psychological Medicine, 2000, **30**, 259–268. Printed in the United Kingdom
© 2000 Cambridge University Press

REVIEW ARTICLE

Interferons, serotonin and neurotoxicity

DAVID B. MENKES[1] AND JAMES A. MACDONALD

From Dunedin School of Medicine, University of Otago and Dunedin Hospital, Dunedin, New Zealand

ABSTRACT

Background. Interferons are a class of cytokines profoundly affecting immune function. Several interferons are now synthesized and used clinically, notably for viral diseases and cancer. In addition to their desired immune effects, interferons cause a number of toxicities, including prominent effects on the nervous system.

Methods. This literature review focused on the incidence of depression associated with interferon treatment. Possible neurochemical mechanisms and remedial strategies were also considered.

Results. Interferon treatment, particularly with the alpha subtype, is unquestionably linked with depression, but the strength of association is uncertain because of erratic ascertainment and pre-treatment co-morbidity. A likely pathogenic mechanism has been described, involving interferon suppression of serotonin synthesis. Controlled treatment trials of interferon-induced depression are not yet available.

Conclusions. Neurotoxicity substantially limits the use of interferons. At least some of the risk of depression appears to derive from their anti-serotonergic effects, consistent with the large body of evidence pointing to a general link between serotonin and affective illness. Vigilant detection and aggressive treatment of depression is necessary to optimize interferon treatment of many patients.

INTRODUCTION

Interferon therapies are proving useful in a remarkable variety of diseases; an equally impressive range of toxicities accompanies their use (Vial & Descotes, 1996; Strander, 1997; Borden & Parkinson, 1998). Most patients experience an acute 'flu-like' syndrome with malaise, fever, chills/rigors and impaired concentration. Irritability, fatigue and pain complaints, typically musculoskeletal, are common both acutely and in the longer term. Continuing treatment over weeks and months is associated with other persistent adverse effects, including depression, anorexia, headache, psychomotor slowing, clumsiness and cognitive impairment. Such symptoms compromise quality of life and often lead to premature termination of treatment (Olsen *et al*. 1989; Gisslinger *et al*. 1991; Levenson & Fallon, 1993; Hill *et al*. 1995; Neilley *et al*. 1996; Wisloff *et al*. 1996; Valentine *et al*. 1998). This article reviews the neurotoxicity of interferons, focusing on depression and specifically considering the possible intermediary role of serotonin.

INTERFERONS AND DEPRESSION

Interferon therapy unquestionably causes some degree of depressive symptoms in a majority of patients, but the rates of more serious disturbances are uncertain. Major depressive illness and attempted or completed suicide comprise roughly 4% of all post-marketing adverse drug

[1] Address for correspondence: Dr David B. Menkes, Liaison Psychiatry, Dunedin Hospital, Private Bag 1921, Dunedin, New Zealand.

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

reaction (ADR) reports (Weiss, 1998). Mood changes and other neurotoxic effects are typically observed after several days of parenteral treatment, corresponding to the appearance of measurable interferon in the cerebrospinal fluid (Farkkila *et al*. 1984). Some of the variability in reported rates of serious mood effects (Table 1) may arise from heterogeneous patient groups, some of which have very high baseline rates of depression (Johnson *et al*. 1998), as well as from differences in ascertainment, interferon type, dose, route of administration and treatment duration (Valentine *et al*. 1998). Only one study compared two different interferons in the same clinical population (hepatitis C patients); in this case depressive symptoms were significantly linked to interferon alpha but not beta (Matsushita *et al*. 1994). Another study found leucocyte-derived interferon alpha less prone to produce depression than other sources of the same cytokine administered in the same dose over 6 months (Malaguarnera *et al*. 1998).

Most interferon treatment studies are flawed by poor methodology, with ascertainment of depression a conspicuous weakness. The one study (McDonald *et al*. 1987) with truly random allocation to interferon *versus* placebo showed a 63% rate of psychiatric disorder in the interferon group, but regrettably did not include sufficient data on control subjects to allow calculation of relative risk. Depression has been linked to therapeutic use of interferon alpha (definite) and beta (probable), but only weakly with gamma, which has the most limited treatment indications (Table 1). On the other hand, increased endogenous interferon gamma has been linked to both depression and cachexia in cancer patients (Iwagaki *et al*. 1997), suggesting that it may also have mood toxicity when used clinically.

There is now considerable evidence implicating immune activation in the aetiology of depression, including elevated interferon gamma (Maes *et al*. 1994; Seidel *et al*. 1995, 1996) and other cytokines, documented in some cases to precede the onset of mood disturbance (Yirmiya, 1996; Connor & Leonard, 1998). Further support for this hypothesis comes from studies indicating that increased levels of neopterin, a sensitive marker of immune activation, are associated with episodes of major depression (Dunbar *et al*. 1992; Bonaccorso *et al*. 1998).

The general toxic reactions to exogenous interferons and to interferon releasers such as interleukin-2 or imiquimod are essentially similar, and it seems likely that their liability to induce depression will also turn out to be similar (Fent & Zbinden, 1987; Goldstein *et al*. 1998). The toxicities of various interferons, their releasers and other pro-inflammatory cytokines (such as interleukin-1) may be comparable because of the extensive cross-talk between them and the fact that they are typically activated concurrently in a cytokine cascade (Recht *et al*. 1991; Dantzer *et al*. 1996). Indeed, most of the behavioural and biochemical effects of interferon in animals are also produced by non-specific cytokine inducers such as lipopolysaccharide, a pyrogen present in the cell wall of gram-negative bacteria (Dantzer *et al*. 1996). On the other hand, some evidence has appeared suggesting that clinical doses of interferon beta may be associated with less neurotoxicity than interferon alpha (Liberati *et al*. 1990), consistent with its apparently lesser risk of provoking depression (Matsushita *et al*. 1994).

Estimating the risk of depression with interferon treatment is complicated by a number of factors: medically-ill populations may have rates of depression 2–4 times those of age-matched controls (Robertson & Katona, 1997; Johnson *et al*. 1998); ascertaining depression in the medically ill is difficult anyway, the more so when treatments (such as interferon) provoke fatigue, anorexia, irritability or other symptoms common in depression (Dalakas *et al*. 1998); interferon administration is often part of a combined treatment protocol that may show additive toxicities (Hill *et al*. 1995; Rajkumar *et al*. 1998); finally, some interferon-treated patients, such as those with hepatitis C, are likely to use illicit drugs as well, further complicating the clinical picture (Johnson *et al*. 1998). Despite these problems, and rather disparate study methodologies, the sum of evidence indicates interferon therapy confers a further risk of depression, even in patients with physical disease improved by interferon treatment. Unfortunately, most depressions fail to be recognized and treated by non-psychiatrists (Goldberg & Blackwell, 1970), particularly in the medically ill (Robertson & Katona, 1997; Koenig, 1998), so it is hardly surprising that interferon-induced depression is not generally well-recognized or managed.

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

Table 1. *Rates of depression and clinical use of interferons*

Interferon type	Year approved	Main indications	Depression reported	Strength of evidence	Suicide reported	References
Alpha	1986	Malignancies (leukaemias, melanoma)	5–36%	++	Yes	(Olsen *et al.* 1989; Steinmann *et al.* 1993; Borden & Parkinson, 1998)
		Viral diseases (hepatitis B, C)	17–40%	+++	Yes	(McDonald *et al.* 1987; Renault *et al.* 1987; Prasad *et al.* 1992; Janssen *et al.* 1994; Kagaya *et al.* 1997)
Beta	1995	Multiple sclerosis	13–41%	+	Yes	(Anonymous, 1995; Neilley *et al.* 1996; Mohr *et al.* 1997)
Gamma	1990	Chronic granulomatous disease	12%	+/−	No	(Janson *et al.* 1993)
Imiquimod		Viral diseases (HIV, HPV)	16%	+/−	No	(Goldstein *et al.* 1998)

Nonetheless, depression remains a major reason for stopping treatment with interferon (Olsen *et al.* 1989; Levenson & Fallon, 1993; Neilley *et al.* 1996; Vial & Descotes, 1996; Pajkos *et al.* 1998). Pre-existing depression in hepatitis C patients is considered a definite contraindication to interferon treatment by some (Weiland *et al.* 1998), but not other authors (Van Thiel *et al.* 1995). Interferon-induced depression typically (McDonald *et al.* 1987; Renault *et al.* 1987), but not always, resolves after treatment withdrawal (Rifflet *et al.* 1998). The importance of detecting and managing interferon-induced psychiatric disorder is underscored by a likely increase in suicide risk (Janssen *et al.* 1994; Anonymous, 1995; Lublin *et al.* 1996; Brenard, 1997; Rifflet *et al.* 1998) and treatment of interferon-induced depression has been shown to improve compliance in a number of disorders, particularly multiple sclerosis (Mohr *et al.* 1997).

INTERFERONS, TRYPTOPHAN AND SEROTONIN

Interferons are a class of polypeptide cytokines involved in immune system activation and modulation (Ucar *et al.* 1995). Once secreted or injected, interferons diffuse through tissue, bind to cell surface receptors, and induce transcription of a variety of genes, the products of which appear to mediate most interferon effects (Boehm *et al.* 1997). Administered interferons (alpha, beta or gamma) initiate a cascade of secondary cytokine release and action in a variety of body systems, including the central nervous system (CNS) (Recht *et al.* 1991; Dantzer *et al.* 1996).

Two interferon-induced enzymes are of interest in both immunology and psychiatry; both degrade tryptophan and thereby prevent its synthesis into proteins or serotonin. Tryptophan dioxygenase, found in liver, is induced by Type I interferons (alpha, beta and omega), whereas the less specific indoleamine dioxygenase is found in all tissues and is powerfully induced by interferons, especially gamma (Type II). Tryptophan depletion, and consequent inhibition of protein synthesis, appears crucial to the toxic and anti-proliferative effects of interferons on microorganisms and cancer cells (Nagineni *et al.* 1996; Mackenzie *et al.* 1998; Mehta *et al.* 1998), and may be similarly involved in interferon-induced apoptosis (Taylor *et al.* 1996). The proposed role of tryptophan depletion in mediating interferon toxicity might be related to its scarcity as an essential aminoacid in both plant and animal protein. Neurotoxic effects of interferon gamma have been linked to accumulation of quinolinic acid, an excitotoxic end product of tryptophan catabolism by indoleamine dioxygenase (Sanni *et al.* 1998).

The idea that exogenous interferon suppresses tryptophan availability has been confirmed in both cancer patients and normal volunteers. Induction of indolamine dioxygenase by interferon gamma profoundly and selectively suppresses plasma tryptophan in a dose-dependent manner – up to 80% after a single intravenous bolus (Byrne *et al.* 1986). Interferon gamma can suppress serotonin availability both directly and indirectly, since indoleamine dioxygenase degrades serotonin as well as its precursor, tryptophan (Taylor & Feng, 1991). It is likely that interferons alpha and beta will share this effect, since both are known to release interferon gamma (Recht *et al.* 1991), and

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

clinical doses of either have been shown to provoke elevations in the gamma marker neopterin (Liberati *et al.* 1994*a*, *b*). Because of their coordinated release with interferons, it is likewise probable that other pro-inflammatory cytokines (e.g. interleukin-2 and others not yet available for clinical use) will share interferon effects on tryptophan availability and serotonin synthesis.

Other antiserotonergic actions of interferons have also been described. Both interferon alpha and gamma induce the transcription of serotonin transporter mRNA and increase imipramine-sensitive serotonin uptake in human cells (Morikawa *et al.* 1998). Interferon alpha also appears to inhibit serotonergic transmission at 5-HT_2 receptor sites in the spinal cord by an opioid-dependent mechanism (Kugaya *et al.* 1996). On the other hand, interferon alpha therapy may also promote the release of available serotonin and catecholamines via interleukin-1-beta, thus transiently boosting the availability of serotonin prior to its long-lasting depletion (Daniels *et al.* 1990; Shintani *et al.* 1993). This intriguing biphasic effect on brain serotonergic tone could account for the evanescent mood lift seen in some patients during day 2 of interferon therapy (Niiranen *et al.* 1988). The relative importance of the various antiserotonergic actions of interferons remains to be established.

TRYPTOPHAN, SEROTONIN AND DEPRESSION

Research findings dating back more than 30 years (Ashcroft *et al.* 1966) gave rise to the hypothesis of serotonergic deficits in affective illness. An abundance of neurochemical, endocrine and pharmacological data has broadly supported this hypothesis (Maes & Meltzer, 1995). The growing evidence of immune activation in depression, mentioned earlier, is relevant because of respective, and possibly related, links with suppressed tryptophan availability (Maes *et al.* 1993, 1994, 1996, 1997). A consequence of reduced serotonin synthesis is likely, because tryptophan (the rate-limiting substrate) availability has been found to be reduced both absolutely and relative to the other amino acids with which it competes for entry into the brain.

Despite the compelling demonstration of serotonergic abnormalities in depression, doubt remains regarding the extent and consistency of serotonin's role. For example, reduced serotonergic activity appears to be a state marker of depression (Anderson *et al.* 1990), but it is unclear whether low tryptophan and serotonin levels are a cause or an effect of the disorder (Quintana, 1992). Depressive subgroups doubtless vary in their pathobiology (Cowen, 1998), and it seems likely that such heterogeneity would extend to variable involvement of serotonergic systems. More uniform, but not necessarily essential, is evidence of serotonergic involvement in antidepressant action. For example, brain serotonergic transmission is enhanced, after a clinically appropriate delay of 1–3 weeks, by diverse antidepressant treatments, including tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and electroconvulsive therapy (Blier & DeMontigny, 1994).

As with protein synthesis, serotonin synthesis is very sensitive to tryptophan availability, due to the fact that the rate-limiting enzyme (tryptophan hydroxylase) is only partially saturated with substrate. Experimental tryptophan depletion (using a tryptophan-free aminoacid drink) can induce dysphoria and subclinical mood changes in some normal individuals (Young, 1991), and striking relapse in patients with depression (Delgado *et al.* 1991; Smith *et al.* 1997). Irritability appears to be a cardinal mood symptom produced by tryptophan depletion, whether by interferon (Strander, 1997) or by diet (Menkes *et al.* 1994). It is notable that both manipulations can suppress tryptophan by up to 90%.

INTERFERONS, SEROTONIN AND PAIN

Another important side-effect of interferon treatment is pain. Apart from the immediate painful effects of injection, interferon alpha treatment commonly produces persistent, generalized pain complaints, especially arthralgias and myalgias (Gisslinger *et al.* 1991; Shtalrid *et al.* 1993; Adam, 1994; Sainokami *et al.* 1994; Arai *et al.* 1995; Wisloff *et al.* 1996). Endogenous interferon alpha may also play a role in non-surgical abdominal pain in children (Chia *et al.* 1993). Interferon gamma treatment has been linked to pain in fewer studies (Steinmann *et al.* 1993; Slovin *et al.* 1998), but CNS mechanisms are better established for this cytokine (see

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

below) and central neurotoxicity involving endogenous interferon gamma has been implicated in the pain syndrome produced by *Trypanosoma brucei* infection (Bentivoglio *et al*. 1994). Patients with haematological malignancies or any advanced cancer commonly have elevated cytokine levels, particularly interferon gamma (Iwagaki *et al*. 1997), which may be linked to the non-specific pain symptoms commonly found in this population.

Serotonin plays a key role in modifying pain transmission in the spinal cord (Jessell, 1982), and its augmentation by antidepressant treatments appears important in their analgesic effects. Accordingly, tryptophan depletion is a plausible mechanism whereby interferon may produce or exacerbate pain perception. This could occur both with interferon treatment, and in individuals with elevated endogenous interferon, such as those with viraemia, cancer or depression. Interferon gamma may also enhance pain signals in the spinal cord by virtue of its induction of nitric oxide synthetase (Meller *et al*. 1994; Xu *et al*. 1994; Robertson *et al*. 1997).

HYPOTHESIS

It is proposed that exogenous interferons cause depression and increased pain sensitivity in susceptible individuals by suppressing tryptophan availability and, consequently, serotonin synthesis. This accords with the earlier suggestion that endogenous interferon production in cancer, systemic viral infection, etc. is responsible for the symptoms of depression, fatigue and weakness common in those conditions (Brown, 1996). Support for this view has come from the finding that depression is associated with high levels of an interferon gamma marker (neopterin) and decreased tryptophan in patients with metastatic cancer (Iwagaki *et al*. 1997) as well as from the large body of work linking immune activation and reduced tryptophan in medically healthy depressives (Maes *et al*. 1994, 1996).

Although immune activation may reduce whole body serotonin synthesis by suppression of circulating tryptophan availability, direct CNS effects of interferons on mood, cognitive function and pain perception (Smith, 1991) are also made plausible by the discovery that interferon-inducible indoleamine dioxygenase is present in human brain (Heyes *et al*. 1996). An analogous effect of interferons on serotonin transmission in the spinal cord may underlie some of their algesic effects. More severe examples of cognitive dysfunction, some of which are irreversible (Valentine *et al*. 1998), might relate to neurotoxic effects of quinolinic acid produced from tryptophan by indoleamine dioxygenase (Sanni *et al*. 1998).

The reduction of tryptophan levels seems to induce depression only in some susceptible individuals. The risk of interferon-induced depression may derive from both individual factors and psychosocial stress (Yokoyama *et al*. 1996) but opinion varies regarding the importance of a previous history of mood disorder. By contrast, the risk factors for neurotoxicity, in particular cognitive impairment, are more generally agreed to include age, a history of CNS disease, cranial irradiation, or intrathecal interferon administration (Steinmann *et al*. 1993; Vial & Descotes, 1996; Valentine *et al*. 1998). Risk of depression could differ for different interferons, as their effects on tryptophan and serotonin do vary to some extent, and they are used for different indications (Table 1). It is not known, for example, whether interferon alpha and beta suppress plasma tryptophan *in vivo* to the same extent as interferon gamma.

Indirect effects on mood mediated by endocrine disturbances are also likely to be relevant, given the striking activation of the hypothalamic–pituitary–adrenal axis caused by pro-inflammatory cytokines (Vial & Descotes, 1996). Elevated glucocorticoids can of course themselves deleteriously affect mood and cognitive function, in a manner not dissimilar to interferons. Adding to the complexity, cytokines can affect glucocorticoid receptor function (McCann *et al*. 1994) while glucocorticoids in turn may modify the effects of interferons, for example by further suppressing tryptophan availability (Maes *et al*. 1990), or, paradoxically, by reversing the induction of brain indoleamine oxygenase (Sanni *et al*. 1998). Interferon treatment is also associated with high rates of thyroid dysfunction, especially immune thyroiditis, suggested to play a role in some cases of interferon-provoked affective disorder (Vial & Descotes, 1996).

In addition to manifold impacts on indoleamine metabolism and function, interferon

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

effects on dopamine may also be important to its mood and behavioural toxicity. Dopaminergic transmission is suppressed, at least in the mouse, by exogenous interferon alpha (Shuto *et al.* 1997), consistent with inhibition of locomotor and especially goal-directed activity (Dantzer *et al.* 1996). On the other hand, another cytokine (interleukin-1) has been reported to stimulate tyrosine hydroxylase activity in brain (Abreu *et al.* 1994), possibly reflecting a compensatory mechanism.

MANAGEMENT

Depression in medical illness confers increased morbidity and mortality and needs to be discerned and treated adequately. This is particularly true when depression is also a complication of needed treatment, as is often the case with interferon therapies (Weiss, 1998). Some studies have shown no net effect (Schwartz *et al.* 1997) or a distinctly deleterious effect (Hill *et al.* 1995) of interferon treatment on quality of life, when both disease progression and drug toxicity are taken into account.

Systematic treatment trials of interferon-induced depression are yet to be published. Case-reports document the usefulness of nortriptyline (Goldman, 1994) and fluoxetine (Levenson & Fallon, 1993); psychostimulants such as methylphenidate (Valentine *et al.* 1998) may also be useful in depressions secondary to treatment with interferon alpha. Depression associated with interferon beta treatment of multiple sclerosis appeared to respond comparably well to either psychotherapy or (unspecified) antidepressants according to a questionnaire survey of 85 patients, 35 of whom had experienced new or worsened depression (Mohr *et al.* 1997). Patients having had either psychotherapy or antidepressants were much more likely to persist with interferon than those whose depression remained untreated (88% *v.* 38%).

To date there is virtually no information available regarding treatment of depression induced by interferon gamma, interleukin-2 or imiquimod, or regarding management (other than treatment withdrawal) for cognitive dysfunction induced by any of the interferons. Management of interferon-induced pain syndromes has been mainly by dose reduction; indomethacin has been shown to be helpful only for the side effect of fever (Miller *et al.* 1989) and antidepressants are yet to be systematically tested.

Antidepressants are worth evaluating in the management of interferon side effects, particularly in light of the discovery that clinical concentrations of tricyclics (clomipramine, imipramine), SSRIs (citalopram, sertraline) or trazodone can, when incubated with leucocytes *in vitro*, suppress endogenous release (Xia *et al.* 1996; Maes *et al.* 1999) of interferon gamma and other cytokines. There is also evidence that antidepressants can affect the expression of genes regulated by interferon gamma (Zhu *et al.* 1994). Moreover, clomipramine and sertraline are able to stimulate release of the anti-inflammatory interleukin-10 (Maes *et al.* 1999), which has been shown to reverse some of the toxic behavioural effects of cytokine activation in animals (Bluthe *et al.* 1999). Antidepressants may thus reduce the effects of interferons on brain function, and may also act to normalize excessive HPA-axis activity by enhancing glucocorticoid negative feedback at the level of the hypothalamus.

Beneficial effects of antidepressants on interferon-induced pain could theoretically arise from a number of mechanisms, including suppression of cytokine release (above), reversal of cytokine stimulation of cyclo-oxygenase or nitric oxide synthase activity, or enhancement of endogenous opioid activity. As noted above, no evidence has yet been reported to support or refute these possibilities.

Although concern has been expressed that antidepressants may promote tumour growth (Storch, 1996), evidence to date has been meagre. One case of mycosis fungoides (Vermeer & Willemze, 1996) was reported to worsen after fluoxetine treatment, possibly indicating a reversal of the benefit of interferon treatment. In any event, untreated depression also confers the risk of immunocompromise and impaired natural killer cell activity, and effective management of depression remains an essential treatment goal.

Focusing on the antiserotonergic effects of interferons, it has been suggested that selective serotonin reuptake inhibitors (SSRIs) are a logical option (Valentine *et al.* 1998). On the other hand, the use of SSRIs may be limited by the extent of tryptophan and serotonin de-

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

pletion, as these drugs do require serotonin in order to work (Blier & DeMontigny, 1994). Since dietary depletion of tryptophan strikingly reverses the efficacy of the SSRIs (Delgado *et al*. 1991), it may turn out that interferon-induced depressions are, somewhat ironically, resistant to the predominantly presynaptic action of the SSRIs. Consistent with this idea, a recent case report suggests reversal of pre-existing SSRI response by interferon alpha (McAllister-Williams *et al*. 2000).

Perhaps a more logical approach to interferon-induced depression would be to offset directly the postulated 'lesion' using tryptophan supplementation. Problems with this strategy include its disappointing efficacy in treating primary depression, probably related to the fact that the lion's share (up to 95%) of oral tryptophan is metabolized not to serotonin but down another (kynurenine) pathway. High doses of tryptophan, like treatment with Type I interferons, induce tryptophan dioxygenase, and would shunt an even larger fraction of the aminoacid away from the serotonin pathway. Even if large doses of supplementary tryptophan were able to restore plasma levels of the aminoacid, such repletion might also reverse the desirable antiproliferative effects (Taylor & Feng, 1991) and potentiate the neurotoxic effects of interferon (Brown, 1996).

Another strategy to offset the impact of interferons on serotonergic function would be to inhibit indoleamine or tryptophan dioxygenase pharmacologically (Brown, 1996). Such inhibitors, not yet tested clinically, may hold promise as antidepressants but would unfortunately also confer the risk of reversing the beneficial immune effects of interferon. On the other hand, if brain indoleamine dioxygenase could be selectively inhibited, this could theoretically reverse CNS effects and preserve the desired peripheral actions of interferon. Dexamethasone, which both inhibits all pro-inflammatory cytokines and appears specifically to block the activation of brain indolemine dioxygenase by interferon gamma (Sanni *et al*. 1998), may also be worth evaluating in this regard. Such a strategy is not without risk, since dexamethasone and other glucocorticoids can induce a variety of CNS side effects similar to interferons (Cowen, 1998), and share with these cytokines the capacity to suppress tryptophan availability (Maes *et al*. 1990) by inducing indoleamine oxygenase in the periphery.

Based on the foregoing, a number of predictions can be made with regard to optimum treatment of interferon-induced neurotoxicity. With regard to antidepressants, there is a potential advantage to those that are able to enhance serotonergic function directly, without depending upon (or offsetting interferon-suppressed) tryptophan hydroxylase activity. One logical strategy would include 5-hydroxytryptophan, which bypasses this rate limiting step and is decarboxylated directly to serotonin in the brain (see Sargent *et al*. 1998). A particularly effective combination might be 5-hydroxytryptophan and peripheral decarboxylase inhibitor (or SSRI). Another strategy would be to use directs acting post-synaptic serotonin receptor agonists, such as buspirone (Glitz & Pohl, 1991), or therapies that enhance the sensitivity of serotonin receptors when given repeatedly, such as tricyclics or ECT (Blier & DeMontigny, 1994).

There would also be theoretical advantage to treatments that have other, non-serotonergic mechanisms of action, including noradrenaline or dopamine enhancers (e.g. reboxetine or bupropion), or alternatively tricyclics or ECT, which produce pervasive changes in neurotransmitter signal transduction pathways (Menkes *et al*. 1983; Avissar *et al*. 1998). We predict such non-SSRI antidepressant treatments will be more resilient to the antiserotonergic effects of interferon (McAllister-Williams *et al*. 2000), just as they appear to be to the effects of dietary tryptophan depletion (Delgado *et al*. 1991; Cassidy *et al*. 1997). Comparative trials of different antidepressant strategies in interferon neurotoxic syndromes will be necessary to establish the clinical utility of these predictions.

REFERENCES

Abreu, P., Llorente, E., Hernandez, M. M. & Gonzalez, M. C. (1994). Interleukin-1 stimulates tyrosine hydroxylase activity in the median eminence. *Neuroreport* **5**, 1356–1358.

Adam, Z. (1994). Adverse effects of interferon alfa. *Vnitrni Lekarstvi* **40**, 127–129.

Anderson, I., Parry-Billings, M., Newholme, E., Poortmans, J. & Cowen, P. (1990). Decreased plasma tryptophan concentration in major depression: relationship to melancholia and weight loss. *Journal of Affective Disorders* **20**, 185–191.

Anonymous (1995). Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and The University of

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

British Columbia MS/MRI Analysis Group. *Neurology* **45**, 1277–1285.
Arai, H., Tanaka, M., Ohta, K., Kojo, T., Niijima, K. & Imawari, M. (1995). Symptomatic myopathy associated with interferon therapy for chronic hepatitis C. *Lancet* **345**, 582.
Ashcroft, G., Crawford, T. & Eccleston, D. (1966). 5-hydroxyindole compounds in the cerebrospinal fluid of patients with psychiatric or neurological diseases. *Lancet* ii, 1049–1050.
Avissar, S., Nechamkin, Y., Roitman, G. & Schreiber, G. (1998). Dynamics of ECT normalization of low G protein function and immunoreactivity in mononuclear leukocytes of patients with major depression. *American Journal of Psychiatry* **155**, 666–671.
Bentivoglio, M., Grassi-Zucconi, G., Olsson, T. & Kristensson, K. (1994). *Trypanosoma brucei* and the nervous system. *Trends in Neurosciences* **17**, 325–329.
Blier, P. & DeMontigny, C. (1994). Current advances and trends in the treatment of depression. *Trends in Pharmacological Sciences* **15**, 220–225.
Bluthe, R. M., Castanon, N., Pousset, F., Bristow, A., Ball, C., Lestage, J., Michaud, B., Kelley, K. W. & Dantzer, R. (1999). Central injection of IL-10 antagonizes the behavioural effects of lipopolysaccharide in rats. *Psychoneuroendocrinology* **24**, 301–311.
Boehm, U., Klamp, T., Groot, M. & Howard, J. C. (1997). Cellular responses to interferon-gamma. *Annual Review of Immunology* **15**, 749–795.
Bonaccorso, S., Lin, A. H., Verkerk, R., Van Hunsel, F., Libbrecht, I., Scharpe, S., DeClerck, L., Biondi, M., Janca, A. & Maes, M. (1998). Immune markers in fibromyalgia: comparison with major depressed patients and normal volunteers. *Journal of Affective Disorders* **48**, 75–82.
Borden, E. C. & Parkinson, D. (1998). A perspective on the clinical effectiveness and tolerance of interferon-alpha. *Seminars in Oncology* **25**, 3–8.
Brenard, R. (1997). Practical management of patients treated with alpha interferon. *Acta Gastroenterologica Belgica* **60**, 211–213.
Brown, R. (1996). Metabolism and biology of tryptophan – some clinical implications. In *Recent Advances in Tryptophan Research* (ed. G. Filippini, C. Costa and A. Bertazzo), pp. 15–25. Plenum: New York.
Byrne, G., Lehmann, L., Kirschbaum, J., Borden, E., Lee, C. & Brown, R. (1986). Induction of tryptophan degradation in vitro and in vivo: a gamma interferon stimulated activity. *Journal of Interferon Research* **6**, 389–396.
Cassidy, F., Murry, E., Weiner, R. & Carroll, B. (1997). Lack of relapse with tryptophan depletion following successful treatment with ECT. *American Journal of Psychiatry* **154**, 1151–1152.
Chia, Y. W., Carachi, R., Armstrong, A. A., McGarry, G. W. & Carrington, D. (1993). Serum alpha interferon in children with right iliac fossa pain. *Journal of the Royal Society of Medicine* **86**, 259–260.
Connor, T. J. & Leonard, B. E. (1998). Depression, stress and immunological activation: the role of cytokines in depressive disorders. *Life Sciences* **62**, 583–606.
Cowen, P. J. (1998). Back to the future: the neurobiology of major depression. *Psychological Medicine* **28**, 253–255.
Dalakas, M. C., Mock, V. & Hawkins, M. J. (1998). Fatigue: definitions, mechanisms, and paradigms for study. *Seminars in Oncology* **25**, 48–53.
Daniels, H. M., Meager, A., Eddleston, A. L., Alexander, G. J. & Williams, R. (1990). Spontaneous production of tumour necrosis factor alpha and interleukin-1 beta during interferon-alpha treatment of chronic HBV infection. *Lancet* **335**, 875–877.
Dantzer, R., Bluthe, R. M., Aubert, A., Goodall, G., Bret-Dibat, J. L., Kent, S., Goujon, E., Laye, S., Parnet, P. & Kelley, P. W. (1996). Cytokine actions on behavior. In *Cytokines in the Nervous System* (ed. N. J. Rothwell), pp. 117–144. Landes Biomedical Publishers: Austin, TX.
Delgado, P., Price, L., Miller, H., Salomon, R., Licinio, J., Krystal, J., Heninger, G. & Charney, D. (1991). Rapid serotonin depletion as a provocative challenge test for patients with major depression. *Psychopharmacology Bulletin* **27**, 321–330.
Dunbar, P. R., Hill, J., Neale, T. J. & Mellsop, G. W. (1992). Neopterin measurement provides evidence of altered cell-mediated immunity in patients with depression but not with schizophrenia. *Psychological Medicine* **22**, 1051–1057.
Farkkila, M., Iivanainen, M., Roine, R., Bergstrom, L., Laaksonen, R., Niemi, M. L. & Cantell, K. (1984). Neurotoxic and other side effects of high-dose interferon in amyotrophic lateral sclerosis. *Acta Neurologica Scandinavica* **70**, 42–46.
Fent, K. & Zbinden, G. (1987). Toxicity of interferon and interleukin. *Trends in Pharmacological Sciences* **8**, 100–105.
Gisslinger, H., Chott, A., Scheithauer, W., Gilly, B., Linkesch, W. & Ludwig, H. (1991). Interferon in essential thrombocythaemia. *British Journal of Haematology* **79** (Suppl. 1), 42–47.
Glitz, D. & Pohl, R. (1991). 5-HT-1a partial agonists – what is their future? *Drugs* **41**, 11–18.
Goldberg, D. & Blackwell, B. (1970). Psychiatric illness in general practice. *British Medical Journal* ii, 439–441.
Goldman, L. (1994). Successful treatment of interferon-alpha-induced mood disorder with nortriptyline. *Psychosomatics* **35**, 412–413.
Goldstein, D., Hertzog, P., Tomkinson, E., Couldwell, D., McCarville, S., Parrish, S., Cunningham, P., Newell, M., Owens, M. & Cooper, D. A. (1998). Administration of imiquimod, an interferon inducer, in asymptomatic human immunodeficiency virus-infected persons to determine safety and biologic response modification. *Journal of Infectious Diseases* **178**, 858–861.
Heyes, M. P., Achim, C. L., Wiley, C. A., Major, E. O., Saito, K. & Markey, S. P. (1996). Human microglia convert l-tryptophan into the neurotoxin quinolinic acid. *Biochemical Journal* **320**, 595–597.
Hill, M., Norman, A., Cunningham, D., Findlay, M., Nicolson, V., Hill, A., Iveson, A., Evans, C., Joffe, J., Nicolson, M. & Hickish, T. (1995). Royal Marsden phase III trial of fluorouracil with or without interferon alfa-2b in advanced colorectal cancer. *Journal of Clinical Oncology* **13**, 1297–1302.
Iwagaki, H., Hizuta, A., Uomoto, M., Takeuchi, Y., Saito, S. & Tanaka, N. (1997). Cancer cachexia and depressive states: a neuroendocrine-immunological disease? *Acta Medica Okayama* **51**, 233–236.
Janson, E. T., Kauppinen, H. L. & Oberg, K. (1993). Combined alpha- and gamma- interferon therapy for malignant midgut carcinoid tumors. A phase I–II trial. *Acta Oncologica* **32**, 231–233.
Janssen, H. L., Brouwer, J. T., van der Mast, R. C. & Schalm, S. W. (1994). Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *Journal of Hepatology* **21**, 241–243.
Jessell, T. (1982). Pain. *Lancet* iv, 1084–1087.
Johnson, M. E., Fisher, D. G., Fenaughty, A. & Theno, S. A. (1998). Hepatitis C virus and depression in drug users. *American Journal of Gastroenterology* **93**, 795–789.
Kagaya, A., Uchitomi, Y., Takezaki, E., Fukue, M., Tsukano, K., Kugaya, A., Minagawa, H., Takebayashi, M., Zensho, H., Oyamada, T. & Yamawaki, S. (1997). Plasma levels of cyclic GMP, immune parameters and depressive status during interferon therapy. A prospective study in Japan. *Neuropsychobiology* **35**, 128–131.
Koenig, H. (1998). Depression in hospitalized older patients with congestive heart failure. *General Hospital Psychiatry* **20**, 29–43.
Kugaya, A., Kagaya, A., Uchitomi, Y., Yokota, N. & Yamawaki, S. (1996). Effect of interferon-alpha on DOI-induced wet-dog shakes in rats. *Journal of Neural Transmission* **103**, 947–955.
Levenson, J. L. & Fallon, H. J. (1993). Fluoxetine treatment of depression caused by interferon-alpha. *American Journal of Gastroenterology* **88**, 760–761.
Liberati, A. M., Biagini, S., Perticoni, G., Ricci, S., D'Alessandro, P., Senatore, M. & Cinieri, S. (1990). Electrophysiological and neuropsychological functions in patients treated with interferon-beta. *Journal of Interferon Research* **10**, 613–619.
Liberati, A. M., Garofani, P., De Angelis, V., Di Clemente, F., Horisberger, M., Cecchini, M., Betti, A. R., Palmisano, L., Astolfi, S., Nastari, A., Villa, A. & Arzano, S. (1994*a*). Double-blind randomized phase I study on the clinical tolerance and pharmacodynamics of natural and recombinant interferon-beta given intravenously. *Journal of Interferon Research* **14**, 61–69.

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

Liberati, A. M., Horisberger, M. A., Garofani, P., De Angelis, V., Ferrajoli, A., Di Clemente, F., Caricchi, P., Adiuto, D., Fedeli, L. & Palumbo, B. (1994*b*). Interferon-alpha-induced biologic modifications in patients with chronic myelogenous leukemia. *Journal of Interferon Research* **14**, 349–355.

Lublin, F., Whitaker, J., Eidelman, B, Miller, A., Arnason, B. & Burks, J. (1996). Management of patients receiving interferon beta-1b for multiple sclerosis. *Neurology* **46**, 12–18.

McAllister-Williams, R. H., Young, A. H. & Menkes, D. B. (2000). Antidepressant response reversed by interferon. *British Journal of Psychiatry* **176**, 93.

McCann, S. M., Lyson, K. & Karanth, S. (1994). Role of the cytokines in the endocrine system. *Annals of the New York Academy of Sciences* **741**, 50–63.

McDonald, E., Mann, A. & Thomas, H. (1987). Interferons as mediators of psychiatric morbidity. *Lancet* iv, 1175–1178.

Mackenzie, C. R., Willberg, C. B. & Daubener, W. (1998). Inhibition of group B streptococcal growth by IFN gamma-activated human glioblastoma cells. *Journal of Neuroimmunology* **89**, 191–197.

Maes, M. & Meltzer, H. Y. (1995). The serotonin hypothesis of major depression. In *Psychopharmacology: The Fourth Generation of Progress*, (ed. F. E. Bloom and D. J. Kupfer), pp. 933–944. Raven Press: New York.

Maes, M., Jacobs, M. P., Suy, E., Minner, B., Leclercq, C., Christiaens, F. & Raus, J. (1990). Suppressant effects of dexamethasone on the availability of plasma L-tryptophan and tyrosine in healthy controls and in depressed patients. *Acta Psychiatrica Scandinavica* **81**, 19–23.

Maes, M., Meltzer, H. Y., Scharpe, S., Bosmans, E., Suy, E., DeMeester, I., Calabrese, J. & Cosyns, P. (1993). Relationships between lower plasma L-tryptophan levels and immune-inflammatory variables in depression. *Psychiatry Research* **49**, 151–165.

Maes, M., Scharpe, S., Meltzer, H. Y., Okayli, G., Bosmans, E., D'Hondt, P., Van den Bossche, B. V. & Cosyns, P. (1994). Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: further evidence for an immune response. *Psychiatry Research* **54**, 143–160.

Maes, M., Wauters, A., Verkerk, R., Demedts, P., Neels, H., Van Gastel, A., Cosyns, P., Scharpe, S. & Desnyder, R. (1996). Lower serum L-tryptophan availability in depression as a marker of a more generalized disorder in protein metabolism. *Neuropsychopharmacology* **15**, 243–251.

Maes, M., Verkerk, R., Vandoolaeghe, E., Van Hunsel, F., Neels, H., Wauters, A., Demedts, P. & Scharpe, S. (1997). Serotonin-immune interactions in major depression: lower serum tryptophan as a marker of an immune-inflammatory response. *European Archives of Psychiatry and Clinical Neuroscience* **247**, 154–161.

Maes, M., Song, C., Lin, A. H., Bonaccorso, S., Kenis, G., DeJongh, R., Bosmans, E. & Scharpe, S. (1999). Immunoregulatory effects of antidepressants: inhibition of interferon-gamma and stimulation of interleukin-10 secretion. *Neuropsychopharmacology* **20**, 370–379.

Malaguarnera, M., Di Fazio, I., Restuccia, S., Pistone, G., Ferlito, L. & Rampello, L. (1998). Interferon alpha-induced depression in chronic hepatitis C patients: comparison between different types of interferon alpha. *Neuropsychobiology* **37**, 93–97.

Matsushita, E., Unoura, M. & Kobayashi, K. (1994). Psychiatric complications of interferon therapy. (In Japanese). *Nippon Rinsho – Japanese Journal of Clinical Medicine* **52**, 1910–1913.

Mehta, S. J., Miller, R. D., Ramirez, J. A. & Summersgill, J. T. (1998). Inhibition of Chlamydia pneumoniae replication in HEp-2 cells by interferon-gamma: role of tryptophan catabolism. *Journal of Infectious Diseases* **177**, 1326–1331.

Meller, S. T., Dykstra, C., Grzybycki, D., Murphy, S. & Gebhart, G. F. (1994). The possible role of glia in nociceptive processing and hyperalgesia in the spinal cord of the rat. *Neuropharmacology* **33**, 1471–1478.

Menkes, D. B., Rasenick, M. M., Wheeler, M. A. & Bitensky, M. W. (1983). Guanosine triphosphate activation of brain adenylate cyclase: enhancement by long-term antidepressant treatment. *Science* **219**, 65–67.

Menkes, D. B., Coates, D. C. & Fawcett, J. P. (1994). Acute tryptophan depletion aggravates premenstrual syndrome. *Journal of Affective Disorders* **32**, 37–44.

Miller, R. L., Steis, R. G., Clark, J. W., Smith, J. W. d., Crum, E., McKnight, J. E., Hawkins, M. J., Jones, M. J., Longo, D. L. & Urba, W. J. (1989). Randomized trial of recombinant alpha 2b-interferon with or without indomethacin in patients with metastatic malignant melanoma. *Cancer Research* **49**, 1871–1876.

Mohr, D. C., Goodkin, D. E., Likosky, W., Gatto, N., Baumann, K. A. & Rudick, R. A. (1997). Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Archives of Neurology* **54**, 531–533.

Morikawa, O., Sakai, N., Obara, H. & Saito, N. (1998). Effects of interferon-alpha, interferon-gamma and cAMP on the transcriptional regulation of the serotonin transporter. *European Journal of Pharmacology* **349**, 317–324.

Nagineni, C. N., Pardhasaradhi, K., Martins, M. C., Detrick, B. & Hooks, J. J. (1996). Mechanisms of interferon-induced inhibition of *Toxoplasma gondii* replication in human retinal pigment epithelial cells. *Infection and Immunity* **64**, 4188–4196.

Neilley, L. K., Goodin, D. S., Goodkin, D. E. & Hauser, S. L. (1996). Side effect profile of interferon beta-1b in MS: results of an open label trial. *Neurology* **46**, 552–554.

Niiranen, A., Laaksonen, R., Iivanainen, M., Mattson, K., Farkkila, M. & Cantell, K. (1988). Behavioral assessment of patients treated with alpha-interferon. *Acta Psychiatrica Scandinavica* **78**, 622–666.

Olsen, E. A., Rosen, S. T., Vollmer, R. T., Variakojis, D., Roenigk, H. H. Jr., Diab, N. & Zeffren, J. (1989). Interferon alfa-2a in the treatment of cutaneous T cell lymphoma. *Journal of the American Academy of Dermatology* **20**, 395–407.

Pajkos, G., Bodoky, G., Padi, E., Izso, J. & Szanto, J. (1998). Low-dose leucovorin and interferon-alpha as modulators of 5-fluorouracil for adjuvant chemotherapy of colorectal cancer. (In Hungarian). *Orvosi Hetilap* **139**, 1571–1575.

Prasad, S., Waters, B. & Hill, P. (1992). Psychiatric side-effects of interferon alfa-2b in patients treated for hepatitis C. *Clinical Research* **40**, 840A.

Quintana, J. (1992). Platelet serotonin and plasma tryptophan decreases in endogenous depression. *Journal of Affective Disorders* **24**, 55–62.

Rajkumar, S. V., Buckner, J. C., Schomberg, P. J., Cascino, T. L., Burch, P. A. & Dinapoli, R. P. (1998). Phase I evaluation of radiation combined with recombinant interferon alpha-2a and BCNU for patients with high-grade glioma. *International Journal of Radiation Oncology, Biology, Physics* **40**, 297–302.

Recht, M., Borden, E. C. & Knight, E., Jr. (1991). A human 15-kDa IFN-induced protein induces the secretion of IFN-gamma. *Journal of Immunology* **147**, 2617–2623.

Renault, P., Hoofnagle, J., Park, Y., Mullen, K., Peters, M., Jones, B., Rustgi, V. & Jones, E. (1987). Psychiatric complications of long-term interferon alpha therapy. *Archives of Intern Medicine* **147**, 1577–1580.

Rifflet, H., Vuillemin, E., Oberti, F., Duverger, P., Laine, P., Garre, J. B. & Cales, P. (1998). Suicidal impulses in patients with chronic viral hepatitis C during or after therapy with interferon alpha. (In French). *Gastroenterologie Clinique et Biologique* **22**, 353–357.

Robertson, B., Xu, X. J., Hao, J. X., Wiesenfeld-Hallin, Z., Mhlanga, J., Grant, G. & Kristensson, K. (1997). Interferon-gamma receptors in nociceptive pathways: role in neuropathic pain-related behaviour. *Neuroreport* **8**, 1311–1316.

Robertson, M. & Katona, C. (eds.) (1997). *Depression and Physical Illness. Perspectives in Psychiatry*. Wiley: Chichester.

Sainokami, S., Hino, K., Shimoda, K. & Niwa, H. (1994). Clinical analysis of patients with chronic hepatitis C who discontinued interferon treatment because of side effects – our experiences and recent reports. (In Japanese). *Nippon Rinsho – Japanese Journal of Clinical Medicine* **52**, 1889–1894.

Sanni, L. A., Thomas, S. R., Tattam, B. N., Moore, D. E., Chaudhri, G., Stocker, R. & Hunt, N. H. (1998). Dramatic changes in oxidative tryptophan metabolism along the kynurenine pathway in experimental cerebral and noncerebral malaria. *American Journal of Pathology* **152**, 611–619.

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press

Sargent, P. A., Quested, D. J. & Cowen, P. J. (1998). Clomipramine enhances the cortisol response to 5-HTP: implications for the therapeutic role of 5-HT2 receptors. *Psychopharmacology* **140**, 120–122.

Schwartz, C. E., Coulthard-Morris, L., Cole, B. & Vollmer, T. (1997). The quality-of-life effects of interferon beta-1b in multiple sclerosis. An extended Q-TWiST analysis. *Archives of Neurology* **54**, 1475–1480.

Seidel, A., Arolt, V. & Hunstiger, M. (1995). Cytokine production and serum proteins in depression. *Scandinavian Journal of Immunology* **41**, 534–538.

Seidel, A., Arolt, V., Hunstiger, M., Rink, L., Behnisch, A. & Kirchner, H. (1996). Increased CD56+ natural killer cells and related cytokines in major depression. *Clinical Immunology and Immunopathology* **78**, 83–85.

Shintani, F., Kanba, S., Nakaki, T., Nibuya, M., Kinoshita, N., Suzuki, E., Yagi, G., Kato, R. & Asai, M. (1993). Interleukin-1 beta augments release of norepinephrine, dopamine, and serotonin in the rat anterior hypothalamus. *Journal of Neuroscience* **13**, 3574–3581.

Shtalrid, M., Lugassy, G., Rosensaft, J. & Berrebi, A. (1993). Treatment of chronic myeloid leukemia with interferon alpha (Roferon): results of the Israeli Study Group on CML. *Leukemia and Lymphoma* **11** (Suppl. 1), 193–197.

Shuto, H., Kataoka, Y., Horikawa, T., Fujihara, N. & Oishi, R. (1997). Repeated interferon-alpha administration inhibits dopaminergic neural activity in the mouse brain. *Brain Research* **747**, 348–351.

Slovin, S. F., Scher, H. I., Divgi, C. R., Reuter, V., Sgouros, G., Moore, M., Weingard, K., Pettengall, R., Imbriaco, M., El-Shirbiny, A., Finn, R., Bronstein, J., Brett, C., Milenic, D., Dnistrian, A., Shapiro, L., Schlom, J. & Larson, S. M. (1998). Interferon-gamma and monoclonal antibody 131I-labeled CC49: outcomes in patients with androgen-independent prostate cancer. *Clinical Cancer Research* **4**, 643–651.

Smith, K., Fairburn, C. & Cowen, P. (1997). Relapse of depression after rapid depletion of tryptophan. *Lancet* **349**, 915–919.

Smith, R. S. (1991). The immune system is a key factor in the etiology of psychosocial disease. *Medical Hypotheses* **34**, 49–57.

Steinmann, G. G., Rosenkaimer, F. & Leitz, G. (1993). Clinical experiences with interferon-alpha and interferon-gamma. *International Review of Experimental Pathology* **34 Pt B**, 193–207.

Storch, D. (1996). Do antidepressants promote tumor growth? *American Journal of Psychiatry* **153**, 446.

Strander, H. (1997). Toxicities of interferons. In *Clinical Applications of the Interferons* (ed. R. Stuart-Harris & R. Penny), pp. 331–363. Chapman & Hall: London.

Taylor, M. & Feng, G. (1991). Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. *FASEB Journal* **5**, 2516–2522.

Taylor, M. W., Konan, V. K. & Yu, D. (1996). Tryptophan starvation is involved in human interferon-gamma mediated apoptosis. *Advances in Experimental Medicine and Biology* **398**, 155–159.

Ucar, R., Sanwo, M., Ucar, K. & Beall, G. (1995). Interferons: their role in clinical practice. *Annals of Allergy, Asthma and Immunology* **75**, 377–386.

Valentine, A. D., Meyers, C. A., Kling, M. A., Richelson, E. & Hauser, P. (1998). Mood and cognitive side effects of interferon-alpha therapy. *Seminars in Oncology* **25**, 39–47.

Van Thiel, D. H., Friedlander, L., Molloy, P. J., Fagiuoli, S., Kania, R. J. & Caraceni, P. (1995). Interferon-alpha can be used successfully in patients with hepatitis C virus-positive chronic hepatitis who have a psychiatric illness. *European Journal of Gastroenterology & Hepatology* **7**, 165–168.

Vermeer, M. & Willemze, R. (1996). Is mycosis fungoides exacerbated by fluoxetine? *Journal of the American Academy of Dermatology* **35**, 635–636.

Vial, T. & Descotes, J. (1996). Drugs acting on the immune system. In *Meyler's Side Effects of Drugs* (ed. M. Dukes), pp. 1090–1165. Elsevier: Amsterdam.

Weiland, O., Danielsson, A. & Loof, L. (1998). Treatment response in chronic hepatitis C. Content of virus in serum is decisive for the outcome. (In Swedish). *Lakartidningen* **95**, 40–43.

Weiss, K. (1998). Safety profile of interferon-alpha therapy. *Seminars in Oncology* **25**, 9–13.

Wisloff, F., Hjorth, M., Kaasa, S. & Westin, J. (1996). Effect of interferon on the health-related quality of life of multiple myeloma patients: results of a Nordic randomized trial comparing melphalan-prednisone to melphalan-prednisone + alpha-interferon. The Nordic Myeloma Study Group. *British Journal of Haematology* **94**, 324–332.

Xia, Z., DePierre, J. W. & Nassberger, L. (1996). Tricyclic antidepressants inhibit IL-6, IL-1 beta and TNF-alpha release in human blood monocytes and IL-2 and interferon-gamma in T cells. *Immunopharmacology* **34**, 27–37.

Xu, X. J., Hao, J. X., Olsson, T., Kristensson, K., van der Meide, P. H. & Wiesenfeld-Hallin, Z. (1994). Intrathecal interferon-gamma facilitates the spinal nociceptive flexor reflex in the rat. *Neuroscience Letters* **182**, 263–266.

Yirmiya, R. (1996). Endotoxin produces a depressive-like episode in rats. *Brain Research* **711**, 163–174.

Yokoyama, A., Kimura, Y. & Shigemura, J. (1996). Psychiatric side effects of interferon. *Journal of Toxicological Sciences* **21**, 93–96.

Young, S. (1991). Some effects of dietary components on brain serotonin synthesis, mood, and behavior. *Canadian Journal of Physiology and Pharmacology* **69**, 893–903.

Zhu, J., Bengtsson, B. O., Mix, E., Thorell, L. H., Olsson, T. & Link, H. (1994). Effect of monoamine reuptake inhibiting antidepressants on major histocompatibility complex expression on macrophages in normal rats and rats with experimental allergic neuritis (EAN). *Immunopharmacology* **27**, 225–244.

https://doi.org/10.1017/S0033291799001774 Published online by Cambridge University Press