THE PSYCHOLOGICAL EFFECTS OF INTERFERON TREATMENT IN PATIENTS WITH HEPATITIS B.

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Submitted in fulfillment of the regulations for the degree of Master of Philosophy of the University of London, 1993.

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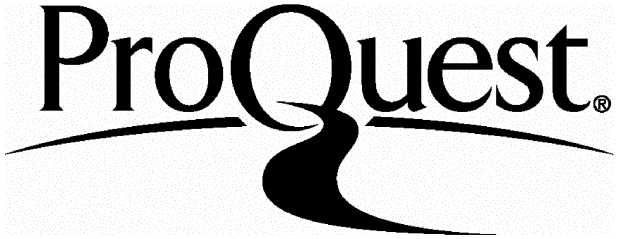


ACKNOWLEDGEMENTS

Grateful acknowledgements to my supervisor Prof. Anthony Mann, to Bob Blizard for statistical assistance, to the patients who agreed to participate in the study and to Prof. H. Thomas, Dr. Linda Scully and other staff in the Medical Unit at the Royal Free Hospital.

ABSTRACT

The study examined psychiatric morbidity in forty-three subjects who were participants in a controlled randomised trial using recombinant alpha 2A interferon to treat chronic hepatitis B infection. Two standardised psychiatric instruments, the General Health Questionnaire and the Clinical Interview Schedule, were used to elicit morbidity in the subjects before treatment with interferon, during treatment and after treatment.

The measures showed a rise in psychiatric symptoms among those on interferon treatment compared with matched controls. The symptoms were non-psychotic in nature, the most commonly reported being fatigue, impaired concentration and irritability. The observed increase in psychiatric morbidity remained even when social stresses and life events were controlled for.

CONTENTS

THE PSYCHOLOGICAL EFFECTS OF INTERFERON TREATMENT IN PATIENTS WITH HEPATITIS B

1. Introduction.

The attempt to understand the relationship between physiological and psychological events is fundamental to philosophical, religious and scientific thought. Philosophers since Plato have debated the relationship between mind and body; and theologians have wrestled with the implications of a universe in which mankind's individual freedom of choice is deemed to be compatible with Divine knowledge of the future or the deterministic laws of Newtonian physics.

Within medicine, a theoretical conception of the relationship between mental and physical events has been central to models of medical intervention since the days where illness was understood as an expression of an imbalance between the four humours. Contrary to what might have been predicted, the advance of empirically-based scientific medicine has served to sharpen rather than dampen down the debate, illustrated, for example, in clashes between advocates of orthodox as opposed to 'holistic' medicine. Nowhere is the controversy more evident than in psychiatry where different schools argue for the relative dominance of psychological as opposed to neurophysiological causation; and where questions are raised in Parliament concerning the nature of so-called 'psychosomatic' conditions such as 'Myalgic Encephalomyelitis'.

It is tempting to conclude that several thousand years of argument have, to date, produced rather more heat than light. However, this would be an over-simplification. It would be more correct to conclude that it is misleading to talk of a single 'relationship' between the mental and the physical. Rather, both science

and experience have shown there to be multiple and complex relationships, relationships which frequently interact with each other to influence human experience and behaviour as well as the workings of the brain and body.

At a practical level, the implication for medical practitioners working in circumstances where both psychological and physical factors are involved, is that care must be exercised in both the giving of treatment and the interpretation of its effects. In routine psychiatry this means that psychiatrists must be alert to the possibility of an organic basis to apparently psychological symptoms; and equally that in the context of physical medicine practitioners need to be aware of the impact of emotional and psychosocial factors. This is particularly relevant where physical treatment is being administered for a physical illness but where both the treatment given and the illness itself have both physical and psychosocial repercussions.

The research described is an investigation into the psychological effects of Alpha interferon treatment in men with chronic Hepatitis B. The project was carried out in the context of a multi-centre trial of recombinant alpha interferon treatment involving the medical unit at the Royal Free Hospital. The medical team had become aware that some individuals in the studies were developing psychiatric symptomatology. The origins and nature of this symptomatology were unclear and the need was thus identified to monitor psychiatric status using standardised psychiatric measures.

The author was seconded for one day a week to the medical team to carry out the research and also to act as a safeguard in the event of severe psychiatric symptoms developing. The research would focus on the occurrence of neurotic symptomatology but that cognisance would also be taken of patients' social situation. The presence of the researcher was also a practical test of the value of a psychiatric attachment within a medical trial.

After the treatment trial had started, an extra dimension was introduced from the discovery of the Human Immunodeficiency Virus and the heightened public awareness of membership of risk groups, in particular homosexuality. At the time, there was no known method of testing for the virus, so the threat of infection hung over the patients who were largely homosexual in the trial. In the event, a significant number of participants were later found to have been HIV+ during the trial. This sub-group became an additional focus of the research.

Before describing the study, the relevant literature on both hepatitis and interferon will be reviewed with particular emphasis on the effects of interferon on the Central Nervous System. Both physical and psychiatric perspectives are taken.

2. Literature Review.

Two bodies of literature were identified as relevant to the study. The first section deals with the nature of hepatitis and the risks associated with chronicity. The second section reviews interferon, its role in health, disease and as a therapeutic agent.

2.1 Hepatitis.

Classic viral hepatitis is caused by four or more distinctive viral agents. Hepatitis A and B are caused by the hepatitis A (HAV) and hepatitis B (HBV) viruses respectively and delta hepatitis is caused by the hepatitis D or delta virus (1). Two of the viruses responsible for what used to be known as non-A,non-B hepatitis, have been characterised in the past three years and their infections are now called hepatitis C and hepatitis E. Hepatitis C is responsible for 95% of post-transfusion hepatitis. There are possibly still other agents to be characterised. Hepatitis B is the infection that this study is concerned with and the following discussion will focus only on hepatitis B. The review describes the virus, its prevalence and its clinical features.

2.1.1 History.

Infections caused by HAV and HBV were observed over a hundred years ago, while hepatitis C and delta hepatitis were only recognised in the past fifteen years (1). The first classic descriptions of hepatitis B were recorded in 1885 (2) when Lurman (3) and Jehn (4) reported the occurrence of catarrhal jaundice in a significant percentage of the workers in a Bremen shipyard and the patients of a Merzig mental hospital who had been vaccinated against smallpox. Epidemiological investigation implicated the vaccine as the supposed cause of the outbreaks.

Subsequent to these reports, the occurrence of unexplained jaundice was observed with increasing frequency in groups of patients who had been treated with parenterally administered medications, particularly after the introduction of Salvarsan and later of insulin. Following this, other reports offered virtually undeniable evidence for an infective aetiology of catarrhal jaundice but the medical establishment of the pre-World WarII era stubbornly refused to accept this. Most of them subscribed to the idea that catarrhal jaundice was caused by an inflammatory mucous plug in the region of the pupilla of Vater, although no-one had documented such a phenomenon. However human-to-human transmission of hepatitis was reported with increasing frequency in individuals who had received plasma or other blood products and this led the way for the acceptance of the viral aetiology of hepatitis B. The final identification and characterisation of HBV took place in the 1960's.

2.1.2 Prevalence.

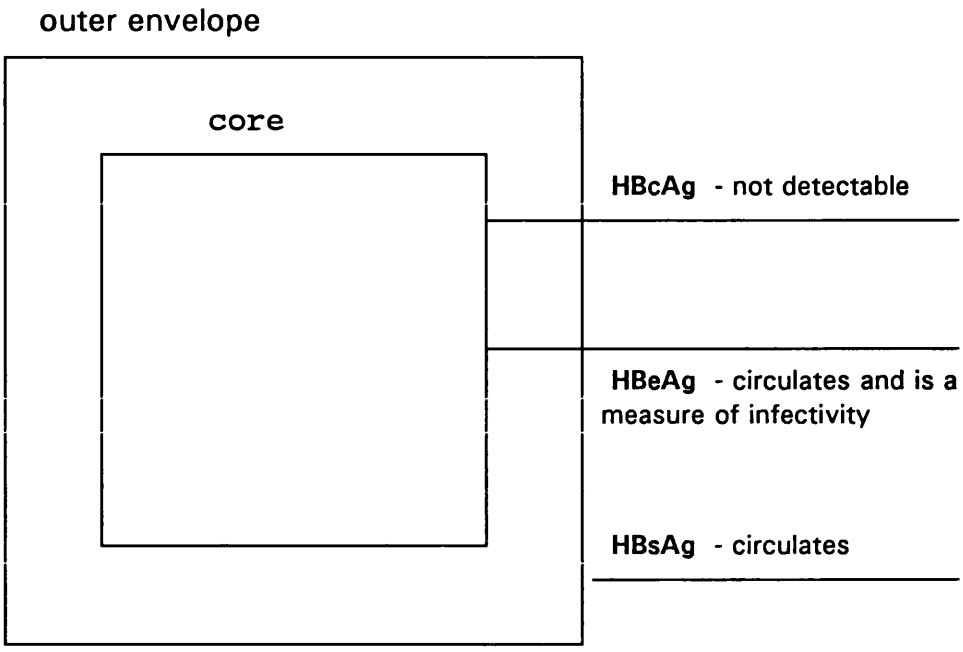
Hepatitis B occurs worldwide but is particularly prevalent in Asian and African countries,where 5% to 20% of the population are chronic carriers. It is rare in the industrialised, developed countries of Western Europe and North America where the carrier rate in the general population is in the region of 0.1%-0.3% (1). However, the carrier state is common in certain high risk groups, including medical personnel (1%), male homosexuals (6%), intravenous drug abusers (7%), dialysis patients (5%) and haemophiliacs (7%) (5). In terms of overall aetiology, hepatitis B accounts for approximately 50% of clinical hepatitis in urban adults in the United States (1).

2.1.3 Hepatitis B Virus.

HBV is a DNA virus that belongs to a group of animal viruses known as the hepadna viruses (6).

The HBV core contains a small circular DNA, which can also be detected in the infected liver cells either as free DNA or in an integrated form. Also within the core of the HBV is the enzyme DNA polymerase and antigenic material known as hepatitis B core antigen (HBcAg). This is not detectable as a circulating particle in the sera of infected patients and is therefore not used for diagnostic serology. The outer envelope of the HBV contains HBsAg, which circulates in huge excess to the number of circulating complete HBV particles. A third distinct antigenic system of the HBV is the hepatitis Be antigen (HBeAg), which appears to be an internal component of the core but is found free in the sera of infected individuals. HBeAg is a marker of infectivity (1). Three antibodies to the three antigens have been identified. Antibody to HBcAg (anti-HBc) is the first to appear in the serum of infected patients and there are two varieties of this antibody, IgM and IgG (7). IgM anti-HBc appears first and lasts for six months after the onset of hepatitis B infection and is a marker for acute or recent hepatitis B infection. After six months it is replaced by IgG anti-HBc. This antibody occurs not only in individuals who recover from hepatitis B, but also in patients who develop chronic hepatitis B infection. Another antibody that follows HBV infection is antibody to HBsAg

Fig.1 Diagrammatic Representation of HBV



(anti-HBs), which is the specific antibody that signals recovery from infection and confers immunity. The third antibody that appears is antibody to HBeAg (anti-HBe). This indicates reduced infectivity.

2.1.4 Transmission.

HBsAg has been detected in saliva and semen and virtually every fluid within and excreted by the body. There are several ways in which hepatitis B can be transmitted. The main mode of transmission in countries where there are high prevalence rates, such as Asia and Africa, is perinatal spread from infected mothers to their newborn infants. In Western countries, it is more commonly spread by transfusion of infectious blood or blood products, inoculation of skin with contaminated needles or instruments, or by close personal contact, especially sexual contact. Data from the Centres for Disease Control regarding cases of hepatitis B for which a source could be determined reveal over one half of cases are attributable to sexual transmission (8).

The sexual transmission of HBV was first recognised in 1971 and susceptible heterosexual partners of persons with acute hepatitis B have a 20% to 40% risk of becoming infected with HBV. Prevalence studies of HBV infection in large populations of homosexual men from several European and U.S. cities reveal that 60% of homosexual men show serological evidence for past or present HBV infection (9).

2.1.5 Clinical features.

The incubation period of hepatitis B has a mean of 12 to 14 weeks but has a wide range, from 50 to 180 days. The symptoms include non-specific influenza-like symptoms of fever, headache, malaise, fatigue, anorexia, nausea, vomiting and

abdominal pain. Patients may experience arthralgia, arthritis, or urticaria. Jaundice appears in one quarter of patients and hepatosplenomegaly and mild hepatic tenderness also occurs. HBV infection in the homosexual man tends to be asymptomatic more often than in the general population (9). Approximately 5% to 10% of patients with acute hep B fail to clear HBsAg within six months and become chronic carriers. These chronically infected patients may be healthy carriers with normal liver chemistries, or may have chronic liver disease with transaminases / abnormal liver function tests. Symptoms associated with chronic hep B are usually mild and non-specific, fatigue being the most common problem. It is often a silent disease and 20% of carriers have chronic active hepatitis with cirrhosis. Ten percent of carriers develop hepatocellular carcinoma. Fulminant hepatitis may follow acute hep B in up to 1% - 2% of infected persons.

A number of factors seem to favour the development of a chronic carrier state (10). These include infection in infancy. The neonatal immune system is less efficient at dealing with viral infections than the mature immune system is and this may in part be due to the presence of immunosuppressive factors such as a-fetoprotein (11). Over 90% of babies born to HBeAg+ HBV carriers become infected and 95% or more of these develop chronic infection. Establishment of chronic infection at this stage is enhanced by the presence of maternal anti-HBc in the fetal circulation (12).

Male gender and generalised host defects such as hypogammaglobulinaemia favour chronicity (10). Chronicity also seems to follow mild anicteric illness rather than a severe attack with deep jaundice. Homosexual men, even those negative for anti-hiv antibody, have immune abnormalities caused by multiple viral and parasitic infections and chronic stimulation by foreign antigenic material. This explains why homosexual men are more likely to have an anicteric illness when infected by HBV and why they are then more likely to become chronic carriers. Approximately 10% of patients with clinically apparent acute hep B can be expected to become chronic carriers. The carrier state is not necessarily lifelong and a small proportion, about 1% to 2% per annum lose the antigen and sero-convert to anti-HBs (13).

The hepatitis B virus is not directly cytopathic and liver injury appears to be the result of the immune response to viral proteins on the hepatocyte membrane. During an acute infection for recovery to occur, cells containing replicating virus must be lysed. Cytotoxic T-cells sensitised to either HBc or HBe antigens are responsible for this process (14). In order for this to occur efficiently, the viral antigens must be displayed along with HLA class 1 protein on the hepatocyte membrane. During acute HBV infection, the amount of this HLA protein increases. However in the majority of patients with chronic hepatitis B, there is no increase in the amount of HLA display. The enhanced display of HLA class 1 proteins during acute infection may be interferon induced and the failure of this process in patients with chronic hepatitis B infection may reflect either impairment of interferon production or impairment of responsiveness of the infected hepatocyte to interferon.

Later in the course of chronic HBV infection, HBV sequences become integrated into the liver cell genome. Many of these cells express HBs-Ag but not HBc-Ag on their surface membranes (15). Therefore for complete elimination of HBV infected cells at this stage, a response must be mounted to both HBc and HBs displaying hepatocytes. In some patients lysis of cells supporting replicating virus may occur but cells containing integrated non-replicating HBV, which do not express HBc, will persist because of a failure of the immune response to HBsAg.

2.1.6 The Psychological and Social Consequences of Chronic Hepatitis B Infection

Aside from some reference to complaints of fatigue (16), there is little formal literature on psychosocial aspects of hepatitis B. However, it would be expected that chronic infection with Hepatitis B would have a broad potential impact on both the person's sense of psychological well-being and their social behaviour.

First, as with any illness, particularly chronic illness, there is the possibility of the

person taking up the 'sick role' as first described by Parsons (17). Although the precise nature of the 'sick role' has been the subject of dispute (18, 19, 20) the main point is that the process of diagnosis itself may have an impact on the person's conception of themselves and their social behaviour. There have not been any studies which examine psychological symptoms in hepatitis B.

Secondly, as with any sexually transmitted disease, the knowledge of being a carrier inevitably brings with it dilemmas concerning who to inform and under what circumstances, and whether and how to modify their sexual behaviour.

A useful feature of the study was that it provided the opportunity for clinical observation of the impact of chronic hepatitis B by a trained psychiatrist. This led to the formation of hypotheses which are described later.

2.2 Interferon.

Interferon is the body's most rapidly produced defence against viruses. This section reviews the history of interferon, its activity in health and disease, its therapeutic potential, its toxicity and its effects on the central nervous system.

2.2.1 History of Interferon.

Interferon (IFN) was discovered by Isaacs and Lindenmann in 1957 during a study of viral interference (21). It was known for some time that if a cell or organism was infected with one virus then a second virus, added subsequently, would not be able to replicate as well as normal (22) and this effect was called virus interference. Isaacs and Lindenmann performed a simple experiment in an attempt to study whether the viral protein or the nucleic acid was essential for establishment of such interference and found that an interfering material was being formed in the cells and released into the fluid. They showed that this substance

was distinct from the virus and they named it "interferon". (It has since been noted that the name is a bigener of Latin and Greek origins, but despite this problem the name has remained (21).

The initial paper by Isaacs and his colleagues was called "The Interferon" (23) as at that time a single substance was thought to be responsible for virus interference. Tyrrell's work in 1959 indicated that there was more than one interferon when he showed that IFN made in calf kidney cells was inactive in chick cells and vice versa (24). He inferred that IFN was only active in the tissue in which it was formed and coined the term "species-specificity". This is an over-simplification and although the word interferon is often used in the singular, the interferons are a family of at least 23 distinct proteins and glycoproteins (25).

2.2.2 Types of Interferons.

The interferons are heterogenous populations of proteins and glycoproteins representing products of at least 23 different genes produced by different types of cells (26). There are three classes of interferon - alpha (a), beta (b) and gamma (g). These types are also described by the cell type in which they are predominantly produced i.e.leucocyte IFN = a-IFN, fibroblast IFN = b-IFN and immune IFN = g-IFN. There are at least 20 sub-types of a-IFN, 2 sub-types of b-IFN and one sub-type of g-IFN.

Interferon-alpha represents a family of structurally similar polypeptides composed of 165-166 amino-acid residues. Interferon-beta has 166 amino-acid residues and is 30% similar to a-interferon. Interferon-gamma is a glycoprotein, which, in humans consists of 143 amino-acid residues and is structurally distinct from alpha- and beta-interferon.

2.2.3 Interferon activity.

Interferons have the ability to affect the regulation of a vast array of cellular

functions. They have anti-viral activities but also possess potent anti-proliferative and immuno-regulatory activities. Alpha and beta interferon are more potent anti-viral agents while gamma-interferon appears to have greater immunomodulatory properties. They induce changes in the cell membrane (e.g.increasing the expression of HLA antigens), in cell size and in the cytoskeleton. Interferon also stimulates the production of prostaglandins and corticosteroids.

Interferons do not inactivate viruses but protect cells by producing a series of alterations to cellular metabolism which interfere with protein nucleic acid and protein synthesis and also with the assembly of virus particles. Interferons are active in very small amounts with only a few molecules per cell required to trigger the response.

The first step of interferon action is the binding of it to specific cell surface receptors. Alpha- and beta-interferon share one class of receptors and gamma-interferon binds to a different receptor (27). Interferon also enters the cell and it is known that coated pits are involved in such a process. It is not clear whether or not this process is essential for the establishment of anti-viral activity. A second messenger is produced which transmits a signal to the appropriate genes. Cyclic AMP has been proposed as a possible messenger. A number of cellular genes are activated and these can be detected by the presence of a series of new proteins in interferon treated cells. Proteins of identified function include 2-5A synthetase, protein kinase, those of the major histocompatibility complex and indolamine 2-3 dioxygenase.

There are three ways in which the viral particles are affected by the host cell coming into contact with interferon. Viral protein synthesis is inhibited and the transcription of some early virus genes is also inhibited. The basis of these effects are complicated and not clearly elucidated. It is known that the sub-viral particles interact with the components of the envelope at the plasma membrane before leaving infected cells by a budding process. In cells that have been treated with interferon these processes are slowed down and the viruses either accumulate

underneath the plasma membrane, or the process continues but the released viruses are defective in some way, which reduces their infectivity (28).

Interferon contributes to host defenses against tumour growth by inhibition of tumour cell proliferation. This is done by inhibiting synthesis of host proteins required for metabolism and also by inhibition of DNA synthesis. Interferon is tumourstatic rather than tumourcidal (29).

2.2.4 Effects of interferon on the immune system.

All three types of interferon have been shown to have potent immunoregulatory activities affecting antibody production, cell-mediated immunity and other immune system functions. Enhancement or suppression of antibody production can result from exposure to interferon, depending on the dose and time of exposure relative to antigenic challenge in vivo. Antibody synthesis can be inhibited by activating suppressor T cells and through maturation of natural killer cells (25). Recruitment of natural killer cells also plays a role in interferons antitumour effect. Gamma-IFN in general is a more potent immunoregulatory agent than a- or b-IFN.

2.2.5 Interferon in health and disease.

Interferon cannot usually be detected in the serum of healthy individuals. However Bocci has proposed that interferon is produced under normal physiological conditions (30).

A mixture of interferons may be produced spontaneously by lymphoid tissue in the gut. This lymphoid tissue is constantly being challenged by old and new antigens absorbed from the gut and it may be that interferon has a role in maintaining immunological homeostasis. Very small amounts of interferon may also be produced continuously in the lungs but this does not appear to enter the

circulation.

Patients with acute viral illnesses have high levels of circulating interferon and in 70% ,their cells are in an anti-viral state (31). Most viruses are good inducers of interferon but a few are conspicuously poor. These include acute hepatitis A and B, glandular fever and respiratory syncytial virus. Some hepatitis B carriers have a reduced capacity to produce alpha and gamma interferon (32) but can respond to exogenous alpha-interferon.

A variety of Gram-positive and Gram-negative bacteria, chlamydiae, mycoplasmas, rickettsiae and coxiella have been shown to induce interferon in vitro and in animals. Circulating interferon has been found in protozoan infections. Interferon has been found in the ear secretions of children with acute otitis media caused by haemophilus influenza.Interferon was demonstrated in the CSF of bacterial as well as aseptic meningitis patients (33). Gamma-interferon has been found in the CSF of patients with acute herpes encephalitis (34) but it is not present in post-infectious encephalitis.Detectable levels of alpha-interferon have been found in the CSF and serum of schizophrenics. However other workers have been unable to replicate these findings (35, 36, 37).

Autoimmunity and immunodeficiency are often associated with the presence of circulating interferon. Many of the non-specific features of auto-immune diseases can be mimicked by injecting interferon. Interferons have been described in the sera of patients with SLE, rheumatoid arthritis, scleroderma, Sjogren's syndrome, vasculitis and Behcet's syndrome (38, 39). An abnormal acid-labile interferon has also been found in the sera of patients with AIDS (40).

2.2.6 Production of Interferon

Viruses were the first recognised inducers of IFNs but it is now known that a wide variety of other natural and synthetic non-viral agents can induce IFNs in animals

and cell cultures. Alpha- and beta-IFN are induced by viruses, double stranded RNAs, bacteria (e.g. brucella, haemophilus), mycobacteria, rickettsia, mycoplasma and chlamydia; a wide variety of protozoa; microbial products; organic polymers and several low-molecular-weight chemicals such as toluidine blue. Some viruses are particularly good inducers of a-interferon e.g. sendai virus, while others are particularly poor e.g.respiratory syncytial virus, which explains the occurrence of protracted upper and lower respiratory tract infections found in infants infected with this virus. Gamma-IFN is primarily produced by T-lymphocytes following exposure to mitogens or specific antigens.

Transcription of a cellular gene has been found to be essential for production of interferon and interferon genes have been found in all vertebrates thus making the IFN system fairly old in evolutionary terms. Genes for human alpha- and beta-interferon are now known to reside on the short arm of chromosome 9, while that of gamma-interferon is on chromosome 12 (41).

The first phase of interferon anti-viral activity occurs when a virus or other inducer enters a cell or attaches to the cell membrane leading to derepression of the interferon gene. Once the genes are activated, messenger RNA (m-RNA) is produced and the interferon protein is formed by translation in the cytoplasmic ribosomes (42). Messenger RNA synthesis starts within a short time after induction, rises to a maximum 2 - 8 hours later and then the concentration falls away.

Some systems fail to form IFN. This has been shown in some cases to be due to the presence of an IFN gene whose action is repressed in some way, as for example in teratocarcinoma cells. These are transformed stem cells and as they differentiate they become capable of producing IFN. This means that the IFN system is not used in the early embryo and may explain the damaging effects of viral infection in the first trimester (22).

Once interferon has been formed by translation of the m-RNA it is rapidly secreted

from the cells into the surrounding areas. Interferon production is short lived (1 -4 days) and is followed by a refractory state lasting 5 to 13 days during which no further IFN is secreted.

2.2.7 Interferon production for clinical trials.

Cantell in Helsinki pioneered the use of human buffy coats from the blood transfusion services to produce a-IFN (43). However the buffy coat supply limits the amount of IFN that can be made in this way. The Wellcome Foundation next developed the use of large fermentation vessels containing human cells growing in suspension which could be induced to form interferon. The cells used are transformed lymphoid cells capable of producing large yields of IFN following induction by the Sendai virus.

The third method of making IFN employs genetic engineering. Recombinant DNA is produced by severing human and bacterial DNA and then recombining the two DNA fragments together. The technology for doing this is now well developed and high yields of IFN are being produced. The product of such a process is a product of a single gene and there is a lot of discussion as to whether trials should be undertaken using a mixture of a-gene products or a single a-gene product (22).

2.2.8 Pharmacokinetics.

Human recombinant alpha interferons are readily absorbed following intramuscular, intraperitoneal or subcutaneous administration. Peak serum concentrations occur in six to eight hours and clearance occurs in 18-36 hours. Blood levels peak later and persist for longer after subcutaneous injection but this route has not been widely adopted for clinical trials. This may be because subcutaneous administration has been associated with local inflammatory reactions (44). High levels of interferon can be achieved immediately after intravenous injection with rapid

clearance from the circulation. Alpha-interferon passes freely from the blood to extra-vascular pools and vice-versa, but does not cross the blood-brain barrier well (45). Interferon can be found in the saliva, CSF, lungs, and nasopharyngeal secretions following administration or in natural infection.

Levels of beta - or gamma-interferon are negligible following i.m. or s.c. injection. The reasons for this have not been fully elucidated but it may be that they are removed slowly from the injection site by the lymphoid system, that differences in structure may lead to increased binding combined with the fact that gamma-interferon is readily inactivated by crude muscle extracts (46). However,these interferons do reach their target organs despite their apparent lack of transport by the circulatory system (47).

Alpha-interferon binds to receptors on the cell membrane during the activation of an anti-viral state. Some interferon then enters the cell and is thought to be inactivated in the lysosomes. Only limited catabolism occurs in the liver. The relatively small size of the interferon molecule allows it to be absorbed from the proximal renal tubule and destroyed there by proteolysis. There is minimal urinary excretion.

Beta- and gamma-interferon are catabolised in the liver.

2.2.9 Interferon as a therapeutic agent in hepatitis B.

Human leucocyte interferon was first shown to inhibit hepatitis B virus replication by Merigan et al in 1976 (48). At this time preparations of interferon were made from human blood buffy coat cells or lymphoblastoid cell lines (49). Limited amounts of interferon were available then as production of interferon using these methods is costly and difficult, so controlled trials could not be mounted. However recent advances in recombinant DNA technology have meant that sufficient quantities of pure a-interferon (99%) can be produced and made available for

clinical trials. Since Merigan's studies, recombinant a-IFN and lymphoblastoid (a mixture of alpha-) interferons have been used in many studies in Europe (50), North America and Japan. Beta-IFN has been used in limited trials in patients who have chronic hepatitis but has been shown to be of little benefit. Gamma-IFN has been insufficiently used for appraisal of it's effectiveness to be made.

The main aims of therapy with alpha-interferon in chronic hepatitis B are:

1. Inhibition of HBV replication to reduce infectivity and the level of hepatocyte necrosis, thereby preventing the development of cirrhosis;

2. Prevention of hepatocellular carcinoma (50).

Patients who benefit from anti-viral therapy are those with active viral replication.

Thrice weekly injections of interferon (alpha) for three to six months has an overall response rate of 50%. Longer treatment periods show no advantage. Patients who respond show loss of HBV DNA and e antigen from the serum. This coincides with a reduction in hepatic inflammatory activity.

People infected in the neonatal period do not respond to this treatment. A reduced effect has also been noted in homosexuals particularly those who are also infected with the human immunodeficiency virus. Prolonged infection is associated with reduced response rates reflecting the inability of interferon to reverse the integration of the virus into the hepatocyte.

2.2.10 Interferon as a therapeutic agent in other illnesses.

Herpes simplex dendritic keratitis, Varicella Zoster in immuno-compromised patients, Cytomegalovirus and viral papillomas respond to interferon treatment. Colds and flus can be modified or prevented by prophylactic interferon. Interferon

has also been used in various malignancies with inconsistent results.

2.2.11 Toxicity.

The reporting of side-effects due to interferon has been consistent. Purification of interferon does not decrease it's toxicity and this toxicity is considered to be inherent to the interferons themselves (36, 51). The effects are dose-related and therefore dose-limiting but reversible on stopping treatment. There is a great range in individual tolerance and tolerance is better with intermittent schedules of administration. Similar toxic effects have been reported for all three classes of interferon.

After a single i.m. injection of more than 10 units of alpha-interferon a symptom complex develops characterised by fever, headache, malaise and myalgia. These symptoms develop about 3 hours after injection and last for 12-20 hours. Reactions after i.v. administration occur earlier but not immediately after injection (52). These effects may be suppressed by giving aspirin (53) or paracetamol, but they are not abolished. When patients are given daily interferon the febrile response decreases and is usually gone within 10 days. The fever is less intense in patients on less frequent doses.

These symptoms are followed by the onset of fatigue and this is the most frequent dose limiting toxic effect.

Gastro-intestinal toxicity is manifested by anorexia, nausea, vomiting and diarrhoea. Increased liver enzymes are found in patients with pre-existing liver disease. Proteinuria is found in 15-20% of patients and acute renal failure and the nephrotic syndrome have also been reported.

Reversible lymphopenia and leucopenia occur commonly and promptly after interferon administration and are due to a reversible block in the release of cells

from the bone marrow.

Cardiovascular effects include hypotension, cardiac dysrhythmia and tachycardia.

Hair loss has been observed after prolonged treatment but this is not uniform (51). Eyelash growth is increased and there is a reported case of growth to 6.5 cm.

2.3. Interferon and the CNS.

The review of interferon so far demonstrates that interferon is a very complex substance. As a consequence the understanding of the underlying mechanisms through which it has an impact on the Central Nervous System is also likely to be complex. In fact, despite the wealth of literature reviewed below, there is currently a limited understanding of how it mediates its effects. The review below examines its neurophysiology, neuropharmacology and neurotoxicity.

2.3.1 Interferon and the blood brain barrier.

In animal experiments it has been shown that though there is a barrier to the penetration of interferon from plasma to CSF and CSF to plasma, some interferon does pass in both directions (54). There was a thirty fold difference between the interferon concentration in the serum and that of the CSF in monkeys who received i.m. interferon. In a further experiment where the monkeys were given intra-thecal interferon, interferon was detectable in the blood following administration. There was a constant ratio between serum and CSF of 4 to 5%.

The CSF in humans has been reported on several occasions to contain measurable levels of systemically acquired interferon (53, 55, 56, 57), particularly following high dose interferon.

2.3.2 Neurophysiology.

Interferon has been shown to enhance the excitability of cultured neurones and that it is not toxic for neurones (58). It's effects on neuronal activity are dose dependent and site specific (59). When interferon was tested on single neuronal activity, it was found that while the cortical cells were excited by interferon, most of the thalamic cells did not respond (60).

EEG recordings made while patients have received interferon therapy are reported as becoming markedly abnormal. The changes are suggestive of an encephalopathy even in patients who have no clinical evidence of CNS toxicity (55). The degree of abnormality found on the EEG does not always reflect the patients clinical state and does not correlate with serum interferon concentrations. The following changes have been observed sequentially:

1. Slowing of the dominant alpha rhythm.
2. Gradual loss of attenuation on eye opening.
3. Appearance of diffuse slow waves (theta then delta.)
4. Intermittent, frontally dominant, rhythmic delta activity (55,57,61).

2.3.3 Neuropharmacology.

There is a structural and functional relationship in the mechanism by which glycoprotein hormones (TSH, LH, HCG, FSH) and interferon act through cell surface receptors. Strong antigenic relatedness, based on structural similarities, has been shown among alpha-interferon, ACTH and the endorphins (62). Anti-ACTH anti-serum and a highly specific rabbit antiendorphin anti-serum have been shown to neutralise human alpha-interferon. ACTH and alpha-interferon may be derived from a common precursor. Peripheral lymphocytes are capable of producing both ACTH and gamma-endorphin related substances.

Human alpha-interferon preparations contain immunologically and biologically recognisable endorphin activities (59). It binds to opiate receptors in vivo (63). When injected intra-cerebrally into mice, it causes potent endorphin-like effects. These are:

1. Lack of spontaneous movement.
2. Catalepsy.
3. Analgesia.

All these actions are prevented by and reversed by giving naloxone. These effects may be related to the fatigue experienced during interferon therapy.

The very high potency of human interferon on the CNS suggests that only small amounts are needed to trigger the system - levels which may be achieved during infection.

Injecting human alpha-interferon prior to chronic morphine treatment in rats reduces addiction (64). Interferon significantly modifies the naloxone induced abstinence syndrome in a characteristic dose response manner in rats. It has been postulated that interferons prevent tolerance and dependence to endogenous opiates.

2.3.4 Neurological and neuropsychiatric side-effects of interferon

Interferons have therapeutic applications in viral infections and cancers but many researchers have drawn attention to the CNS toxicity that accompanies such therapy (55, 57, 61, 65, 66). The toxicity is dose-related and dose limiting particularly in high dose infusions of interferon. All toxic effects are found to be reversible on stopping interferon. CNS disturbance has also been noted to be more prevalent in older patients.

Neuropsychological testing has illustrated that patients on low dose interferon are

slower at responding to a visual task when they were uncertain when a target stimulus would appear (67). (This deficit is also found in patients with influenza.) Patients on daily infusions of interferon showed impairment of memory for digits backward, slowed finger tapping speed and decreased motor accuracy and motor co-ordination (56).

Neurological effects have been reported in patients on high dose interferon and they include paraesthesia, signs of an upper motor neurone lesion (65), loss of smell and taste, perseveration, loss of tendon reflexes, slowing of motor and sensory conduction velocities on the ENMG (57). Mild papilloedema, slowing of visual and auditory evoked potentials, coma and seizures have also been observed.

Changes on EEG have already been discussed.

The most commonly reported neuropsychiatric symptoms are fatigue, psychomotor retardation, poor concentration, irritability, depression, anxiety, withdrawal, drowsiness, hypersomnia and lack of initiative and energy. Confusion, disorientation, agitation and visual hallucinations have been noted (55, 66, 67). The most important of these symptoms is fatigue as it does not require large doses of interferon to be present for it to occur. It is the most common side-effect and also the most common reason for interferon therapy to be stopped. No satisfactory cause for the fatigue has emerged but it has been suggested that the intense fatigue may be a manifestation of a complex neurotoxicity particularly affecting the frontal lobe (61).

The reported neurological and neuropsychiatric side effects of interferon are summarised in Table 1.

2.4 Summary

In the light of the above review, the inclusion of a psychiatric component to a research programme involving interferon therapy in chronic hepatitis B was justified by:

(i) anticipation of the possible direct effects of interferon on the CNS,

(ii) the potential impact of both hepatitis B and interferon treatment on the patients' psychological state.

Table 1: Reported Neurological & Neuropsychiatric Side Effects of Interferon

- drowsiness
- fatigue
- disorientation
- psychomotor retardation
- withdrawal
- lack of initiative
- decreased energy & libido
- anxiety
- depression
- agitation
- hallucinations
- abnormal mood states
- irritability
- tearfulness
- inattention
- perseveration
- paresthesia
- loss of smell & taste
- loss of tendon reflexes
- mild papilloedema
- slowing of auditory & visually evoked potentials
- signs of an upper motor neurone lesion
- slowing of sensory and motor conduction velocities on ENMG
- visuoconstructional dysfunction
- decreased finger tapping speed

As reported in the literature.

3. Methodology.

The psychiatric study described in this thesis was inserted into a controlled randomised trial using recombinant alpha 2A interferon for the treatment of chronic HBV infection. The Academic Department of Medicine at the Royal Free Hospital had been involved in a multi-centre trial of recombinant alpha interferon treatment for some time and had become aware that some individuals in the studies were developing psychiatric symptomatology. From a review of the literature, there was evidence that this could occur and that such symptomatology would be predominantly neurotic rather than psychotic in nature.

The following hypotheses were to be tested:

1. Interferon therapy produces significant psychiatric symptomatology.

2. The psychiatric morbidity observed in the study would be independent of social stresses and life events.

3. Pre-treatment psychiatric morbidity would predict an accentuation of symptoms during treatment.

A subsidiary hypothesis was also formulated in the light of the then current state of knowledge of human immunodeficiency virus infection:

4. HIV infection would not influence the course of psychiatric morbidity in the study.

3.1 The Interferon trial.

Fifty-nine male subjects who were Hepatitis B s antigen (HBsAg) and HBV-DNA

positive for greater than six months were recruited from general physicians and consultants in sexually transmitted disease clinics for the trial. Once the presence of chronic active hepatitis was established, consent was obtained for participation in the interferon trial. The patients were randomised into four groups, three treatment and one control, by the opening of numbered computer-generated randomisation envelopes in sequential order. The treated groups received recombinant interferon alpha A at the doses of 2.5, 5.0 and 10.0mU/m2 intra-muscularly three times a week. Most patients were taught self-administration of the drug which was injected at night. It was helpful if the patients could sleep through the worst of the side-effects. Those who were unable to self-administer the drug came to the hospital three times a week and were given the drug by the trial nurse. The control group received no treatment (but were offered interferon therapy after 3 months as controls.)

All subjects were seen weekly at the hospital for two weeks by the research physician and nurse, then every two weeks until the end of the trial. Treatment lasted for six months. At each visit the patients were examined physically and blood was taken for biochemical and haematological assessments. (Urea and electrolytes, liver function tests, full blood count and markers for hepatitis B). The control group were seen at the same intervals and received the same physical and biochemical assessments as the treated group.

The HIV antibody test became available during the course of the interferon trial. Stored serum was available for all subjects and therefore pre-treatment HIV status could be determined. For most of the trial neither patients nor research workers knew the HIV status of the individuals in the study.

3.2 The Psychiatric Study.

3.2.1 Site.

Patients were seen in one of the clinical rooms in the medical unit at the Royal Free

Hospital which was also used by the physicians in the trial. One of the psychiatrist's sessions was timed to coincide with one of the physician's clinics concerned with the trial and another session took place in the evening.

3.2.2 Design.

The study was designed to elicit and quantify psychiatric morbidity in the patients before treatment, at intervals during treatment and after treatment had ended. The instruments used were selected to measure minor psychiatric disorder (i.e. neurotic rather than psychotic phenomena) and to be as free from observer bias as possible. In order to test the specific hypotheses about the potential for interferon to induce psychiatric side-effects, it was considered necessary to control for current events and social stresses so that observed psychiatric morbidity could be attributed to interferon treatment rather than the patients environment.

The patients were assessed by the research psychiatrist before treatment, at two, six, and twelve weeks after the start of treatment, and three months after the end of treatment. In addition, the patients could also be seen by the psychiatrist if the research physicians were concerned about change in a patient's mental state.

3.2.3 Instrumentation.

Patients were informed of the psychiatric arm of the study by the research physician and invited to participate. If the patient agreed to take part an appointment was made to see the psychiatrist. Often the psychiatrist was available to be introduced to the patient by the physician. The patient was informed of the aims of the study.

The psychiatric assessment instruments consisted of the following:

(a) The General Health Questionnaire,

(b) The Clinical Interview Schedule,

(c) The Social Stress and Supports Interview,

(d) A brief inventory of life events.

These are described below.

The initial assessment also included the taking of a thorough personal and family history which provided essential background information and facilitated the development of a rapport between the researcher and each patient in the study.

3.2.3.1 The General Health Questionnaire.

In 1972, Goldberg devised the GHQ to be a screening instrument which was to be used to identify patients in General Practice and community settings who are suffering from non-psychotic psychiatric morbidity (68, Appendix 1). It was also to be capable of distinguishing personality traits from symptoms. Once current emotional disturbance was detected, the psychiatric morbidity should then be confirmed by interview.

Goldberg selected 140 items used in other scales that met the two criteria above. These items were then administered to groups of severely ill, mildly ill and normal subjects. The 93 most discriminant items were selected for principal component analysis which defined five factors to be described:

(1) The general factor: severity of illness,

(2) Psychic depression versus somatic depression,

(3) Agitation versus apathy,

(4) Anxiety at night versus anxiety during the daytime and

(5) Personal neglect versus irritability (69).

Later studies have re-interpreted these into four factors as follows:

(1) Somatic symptoms,
(2) Anxiety and insomnia,
(3) Social dysfunction and
(4) Severe depression.

Sixty of the 93 items with the best correlation with these factors became the final questionnaire. Various versions of the instrument exist of which the 60-item and 30-item versions are most widely used. The briefer 30- item version was used in this study.

The answer to each question of the GHQ is on a four point Likert scale. The respondent indicates whether a symptom is present much more, more, the same as usual or less than usual and the responses refer to symptoms experienced during the past two weeks. This design is to ensure that symptoms and not traits are elicited. The questionnaire design also tries to eliminate the effects of bias towards the middle. Each question's response scores either 0 or 1 and the total score is calculated by adding together each response score from the 30 questions.

A patient's score on the GHQ has been described as analogous to the erythrocyte sedimentation rate (ESR) in general medicine in that a high score indicates morbidity without specifying a diagnosis (70). However the GHQ is likely to miss chronic illnesses where subjects would tick the non-scoring reply of "no recent change" for many questions. It may score "false positive" for those who are physically ill and "false negative" for those wishing to fake being healthy (71).

The GHQ is a sensitive and specific screening tool for the detection of psychiatric disturbance in General Practice settings and it has been used to detect the prevalence of minor psychiatric morbidity in the community (72, 73). (Sensitivity = 70%, specificity = 90%). It has been used in numerous other studies including the psychological effects of screening for hypertension (74), the relationship between psychiatric and physical ill-health in general and specialised medical settings (75, 76, 77), the assessment of psychiatric morbidity during the

menopause (78), the psychological and social aspects of pre-menstrual complaint (79) and the relationship between aircraft noise, occupational stress and psychiatric ill-health (80). The GHQ can also be used to follow the progress of a group of patients as it is sensitive to change.

The GHQ was used in this study to provide assessments at intervals of the psychiatric morbidity in the group that were completely free from observer bias. It was completed each time the patient came to the clinic.

3.2.3.2 The Clinical Interview Schedule.

The Clinical Interview Schedule is a standardised, semi-structured interview designed for use in general practice and community studies (81, Appendix 1). It was devised in 1970 by Goldberg and had not been modified by any significant extent until 1992 when Lewis and Pelosi designed the revised version of the Clinical Interview Schedule (the CIS-R) (82). This study used the original CIS.

The interview is divided into four sections. The first section is unstructured and allows the interviewer to obtain a brief account of the patient's past and current medical and psychiatric history.

The second section is a detailed and systematic enquiry about any psychiatric symptoms experienced in the past week. For each symptom there is a mandatory question followed by a series of probes. The frequency and intensity of each symptom contributes to the rating which is on a 5-point scale. The questions for each symptom are administered in the following order:

Somatic symptoms,
Fatigue,
Sleep disturbance,
Hypnotics,

Irritability,
Lack of concentration,
Depression,
Anxiety and worry,
Phobias,
Obsessions and compulsions,
Depersonalisation.

Use of hypnotics is also quantified. Delusions, hallucinations and cognitive impairment are not assessed unless the interviewer suspects that the patient is symptomatic in that area.

The third section is unstructured and allows the interviewer to collect information about the patient's personal and family history.

The fourth section allows the interviewer to rate the "manifest abnormalities" observed by him/her at the interview. These are distinct from the symptoms already rated. There are three scales for abnormal behavior, four for abnormal moods and five for perceptual and cognitive abnormalities. There are few items dealing with psychotic phenomena (which is in keeping with the relative rarity of psychotic disorders in general practice and community settings). The following list shows the content and order of the manifest abnormalities:

Slow, lacking spontaneity,
Suspicious, defensive,
Histrionic,
Depressed,
Anxious, tense,
Elated, euphoric,
Flattened, incongruous,
Excessive concern with bodily functions,
Depressive thought content,

Thought disorder, delusions, misinterpretations,
Hallucinations,
Intellectual impairment.

Each rating is made on a five-point scale and there are 23 ratings in all. A rating of 0 indicates the absence of a symptom. A rating of 1 indicates a habitual trait or borderline symptom which does not cause distress or require treatment. Ratings of 2, 3 and 4 indicate, respectively, mild, moderate and severe degrees of clinical severity of a definite symptom. The individual ratings can be treated in several ways. The 23 ratings for each patient can be summed and weighted to give an overall index of clinical severity. The best agreement with clinical judgement has been obtained by taking the sum of the symptom ratings plus twice the sum of the manifest abnormality ratings.

The overall CIS rating can be used to make an evaluation of "caseness". It is possible to use a number of different cut-off points to indicate 'caseness', the usual ones on the CIS being over a total score of 12 or more or 15 or more. The one adopted will vary according to the characteristics of the patient populations and the objectives of the study. The lower criterion indicates a level where a GP would become aware of and wish to intervene with a patient's psychiatric morbidity. Below the level of "caseness" there are those who are symptom-free and those who have some symptoms which do not warrant an assignation of morbidity.

Persons administering the CIS must be trained in its use. A manual is provided where all operational terms are defined and detailed criteria for rating are provided. The interview lasts from 20 to 60 minutes.

The reliability of this standardised psychiatric interview was assessed in a study in which six psychiatrists and 40 patients took part (83). Each patient was assessed by two psychiatrists where one conducted the interview and the other observed as a co-rater.An overall reliability co-efficient was computed between

interviewer and co-rater on the results of a three way analysis of variance. Separate reliability co-efficients were also computed for each reported symptom or manifest abnormality. The individual reliability co-efficients proved to be comparable to those reported for other standardised interviews (84) and the overall reliability coefficient derived from the analysis of variance is +0.92.

The CIS has been used in surveys as the second stage of a case-finding procedure (81, 83), in studies to test for associations between psychiatric morbidity and clinical or social variables (74, 77, 85, 86) and as a measure of change over time (87). It has also been used to evaluate the effect of social workers' management of psychiatric patients in general practice (88).

3.2.3.3. The Social Stress and Supports Instrument.

The social stress and supports instrument (SSSI) was administered before treatment. It is a brief, standardised and semi-structured social screening interview that assesses and quantifies the subject's own perception of current stresses and support in the environment (89). It takes about 10 minutes to administer and rate.

The following areas in which stresses or supports may be manifest are used:

Occupation,
Housing,
Finance,
Social life,
Family relationships,
Marriage /intimate relationship.

Each area is examined in a semi-structured way in order to establish the patient's view of how the circumstances he describes affect him and their major advantages and disadvantages. The extent to which a circumstance is stressful or supportive

is for the subject rather than the interviewer to decide.

Each area is rated on a three point scale. A rating of -1 is given if the area is a source of overall stress, +1 is given if the area is one of overall support and 0 is given if stress and support are both present in the same area or if neither stress nor support exists. Only the current position is rated. Events in the distant past are not considered but recent events where the patient still considers himself to be significantly troubled by it or it's consequences is rated.

The SSSI total score used in the analysis is obtained by adding together the scores obtained in the individual areas of the instrument.

3.2.3.4 Brief inventory of Current Life Events.

A brief inventory of current life events was used in the trial to elicit any major changes in circumstances that might have affected mental state during the trial. At each interview the patient was asked 'Has anything major happened in your life since I saw you last?' This was followed by probes into the areas covered in the SSSI (i.e. finance, occupation, housing, family, social network and intimate relationships). Further questions were asked about AIDS related events in the patients life as to whether he, his partner or anyone in his social network were affected. Codes were allocated according to whether (i) no new major event occurred, (ii) a major event occurred that was HIV/AIDS related and (iii) any other major event. It was possible for a single patient to receive codes on both (ii) and (iii).

This was not intended to be a measure of life events but an attempt to check that the treated and control groups were not markedly disparate in their occurrence.

3.2.3.5 Reliability

It was considered important to demonstrate that high reliability was being achieved by the researcher, particularly on the CIS, the key psychiatric assessment instrument used in the study.

In order to do this, the researcher's supervisor observed the researcher interviewing 11 patients. Researcher and supervisor independently rated the patients during the interviews. The 23 items included the psychiatric symptoms and the manifest abnormalities on the CIS.

Of the 253 items co-rated there was disagreement on 10. Six of these related to the anxiety symptom and the manifest anxiety items. Of the ten items there was partial agreement on 4, in the sense that the raters agreed on the presence of the item but disagreed as to its severity. In 8 out of the 10 items the researcher scored more highly than the observer (chi-square = 3.6, $p = 0.058$).

The level of reliability was calculated using Kappa. This test was introduced by Cohen and developed to give a weighting for partial agreement in the form of weighted kappa (90). The tool was further developed by Cicchetti (91) to discriminate between scales which are continuous-ordinal (with no point of 'absence') and those which are dichotomous ordinal (with a point of 'absence'). Both types assume a linear weighting across the rating scale.

In the case of the CIS the weightings appropriate to a dichotomous-ordinal scale were used, in order to emphasise disagreements over the presence or absence of a problem rather than discrepancies in its assessed severity. The value of weighted kappa was 0.98, indicating a very high level of overall agreement.

3.3. Methods of analysis

In view of the high level of morbidity in the population as a whole, for purposes of

analysis a stricter criterion of "caseness" was adopted. A "case" was defined as a subject who has an overall severity score of 15 or more on the CIS.

3.4. Statistical Techniques Used

The study was primarily descriptive and therefore much of the analysis uses basic descriptive statistics - frequencies, cross-tabulations and mean scores. Pearson's correlation co-efficient (92) was used to examine relationships between items such as individual symptom scores on the CIS.

In order to test the hypothesis that interferon therapy produces significant psychiatric morbidity the significance of differences in mean scores across populations and points in time were studied. Where the comparison to be made was straightforward, between two sets of observations e.g. the mean CIS score of the treatment and control groups at time 1, T-tests were used to test the null hypothesis that there was no difference between treatment and control groups (93). Where several sets of observations were to be compared one way analysis of variance was used to establish the extent to which variation on scores was attributable to variability within or between groups (94).

The analysis had to address the issue of how to control for the effect of variables other than interferon treatment on psychiatric status. In such cases, for example in relation to social support, analysis of covariance was used (94).

A final issue to be dealt with by the analysis was the large volume of data collected on a relatively small number of patients. In such circumstances there may be a high probability of obtaining false positive results. The data was therefore aggregated to more global descriptive variables in three ways. First, the CIS score was used as an overall index of psychiatric morbidity. This was chosen over the GHQ as it is a more robust measure of psychiatric morbidity, the GHQ being essentially a screening instrument. Secondly, the treatment groups were collapsed into a single group (see 4.1.8 and 4.2.1) since the numbers receiving each dosage were small. Thirdly, assessments made at three points during treatment were

collapsed into a single during treatment score (see 4.2.1 and 4.2.2). This simplified analysis of changes over time.

4. Results.

4.1 The Population.

Fifty-nine male subjects were recruited for the trial. Ten patients lived abroad and received their treatment and clinical and biochemical evaluations there. Forty-three patients were found to be stable residents in London and were willing to participate in the study to evaluate the effects of interferon therapy on mental state.

There was data available on 43 patients at initial interview, 40 throughout the whole trial period and 33 at the final follow-up post-trial.

Of the forty-three, twenty-nine patients were allocated to the treatment groups (11 on 2.5mU/m2, 9 on 5.0mU/m2, 9 on 10.0mU/m2). Fourteen patients were controls.

Three patients dropped out of the study, two treatment and one control subject. One died from Acquired Immuno-deficiency Disease, one withdrew from the study because he did not wish to be in a control group and one moved out of London. For this reason, where more appropriate for comparative purposes, data are at times presented with n = 40 rather than n = 43.

4.1.1 Age

The patients were aged between 18 and 58 years, (mean = 33.7, s.d.9.0). Age did not differ significantly between controls and treated groups nor between those who participated in the psychiatric study and those who did not.

4.1.2 Employment status.

Thirty-four were employed, eight were unemployed and one was a student. There was no significant difference between the treated and control groups in

employment status.

4.1.3 Sexual Orientation.

Forty-two of the forty-three patients in the study were homosexual. Of these 20 had a stable partner. The heterosexual patient was single.

4.1.4 HIV status

40% of the subjects proved to be HIV-antibody positive, 7 in the control group and 10 in the treatment group. The two groups did not differ significantly in this respect. The interviewer was blind to the HIV status of the individuals in the study as were the patients themselves. One of these patients died of AIDS during the study period.

4.1.5 Social support.

The total score obtained in the Social Supports and Stresses Instrument was taken as a measure of supports and stresses as experienced by the individual in his environment. Table 2 below compares the scores of individuals in the control and treated groups.

The covariate social support, measured on a single occasion pretreatment, proved to exert a significant negative influence on the CIS score ($p = 0.004$). The effect of the covariate did not differ between the groups ($p = 0.22$). The mean SSSI score for the control group was 0.64 (s.d. = 2.1) and for the treated group 1.07 (s.d.2.4). This was not significantly different ($p = 0.21$, mean square = 9.1, $F = 1.65$).

HIV+ patients reported fewer social supports than the HIV- group. The mean score for the HIV+ group was 0.53 (s.d.1.9) and for the HIV- group 1.19 (2.5). This was also non-significant ($p = 0.381$, mean square = 4.52, $F = 0.78$). There was also

Table 2: Scores on The Social Stresses and Supports Instrument (n=43)

Score	Control (n=14)	Treatment (n=29)	HIV+ (n=17)	HIV- (n=26)
-3	1	1	1	1
-2	4	4	3	5
-1	0	5	4	1
0	1	2	1	2
+1	2	4	3	3
+2	1	4	0	5
+3	4	4	2	6
+4	1	3	2	2
+5	0	1	1	0
+6	0	1	0	1

Mean SSSI Score

Controls: 0.64 Treated: 1.07 (p=0.021, t-test)

HIV+: 0.53 HIV-: 1.19 (p=0.381, t-test)

no difference in social support when the sample was broken down by both HIV status and treatment status (p=0.66, mean square=1.2, F=0.20).

4.1.6 Life events.

The control group (n=14) were subject to proportionally more external life events than the treatment group (n=29) throughout the trial period. Controls and treatment group were subject to precisely the same number of life events at each stage: four pre-treatment, (of which one of the controls was HIV-related); eight during the trial (of which one of the controls and two of the treatment group were HIV-related); and two post-treatment (of which both in each group were HIV-related). Although not approaching statistical significance, there were therefore proportionally more life events in the control group.

4.1.7 Initial psychiatric status.

Before treatment 10 (34%) of the treatment group and 6 (43%) of the controls gave positive responses to the GHQ indicating likely psychiatric morbidity (mean scores 4.7 (s.d. = 5.42) and 3.8 (s.d. = 4.22) respectively).

On the CIS, six (21%) of those on the treatment regime and 2 (14%) of the controls were designated as cases (overall severity rating > 15). Figure 2 overleaf shows the overall distribution of CIS scores.

The mean CIS and GHQ scores at the beginning of treatment are shown in Table 3. There was no statistically significant difference in overall CIS score between treatment and controls at this point (t-test, p = 0.45).

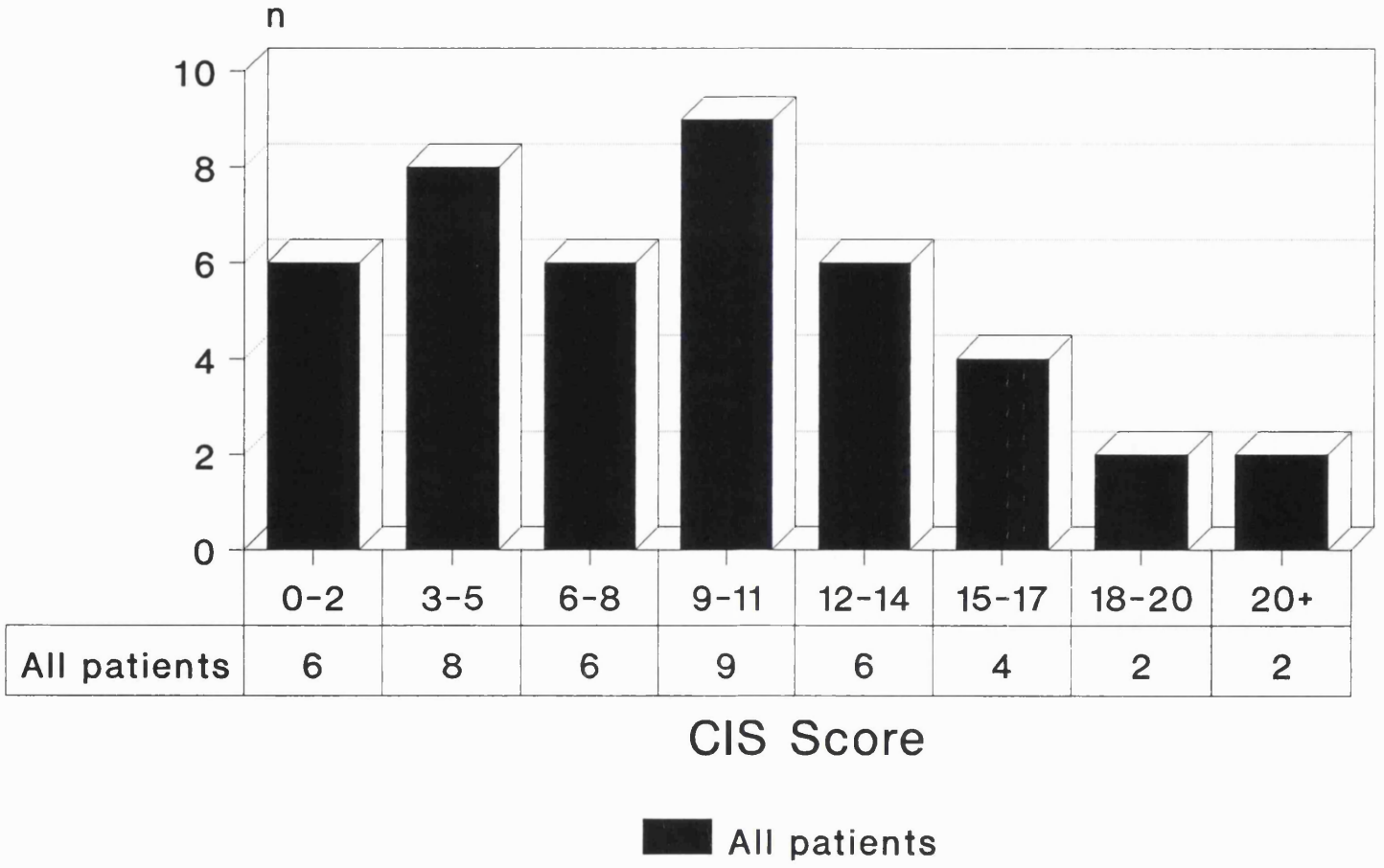
Table 3: Change in Psychiatric Status as Measured by the GHQ and CIS Before and During Treatment

Measure	Group	Pre-treatment (n = 43)	During treatment (n = 40)
GHQ	Control	Mean 3.79 S.D. 4.22	Mean 3.20 S.D. 4.3
GHQ	Treatment	Mean 4.69 S.D. 5.42	Mean 8.36 S.D. 8.56
CIS	Control	Mean 8.69 S.D. 5.6	Mean 9.93 S.D. 6.89
CIS	Treatment	Mean 6.94 S.D. 5.24	Mean 12.64 S.D. 6.84

Controls compared to treatment groups (t-tests):

(i) On the GHQ pre-treatment: p = 0.36.
(ii) On the CIS pre-treatment: p = 0.45.
(iii) On the GHQ during treatment: p = 0.04.
(iv) On the CIS during treatment: p = 0.019.

Fig.2: Clinical Interview Schedule scores at initial interview



N=43, Case= score >14.

Social score (an aggregate of the six areas assessed), proved to be inversely related to psychiatric morbidity as indicated by a positive response on the GHQ and caseness on the CIS (B = -1.11, p = 0.004 between the CIS and SSSI). In view of this relation between psychiatric morbidity and social support, the results for CIS and GHQ were adjusted for social support in the subsequent analysis.
(Addendum 1)

4.1.8 Initial comparison of treatment groups.

One-way analysis of variance was used to examine differences in psychiatric symptomatology between the three treatment groups at the beginning of the study. Although not quite statistically significant (p = 0.055, mean square = 72.3, F = 3.49) it appeared that the low dosage treatment group had a lower initial CIS score.

4.2 Changes During the Trial

4.2.1 Comparison of treatment groups throughout the trial.

One-way analysis of variance was again used to look at differences in psychiatric symptomatology between the three treatment groups at each point during the trial. At no stage did differences between the groups approach significance (time 2: p = 0.417, mean square = 53.6, F = 0.925; time 3: p = 0.489, mean square = 61, F = 0.75; time 4: p = 0.905, mean square = 7.07, F = 0.10). In view of this and the small numbers in each group, the treatment groups were collapsed into a single treatment group for purposes of further analysis.

In order to further simplify the data paired t-tests were used to examine differences in CIS scores during treatment (at times 2, 3 & 4) for the combined treatment

group. When time 2 was compared with time 3, two-tailed probability was 0.328, S.D. = 8.75; when time 3 was compared with time 4, two-tailed probability was 0.942, S.D. = 8.34; and when time 3 was compared with time 4, two-tailed probability was 0.642, S.D. = 9.55. In view of these findings further presentation and analysis of the data collapses scores at each of the three time points into a single 'during treatment' score.

4.2.2. Comparison of control group throughout the trial.

Control group CIS scores were also compared using paired t-tests. When time 2 was compared with time 3, two-tailed probability was 0.096, S.D. = 7.22; when time 3 was compared with time 4, two-tailed probability was 0.075, S.D. = 9.24; and when time 3 was compared with time 4, two-tailed probability was 0.366, S.D. = 7.96. In view of these findings further presentation and analysis of the data also collapses the three time points for controls into a single 'during treatment' score.

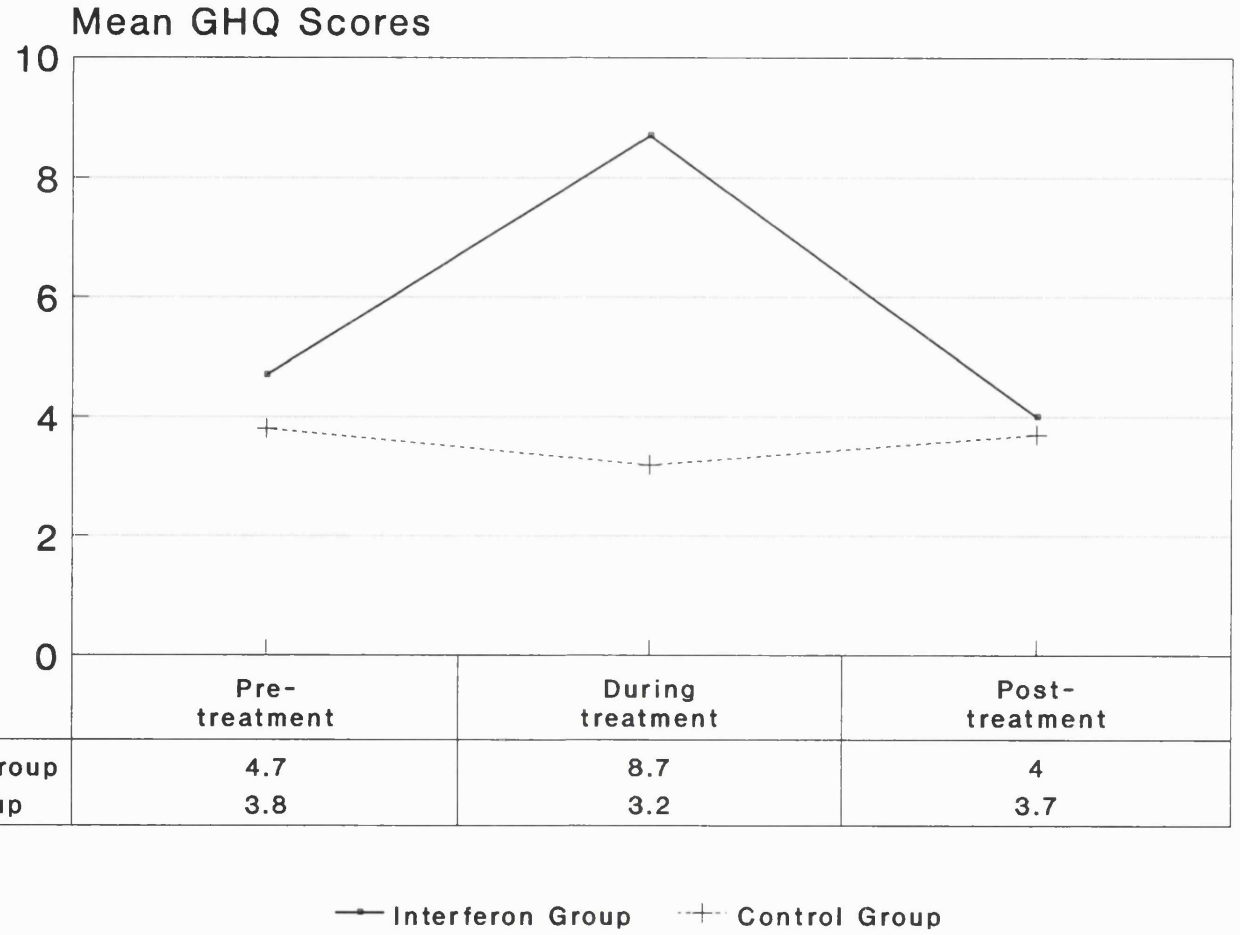
4.2.3 Overall changes in psychiatric symptomatology.

The initial analysis concentrated on the changes in psychiatric morbidity as determined by the GHQ and CIS response in relation to the presence of active interferon. A further set of analyses, reported on in section 4.3, took account of HIV status.

4.2.4 Changes in GHQ and CIS Scores

Figures 3 and 4 below show that there was a rise in the levels of psychiatric symptomatology in the treatment group on both the CIS and the GHQ score but there was no corresponding rise in the control group. After adjustment for social support the between subjects analysis revealed a significant drug effect, the

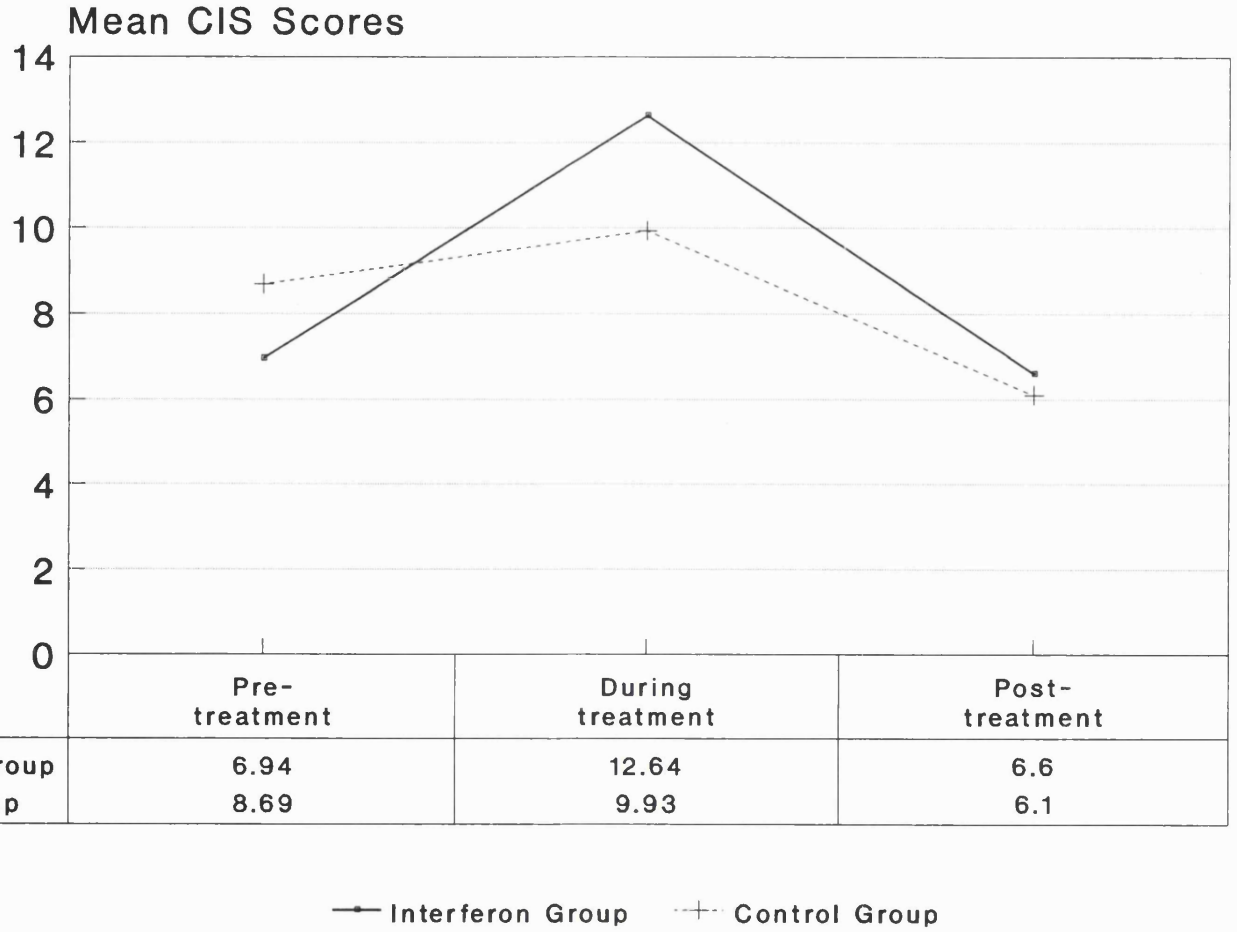
Fig. 3: General Health Questionnaire Scores Throughout The Study Period



	Pre-treatment	During treatment	Post-treatment
Interferon Group	4.7	8.7	4
Control Group	3.8	3.2	3.7

See also Table 3.

Fig. 4: Clinical Interview Schedule Scores Throughout the Study Period



	Pre-treatment	During treatment	Post-treatment
Interferon Group	6.94	12.64	6.6
Control Group	8.69	9.93	6.1

n=43

control group (no drug) scoring lower than the treated group. The effect of the interferon treatment was significant in relation to both the CIS (t-test, $p=0.019$) and the GHQ (t-test, $p=0.04$).

The within subject analysis, which compares the performances of the groups over time, demonstrated a significant drug by time interaction ($p=0.023$), illustrated by the raised CIS scores for the treated group during the treatment. The effects of time ($p=0.42$) were not significant.

4.2.5 Caseness

Pre-treatment there were 35 non-cases and 8 cases on the CIS. During treatment there were 18 non-cases and 25 cases. Of the latter, 20 were on treatment and 5 were controls. 14 people were never cases during the study, 4 people were always cases, 17 became cases during treatment and 4 became non-cases during the treatment period.

Of those who were not cases at the beginning of the trial, three out of twelve controls (25%) became a case at some point during the trial and fourteen out of twenty-three treatment subjects became a case (60%), making a total of five controls who were a case either pre- or during treatment compared to twenty of the treatment group.

4.2.6 Effects of dosage

Table 4 below shows the mean GHQ and CIS scores over time between the three different dosages of interferon. The small numbers in each group meant that there was limited scope for statistical analysis.

There appears to be a disparity between the pre-treatment scores of the high dosage group on the GHQ, where they were comparable to the medium and low

Table 4: General Health Questionnaire & Clinical Interview Schedule Scores by Dosage over Time

	Dosage	Pre- treatment	During treatment	Post-treatment
GHQ	Control	3.79 (n=14) s.d.4.08	3.2 (n=13) s.d.4.25	3.55 (n=11) s.d.5.39
	Low dose (2.5mU/m2)	3.64 (n=11) s.d.6.83	7.0 (n=11) s.d.9.7	1.67 (n=9) s.d.3.08
	Medium dose (5.0mU/m2)	5.89 (n=9) s.d.5.75	6.7 (n=7) s.d.4.76	7.13 (n=7) s.d.8.84
	High dose (10.0mU/m2)	4.78 (n=9) s.d.5.07	11.67 (n=9) s.d.9.85	3.67 (n=6) s.d.8.02
CIS	Control	8.21 (n=14) s.d.5.74	6.95 (n=13) s.d.5.04	6.0 (n=11) s.d.5.06
	Low dose (2.5mU/m2)	7.0 (n=11) s.d.5.33	11.41 (n=11) s.d.9.35	4.0 (n=9) s.d.4.15
	Medium dose (5mU/m2)	10.78 (n=9) s.d.9.10	13.0 (n=7) s.d.6.75	9.14 (n=7) s.d.10.93
	High dose (10mU/m2)	12.67 (n=9) s.d.6.56	13.78 (n=9) s.d.8.57	7.5 (n=6) s.d.9.87

dosage groups, and on the CIS where there seemed to be a particularly high level of morbidity pre-treatment in the high dosage group. Examination of individual cases showed that some individuals who had scored very highly on the CIS had a very low score. For example, one individual scored 20 on the CIS and 3 on the GHQ.

All treatment groups showed an increase in symptomatology on both measures during treatment.

As measured by the CIS, by far the largest increase in symptomatology was in the low dosage group. The medium and high dosage groups had much higher baseline levels of morbidity as measured by the CIS, the mean score of the high dosage

group pre-treatment being particularly high. During treatment there was no apparent trend in the direction of higher dosages of interferon being associated with higher absolute levels of psychiatric symptomatology. The relative increase in levels of symptomatology was highest in the low dosage group.

On the GHQ, raised morbidity pre-treatment in the high dosage group was not evident. During treatment there was a similar pattern of all treatment groups reporting higher levels of symptomatology during treatment. The increase in reported symptomatology was particularly high in the high dosage group.

4.2.7 Changes in pattern of psychiatric symptomatology.

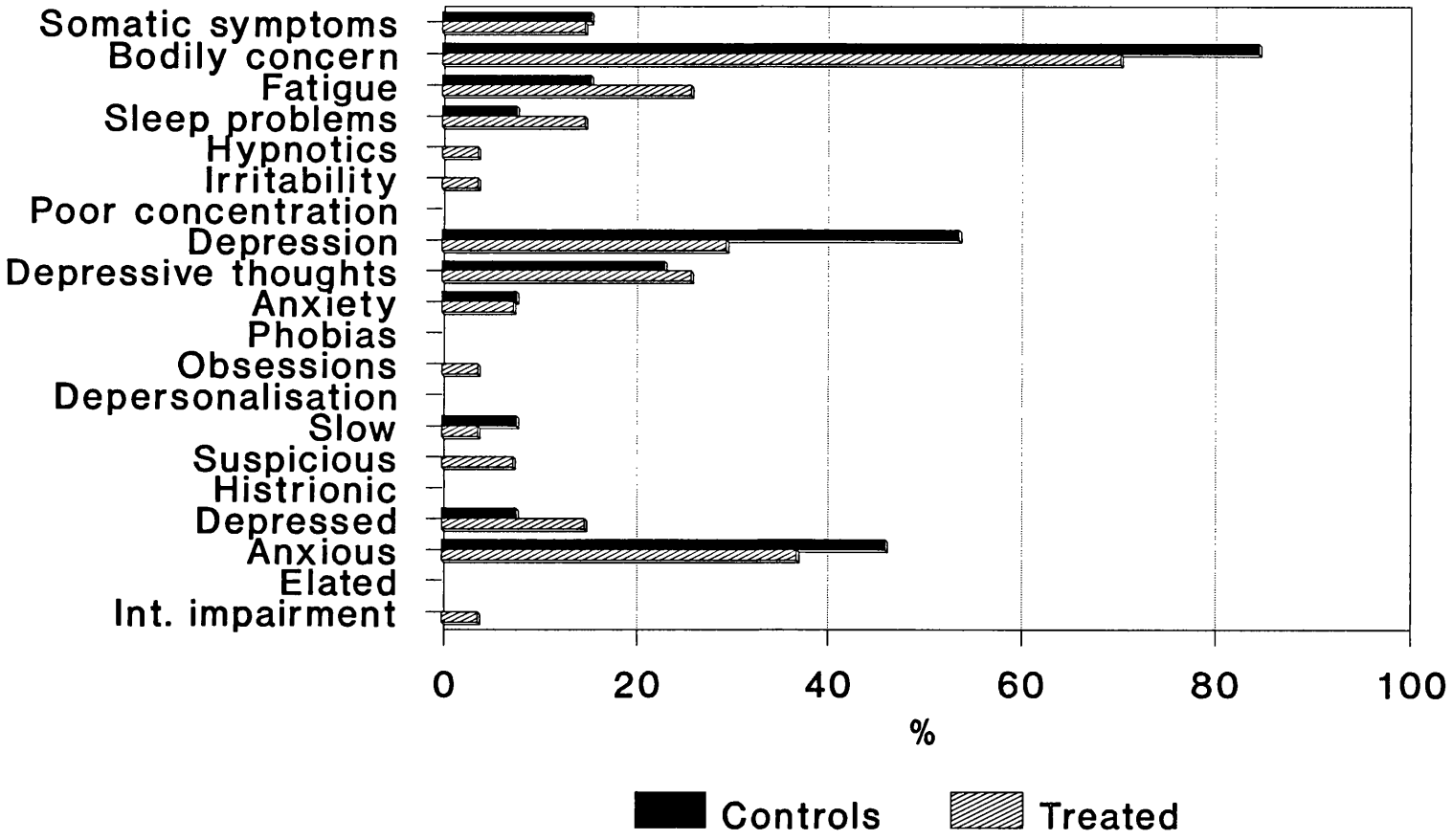
The pattern of psychiatric symptomatology was examined by comparing the percentage of people complaining of each symptom in both control and treatment groups on the individual items of the CIS (Figures 5 & 6). In order to be included, patients had to score 2 or more on the individual CIS item.

Pre-treatment, bodily concern, depression and anxiety figured strongly in the profiles of both groups. During treatment, however, as already noted, the treated patients exhibited a wider range of symptoms than the control group. Fatigue, concentration, irritability and depression were especially prominent.

The contributions of these symptoms to the overall CIS score were examined using Pearson's correlation co-efficient. The items contributing most to CIS scores at the different stages of the study are shown in Table 5 below. The table shows only those items with a correlation of greater than 0.3 either pre- or during treatment. All remaining CIS items had a correlation of greater than -0.1 (i.e. closer to zero than -0.1).

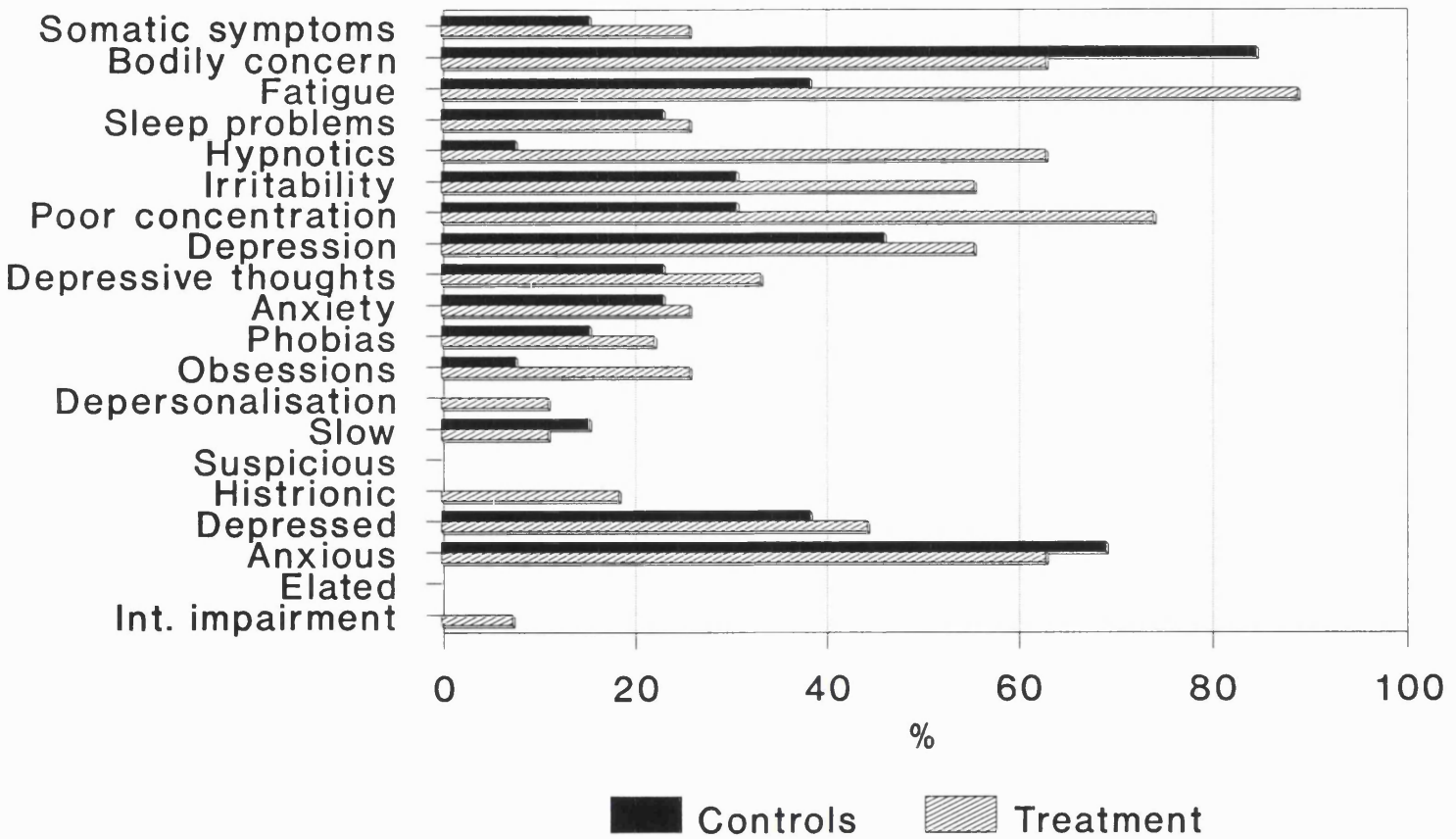
Pre-treatment the inter-correlations with a correlation co-efficient of greater than 0.5 were:

Fig.5: Psychiatric Symptoms
Pre-treatment



Controls n=13, Treated n=27

Fig.6: Psychiatric Symptoms
During Treatment



Controls n=13, Treatment n=27

(i) fatigue and somatic symptoms (0.544)

(ii) use of hypnotics and sleep disturbance (0.520)

(iii) depressive thoughts and depression (0.556)

Table 5: Positive Correlations Between Clinical Interview Schedule Items and Total Clinical Interview Schedule Score

CIS Item	Correlation Pre-treatment (n = 43)	Correlation During Treatment (n = 40)
Somatic symptoms	0.597	0.596
Bodily concern	0.371	0.530
Fatigue	0.357	0.729
Sleep	0.440	0.577
Hypnotics	0.308	0.312
Irritability	0.201	0.712
Concentration	0.422	0.677
Depression	0.694	0.774
Depressive thoughts	0.694	0.585
Anxiety	0.535	0.585
Phobias	0.252	0.077
Obsessions	0.576	0.687
Depersonalisation	-0.29	0.360

During treatment the inter-correlations with a value of greater than 0.5 were:

(i) fatigue and irritability (0.505)

(ii) fatigue and poor concentration (0.675)

(iii) poor concentration and irritability (0.632)

(iv) depression and irritability (0.689)

(v) depressive thoughts and irritability (0.673)

(vi) depressive thoughts and depression (0.832)

(vii) depression and anxiety (0.568)

(viii) obsessions and anxiety (0.585)

(ix) obsessions and bodily concern (0.530)

Closer examination of symptoms on the CIS revealed that impaired concentration, irritability and fatigue were significantly different in the interferon group. It is evident that interferon treatment is associated with an increase in severity of these symptoms (figures 7-9 below). The statistical relationships between these symptoms and social support, drug treatment, time and drug by time are shown in Table 6. With fatigue, the effect was significant in relation to time ($p = 0.002$),

Table 6: Individual Symptoms on the CIS which were Statistically Significantly Different in the Interferon Group During Treatment

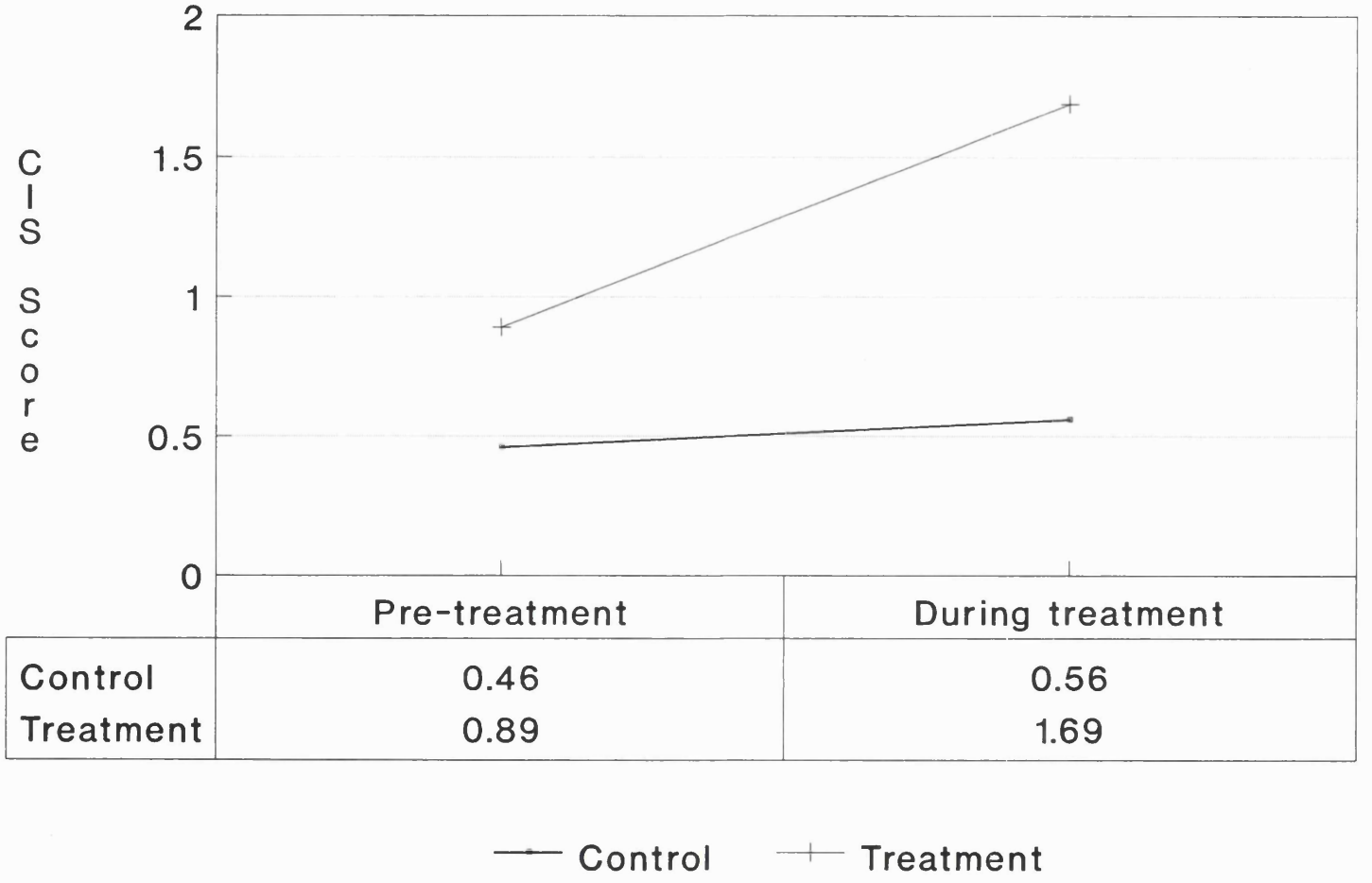
Symptom	Social Support	Drug Treatment	Time	Drug by Time
Fatigue	No effect	$p = 0.008$	$p = 0.002$	$p = 0.014$
Irritability	No effect	$p = 0.003$	$p = 0.057$	$p = 0.011$
Concentration	$p = 0.009$	$p = 0.009$	$p = 0.001$	$p = 0.004$

drug treatment ($p = 0.008$) and drug by time ($p = 0.014$) and was not significant in relation to social support. In the case of irritability, the effect was significant in relation to drug treatment ($p = 0.03$) and drug by time ($p = 0.011$) and approached significance by time ($p = 0.057$). Social support had no effect. In the case of concentration, the effect was significant in relation to drug treatment ($p = 0.008$), time ($p = 0.001$) and drug by time ($p = 0.004$). There was also an effect of social support ($p = 0.009$).

4.2.8 Phenomenology

As indicated by the CIS and GHQ scores, patients commonly reported neurotic

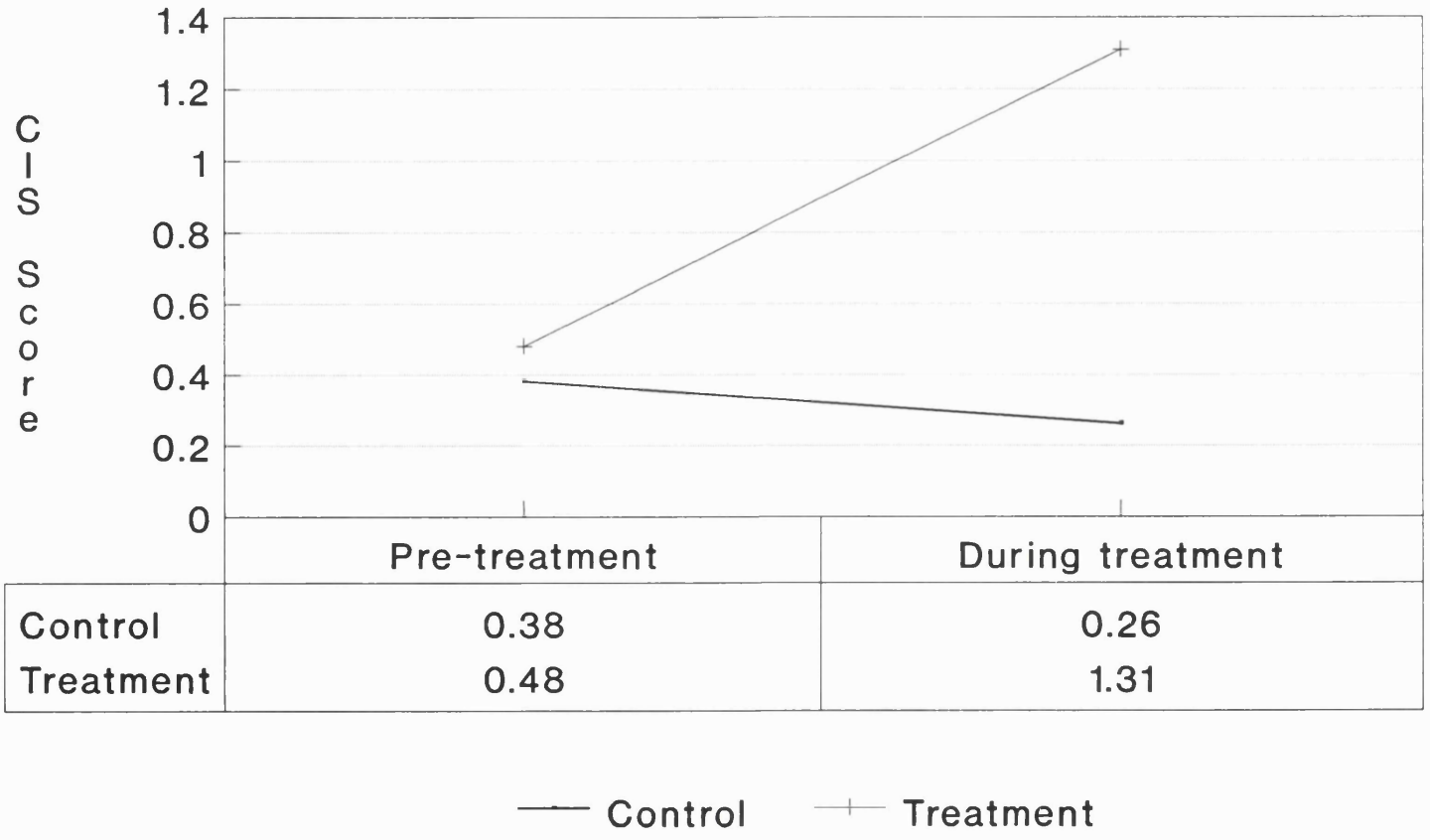
Fig.7: Fatigue Scores on the CIS



	Pre-treatment	During treatment
Control	0.46	0.56
Treatment	0.89	1.69

n=43

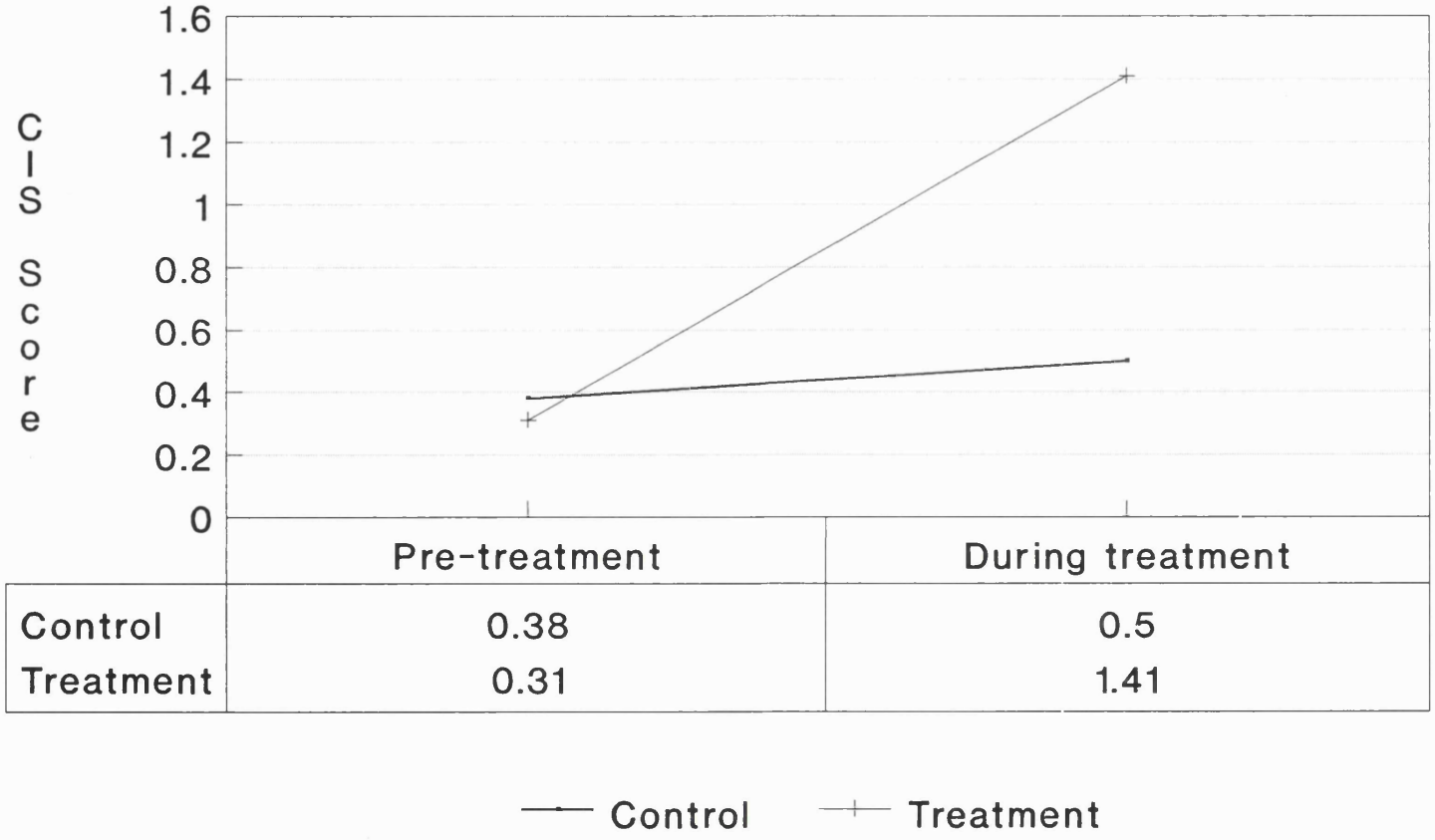
Fig.8: Irritability Scores on the CIS



	Pre-treatment	During treatment
Control	0.38	0.26
Treatment	0.48	1.31

n=43

Fig.9: Concentration Scores on the CIS



	Pre-treatment	During treatment
Control	0.38	0.5
Treatment	0.31	1.41

n=43

symptoms, particularly fatigue, loss of interest, lack of concentration, anxiety and depression.

Of the 20 patients on interferon who became psychiatric cases, 6 patients were referred to a psychiatrist or psychologist in their own catchment area for treatment. Four of these patients had severe anxiety and depressive symptoms, one had a worsening of his pre-existing agoraphobia and one complained of severe memory problems. One patient was referred to a psychosexual clinic because of impotence related to anxiety about sexual performance.

On assessment none of the patients had evidence of disorientation or clouding of consciousness. Paranoid ideas about homosexuality developed in one patient before he disclosed that he was homosexual, which he had denied when initially seen. No other psychotic phenomena were reported or observed.

To test the hypothesis that pre-existing symptomatology would worsen during treatment phobic symptoms and obsessionality were examined in some depth.

4.2.8.1 Obsessionality.

Twenty-five out of the forty-three subjects in the trial were found to have an obsessional trait during the initial interview (eighteen treatment and seven controls). Of these, ten became symptomatic during the treatment period (eight in the treatment group and two in the control group), that is, they scored 2 or more on the relevant CIS item. Only one had scored two at the initial interview. Thus, equal proportions in the treatment and control groups developed obsessional symptoms during the treatment period.

4.2.8.2 Phobias.

Twenty out of the forty-three subjects in the trial were found to have a phobic trait

during the initial interview (twelve treatment and four controls). Of these, three in the treatment group became symptomatic and one of the controls. However, a further four subjects in the treatment group developed new phobic symptoms during the treatment period. This would therefore seem to be a direct consequence of interferon therapy. A particularly striking case was one patient who became phobic to pigeons while on treatment, but the phobia disappeared once interferon was stopped. A vignette of this case is given in appendix 2.

4.2.9 Changes associated with HIV status

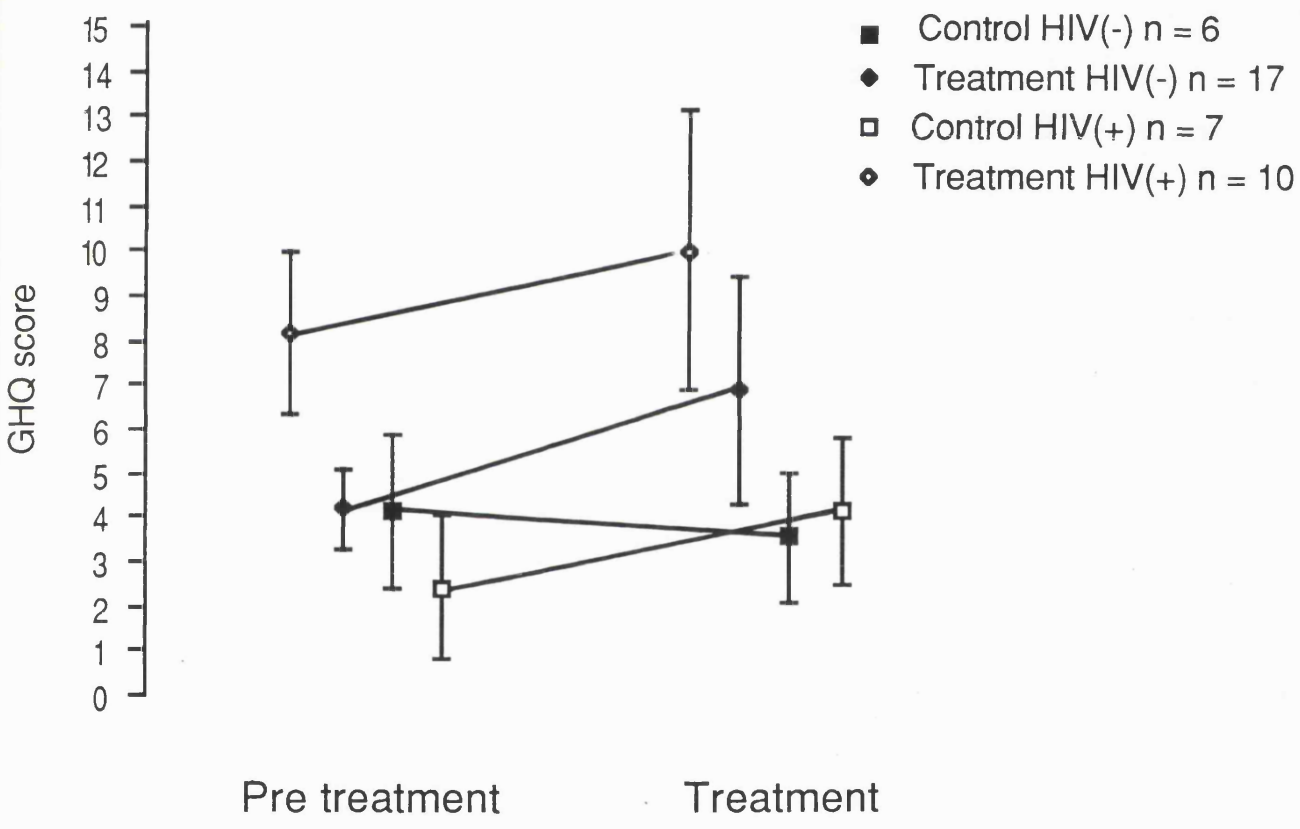
Figures 10 and 11 below and Table 7 show the change between pre-treatment and the average "during treatment" score for the GHQ and mean CIS score in treated and control groups, each subdivided according to HIV status. In view of the association between the psychiatric morbidity and social support, these graphs

Table 7: Mean (se) Pretreatment and Treatment GHQ and CIS Scores (adjusted for social support) for patients on interferon and controls (n=40)

	GHQ Score	GHQ Score	CIS Score	CIS Score
	Pre-treatment	Treatment	Pre-treatment	Treatment
Control, HIV-ve (n=6)	4.10 (1.73)	2.38 (1.62)	7.25 (2.52)	6.57 (2.20)
Treatment, HIV-ve (n=17)	4.15 (0.91)	8.14 (1.80)	9.94 (1.18)	11.10 (1.01)
Control, HIV+ve (n=7)	3.54 (1.46)	4.10 (1.64)	10.00 (1.67)	7.32 (1.94)
Treatment, HIV+ve (n=10)	6.84 (2.59)	9.98 (3.14)	11.55 (3.24)	17.29 (3.62)

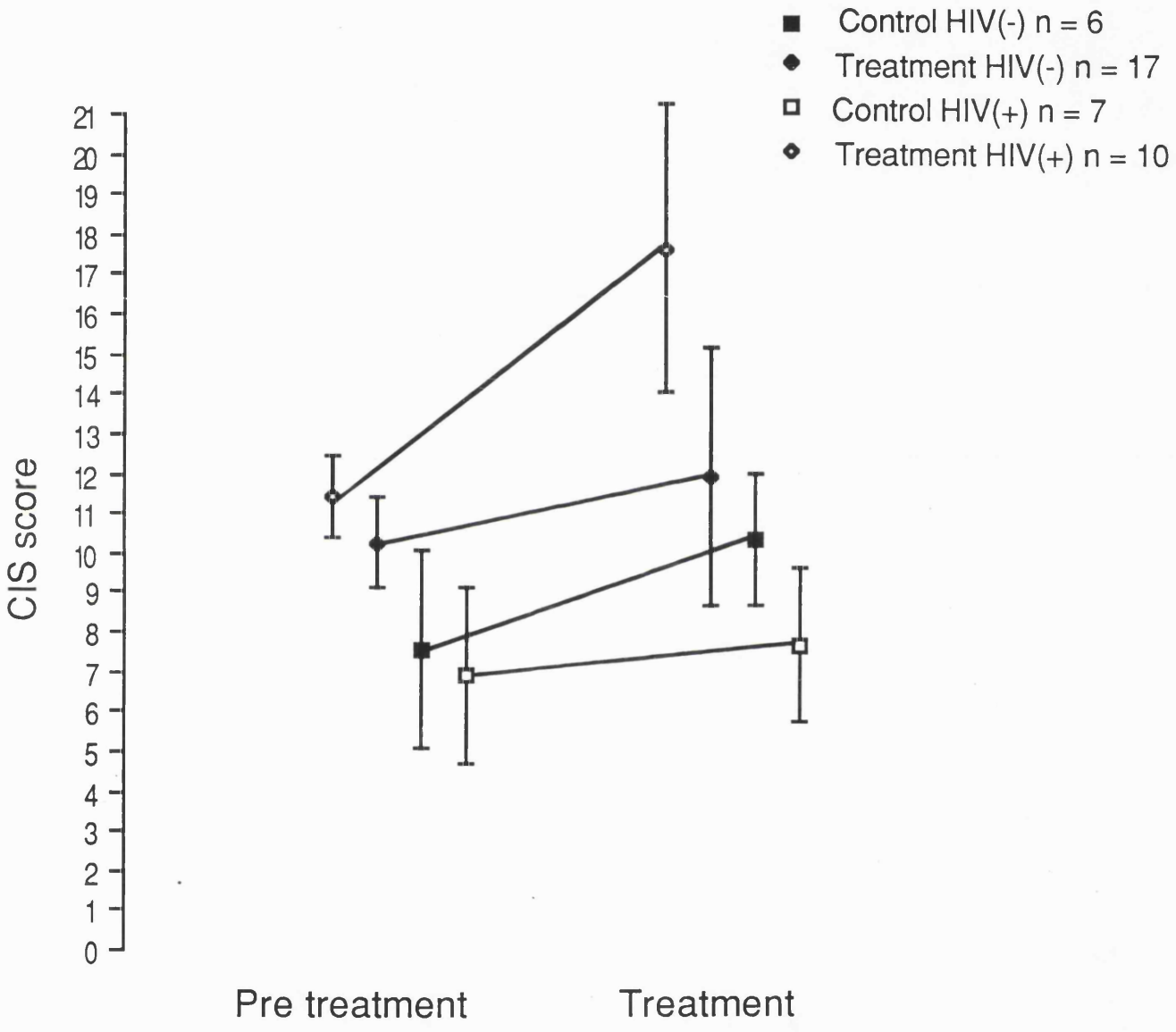
HIV status p=0.15 Time p=0.42
HIV X Drug p=0.58 HIV X Time p=0.14

Figure 10: GHQ Score by Treatment and HIV Status



GHQ: mean (S.E.) Pretreatment and treatment scores (adjusted for social support) for subjects on interferon and controls.

Figure 11 : CIS Score by Treatment and HIV Status
(adjusted for social support)



have been adjusted for social support scores. (Similar slopes are obtained if the scores at each assessment are plotted as separate points.) The graphs show a rise in psychiatric morbidity with treatment in the treated group compared to the controls. However, for the CIS, the increase is most marked amongst the treated HIV positive group, suggesting an interaction between treatment and HIV-status. Psychiatric morbidity decreased in HIV+ controls and other controls over the same period. However, neither the effect of HIV status ($p=0.15$) nor the interaction between HIV and drug ($p=0.58$) reached significance. The effects of time ($p=0.42$), and HIV status by time ($p=0.14$) were not significant. The significance figure attached to the last interaction suggests that some residual variation might be accounted for by the HIV status influencing CIS scores differently between the treated and control groups.

Figures 12 to 14 below compare the scores on individual symptoms on the CIS of HIV+ and HIV- patients at the main three points during the study. Pre-treatment and during treatment HIV+ individuals appeared to have more symptoms than HIV- patients. Table 8 below shows the numbers in each group who scored 2 or more on individual symptoms on the CIS.

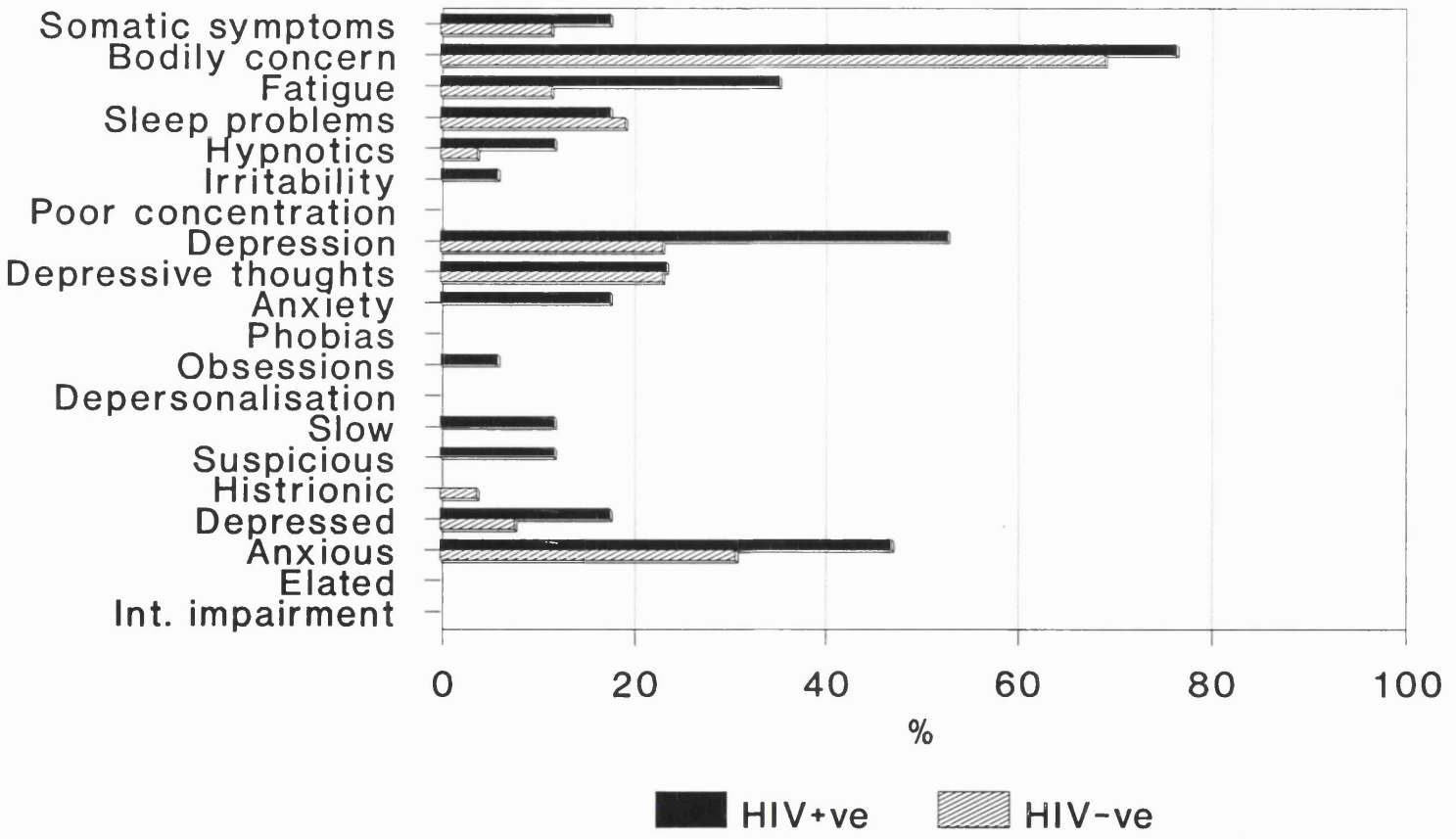
4.2.10 Post-treatment scores

It was only possible to follow up 33 patients. For various reasons, including the fact that several controls were by then on treatment, seven of the forty patients who remained in the trial were unavailable for follow-up.

Figure 15 compares the distribution of psychiatric symptoms at follow-up of treatment and control groups. There remains much bodily concern in both groups, but particularly in the controls (62% versus 45%). However, there is less depression and anxiety in both groups than during treatment.

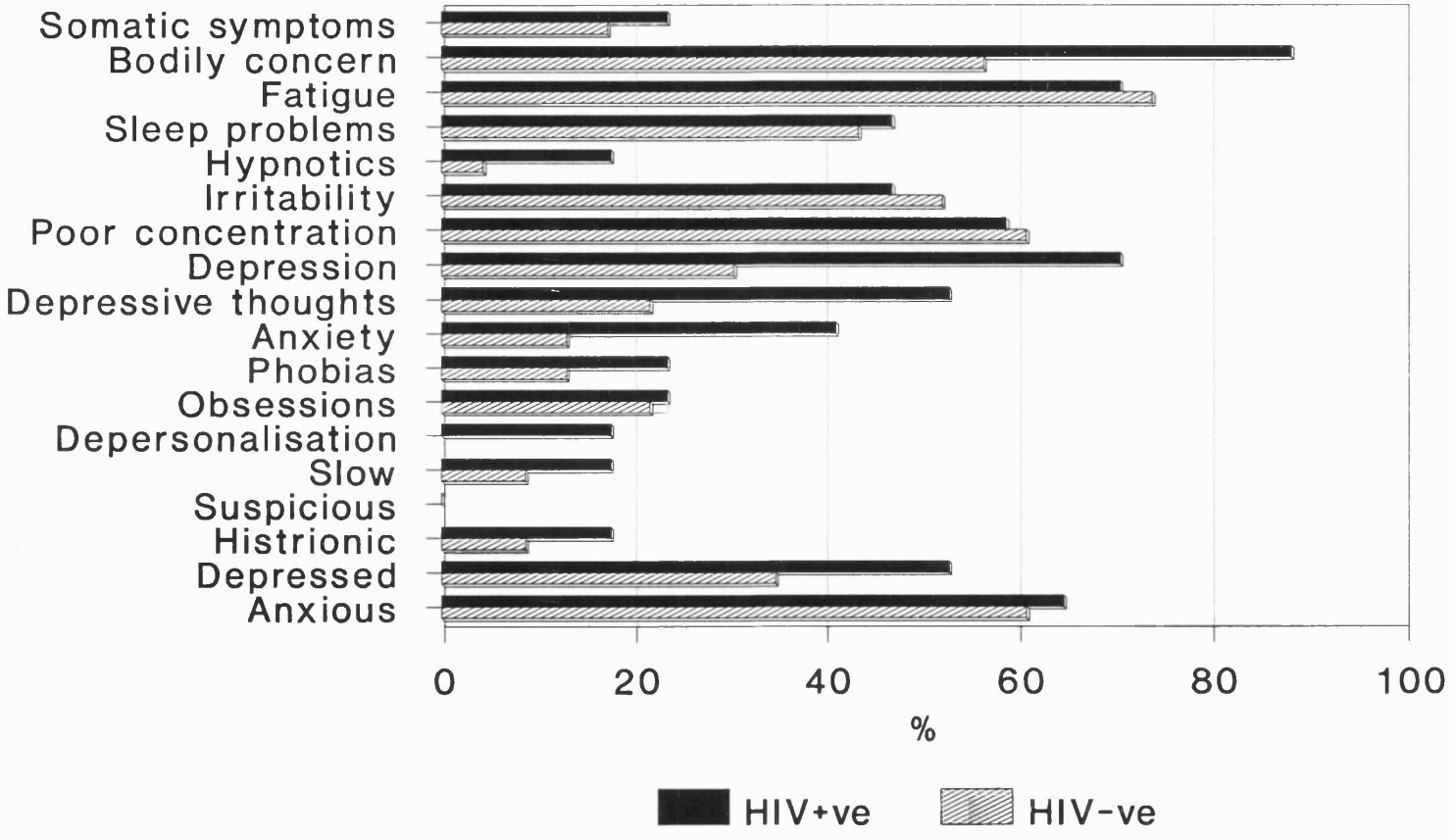
Three months after treatment the mean scores in the control group were 3.55

Fig.12: Psychiatric Symptoms
Pre-treatment in HIV



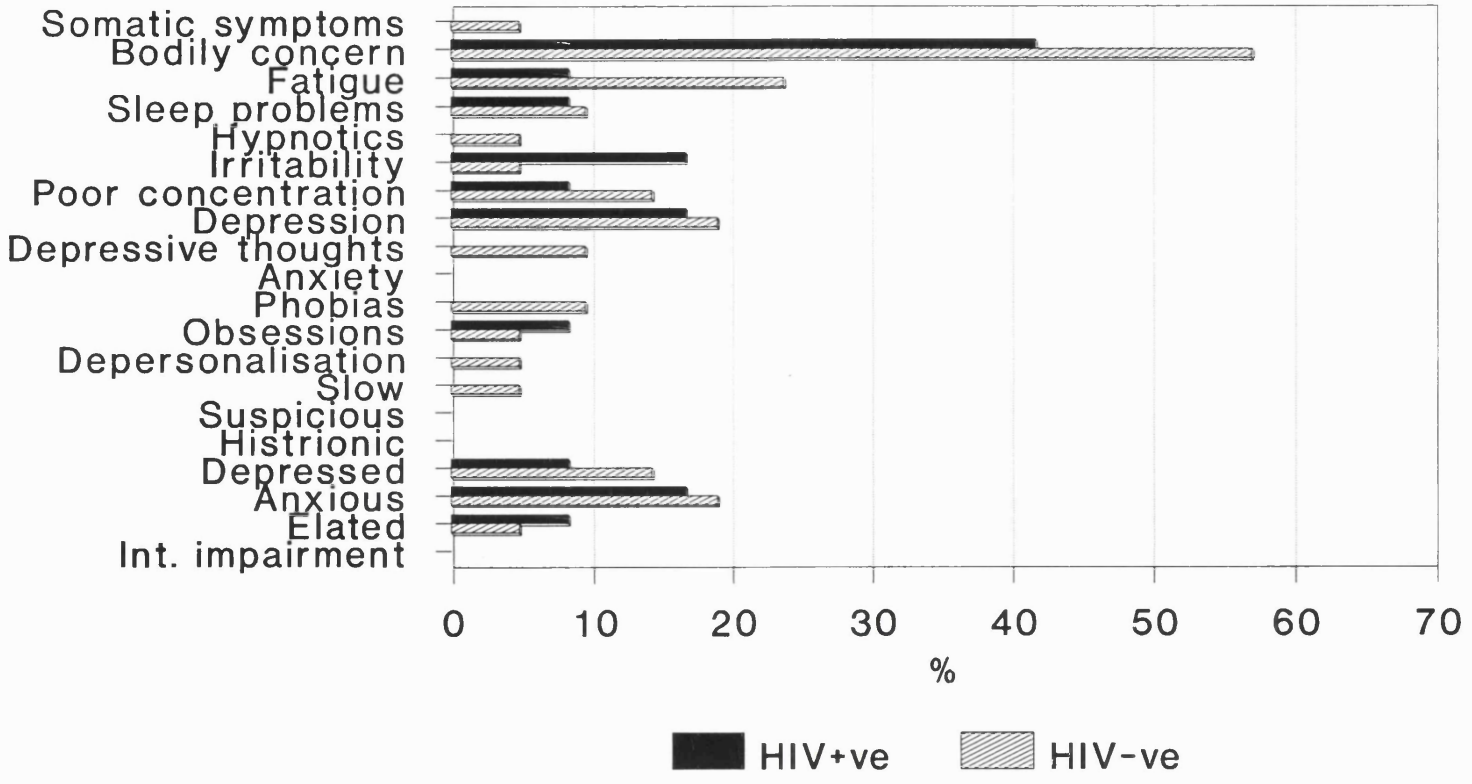
HIV+ve n=17, HIV-ve n=26

Fig.13: Psychiatric Symptoms
During treatment in HIV



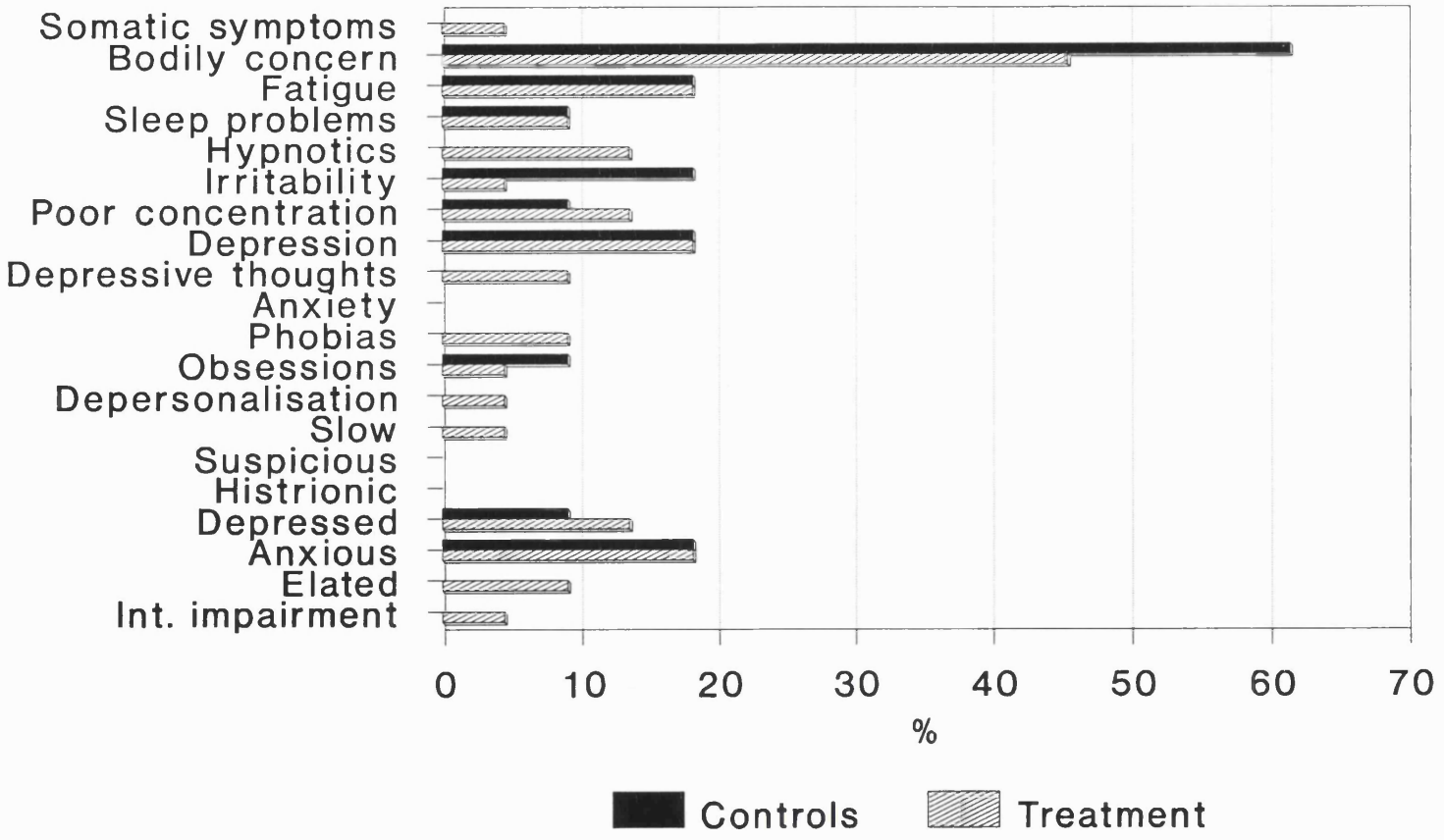
HIV+ve n=17, HIV-ve n=26

Fig. 14: Psychiatric Symptoms
Post-treatment in HIV



HIV+ve n=12, HIV-ve n=21
HIV+ve drop-out rate=29.4%, 1 died,
2 severe psychiatric problems, 2 moved

Fig.15: Psychiatric Symptoms
at follow-up



Controls n=11, Treatment n=22

Table 8: Individual Clinical Interview Schedule Symptoms During Treatment By HIV and Treatment Status

Symptom	HIV+ Control (n=7)	HIV+ Treatment (n=10)	HIV- Control (n=6)	HIV- Treatment (n=17)
Somatic symptoms	0	4	2	2
Bodily concern	6	9	5	8
Fatigue	4	8	1	16
Sleep	1	7	2	8
Hypnotics	1	2	0	1
Irritability	1	7	2	10
Concentration	3	7	1	13
Depression	4	8	2	5
Depressive thoughts	1	8	2	3
Anxiety	1	6	2	1
Phobias	0	4	1	2
Obsessions	1	3	1	4
Depersonalisation	0	3	0	0
Slow	2	1	0	2
Histrionic	0	3	0	2
Depressed	2	7	3	5
Anxious, tense	4	7	4	10

(s.d. 5.39) for the GHQ and 6.00 (s.d. 5.06) for the CIS. For the treatment group the equivalent mean scores were 4.09 (s.d. 6.98) and 6.59 (s.d.=8.32), respectively. Thus control and treatment group scores no longer differed and for the two groups the mean scores had reverted to a level that did not differ from that at the outset.

5. Discussion.

The following main hypotheses were tested:

1. Interferon therapy produces significant psychiatric symptomatology.

2. The psychiatric morbidity observed in the study would be independent of social stresses and life events.

The discussion will first focus on the methodological limitations of the study and then go on to examine the results in the light of these hypotheses. In conclusion, broader issues concerning the role of the psychiatrist, and further research suggested by the current study are discussed.

5.1. Methodological limitations

The strengths of the study are first that it was prospective. Secondly, psychiatric assessment was regular, reliable and valid. It was based upon the use standardised instruments with known wide applicability. Furthermore, the use of both a self-report measure (the GHQ) and an interview-based measure (the CIS) meant that the clinician's view could be cross-validated with the patients' view. This is particularly relevant to a study such as this where numbers are small.

Thirdly, key confounding variables in studies of this type, namely, social stresses, supports, and changing life events - have been assessed and controlled for in the analysis.

There are a number of limitations in the methodology of the study.

First, the small sample size reduced the scope of the analysis and raised the possibility of occurrence of either Type 1 (false positive) or Type 2 errors (false

negative). The small sample size also meant that limited analysis was possible of the effects of the different dosages of interferon.

Secondly, it was not possible to introduce a placebo into the clinical trial. One possibility considered was to give placebo injections but this was judged unethical. As a consequence, patients knew if they were on treatment or not and the interviewer was inevitably told by the patients whether or not they were on treatment or were controls. This introduced the possibility of observer bias. Such a bias can be partly discounted by the standard nature of the assessment interview and avoided altogether by the parallel use of the self-administered GHQ as a measure of psychiatric morbidity. In fact, the changes in psychiatric morbidity are much the same whether the CIS or GHQ is used. In addition, the high level of inter-rater reliability between the researcher and supervisor who was not aware of treatment status suggests that bias was not a significant factor in the results.

Thirdly, the neuropsychiatric changes reported in the literature review suggest that it would have been valuable to have more direct neuropsychiatric data. Psychometry and EEGs would have been valuable in detecting possible sub-clinical changes.

Fourthly, there were two main differences between the control and treatment groups at outset:

(i) The control group appeared to have greater psychiatric morbidity at outset (as measured by the GHQ and CIS), although this was not statistically significant. This would enhance the possibility of a Type 2 error in relation to Hypothesis 1.

(ii) The control group also had have less social support at outset than the treatment group, although again this was not statistically significant. This would also enhance the possibility of a Type 2 error in relation to Hypothesis 1.

In fact, despite these two differences, the treatment group still had significantly greater morbidity during treatment than the controls as measured by both the GHQ and CIS. It can therefore be concluded that it is unlikely that the pre-treatment differences had a significant bearing upon the results.

Fifthly, all dosage regimes were collapsed into one treatment group because of the small numbers on each regime and because of the difference in pre-treatment psychiatric morbidity in the dosage groups. The high level of pre-treatment morbidity in the high dosage group made it unlikely that an enhanced impact of high dosage would be measurable, therefore increasing the chance of a Type 2 error in relation to the hypothesis that increased dosage would be associated with increased symptomatology.

In addition to masking differences in effects of dosage, the decision to collapse the dosage groups into one would also increase the likelihood of a Type 2 error in relation to Hypothesis 1. The literature indicates that the higher the dosage the more severe the symptoms and the more likely patients are to drop out due to symptoms. Were increases in psychiatric symptomatology to be only associated with high dosages then the mean increase in symptomatology would be decreased by collapsing the groups into one, therefore making it less likely that an effect of interferon would be picked up.

Finally, there were lower follow-up numbers than would have been ideal. About 15% of both the control and treatment groups were not available for follow-up. If there had been a general tendency for those with higher psychiatric morbidity in the treatment group not to be available at follow-up this would potentially give a false picture of the relationship between post-treatment morbidity and pre-treatment morbidity. In the event, this effect was only apparent in one group, the high dosage treatment group, where the mean 'during treatment' score of those who subsequently dropped out was 20.1 on the CIS. This explains why the mean post-treatment CIS score in this group (7.5) was so much lower than the mean pre-treatment score (12.7).

5.2 Interpretation of results.

The results pertaining to each of the main hypotheses are considered in turn.

1. Interferon therapy produces significant psychiatric symptomatology.
The study showed a rise in psychiatric symptoms among those on interferon treatment compared with matched controls. Hypothesis 1 was thus confirmed.

This rise occurred despite the decision to collapse the assessments made over time during treatment into one result based upon the mean score during treatment. This increased the likelihood of a type 1 error in relation to Hypothesis 1, since, for example, were interferon treatment to produce an initial increase in symptomatology which then tailed off it would be possible for this effect to be masked by data based upon mean scores. The fact that a difference was evident based upon the mean scores, thus strengthened the degree of confirmation of Hypothesis 1.

The psychiatric symptoms were non-psychotic in nature, the most commonly reported symptoms being fatigue, impaired concentration and irritability.

The pre-treatment correlations were as expected. Of particular interest in the correlations during treatment are the linkage of fatigue to psychiatric rather than physical symptoms; the increased predominance of depression; and the emergence of obsessional symptoms as a significant contributor to the overall pattern of CIS scores.

These changes were reversible on stopping interferon treatment.

2. The psychiatric morbidity observed in the study would be independent of social stresses and life events.

The observed increase in psychiatric morbidity remained even when social score

was controlled for. Hypothesis 2 was thus also confirmed.

During treatment the control group were subject to proportionally more life events, although this difference did not reach statistical significance. If anything, the greater proportion of life events in the control group would have been expected to be associated with heightened psychiatric morbidity in this group, thus reducing the likelihood of Hypothesis 2 being supported.

5.3 Subsidiary hypothesis.

The following subsidiary hypothesis was tested:

> 3. HIV infection would not influence the course of psychiatric morbidity in the study.

This hypothesis was disconfirmed. Multivariate analysis could only detect an effect of HIV status that was of borderline significance after other variables were controlled for, but the contrast between the changes in psychiatric morbidity of HIV-positive subjects on and off treatment is very striking.

HIV-positive status may therefore be an important determination of rise in psychiatric morbidity, although the small size of the subgroups and the post-hoc nature of this finding makes this observation tentative.

5.4 Additional observations.

There was a high level of observed psychiatric morbidity in the population. Bodily concern was high in controls and treated groups but this dropped during the course of the study (controls 86% to 62% and treated 70% to 45%). This implies either that high bodily concern was related to initial involvement in the study or that it was lowered by involvement in the study.

There were also fewer patients complaining of anxiety and depression at follow-up than initially. This may have been an effect of the presence of a psychiatric 'sympathetic ear' and the care given by the doctors and nurse involved with the study.

5.5. Implications of findings

The implication of the main finding, that interferon causes psychiatric morbidity, is that clinicians planning to use interferon should have available some form of psychiatric monitoring. The use of a screening instrument such as the GHQ would help in the early detection of cases needing intervention. Availability of a psychiatrist for purposes of consultation and treatment or referral for treatment would enhance sensitivity of treatment programmes to their impact on patients' quality of life.

Many patients treated with interferon reach symptom levels that a standard psychiatric assessment would class as of 'caseness severity' - implying that treatment is appropriate. Although such changes were caused by exogenous interferon it does raise the question of the role of endogenously produced interferons in the production of abnormal mental states. The abnormal states reported in this study are very reminiscent of many persistent complaint syndromes that present to psychiatrists after viral infections or trauma and which are labelled as chronic neuroses. Until now the investigation of the role of endogenous interferons in psychiatry has focused on either organic changes or the psychoses. but the observations of this study suggest it may be worth exploring their role in the production of other types of psychiatric morbidity.

Finally, the fact that changes in psychiatric morbidity seem largely to occur in the HIV-positive subgroup is noteworthy. These subjects are already producing acid-labile interferon because of their infection by HIV virus or other viruses and in these circumstances the exogenous interferons may well have their most potent effect.

This raises the question whether it is solely the amount of interferon that causes psychiatric symptoms regardless of the source of the interferon or whether a virus need to be present in the CNS in order for the effects of interferon (i.e. induction of enzymes leading to the destruction of cellular RNA) to occur. A larger scale investigation would be needed to study the potential beneficial or harmful effects of therapeutically administered interferon on CNS function.

5.6 Conclusions

The conclusions are first that interferon does cause an increase in psychiatric morbidity, even after social scores are controlled for, and that these changes remit after treatment is discontinued.

Second, the psychiatric symptoms seem to be non-psychotic, the most commonly reported being fatigue, impaired concentration, anxiety and depression. Also noticeable was an accentuation of existing symptoms, be they phobia or obsessional ruminations, among those who have reported minor complaints of this sort before treatment.

Thirdly, organic changes were not noticeable in the study at a clinical level, although psychometry and electroencephalography would have been valuable adjuncts to detect subclinical changes.

Fourthly, a subdivision of the population by treatment and HIV status has produced interesting results but since subgroups were small conclusions from this analysis must be tentative.

Fifthly, interferon treatment should be accompanied by psychiatric monitoring.

Finally, the successful insertion of a psychiatric dimension into a study focused on a physical disorder implies that there may be a useful role for psychiatrists in further studies of this kind.

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Appendix 1: The General Health Questionnaire and Clinical Interview Schedule.

GENERAL HEALTH QUESTIONNAIRE

Please read this carefully:

We should like to know if you have had any medical complaints, and how your health has been in general, over the past few weeks. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL the questions.

Thank you very much for your co-operation.

HAVE YOU RECENTLY:-

1. -	been able to concentrate on whatever you're doing?	Better than usual	Same as usual	Less than usual	Much less than usual
2. -	lost much sleep over worry?	Not at all	No more than usual	Rather more than usual	Much more than usual
3. -	been having restless, disturbed nights?	Not at all	No more than usual	Rather more than usual	Much more than usual
4. -	been managing to keep yourself busy and occupied?	More so than usual	Same as usual	Rather less than usual	Much less than usual
5. -	been getting out of the house as much as usual?	More so than usual	Same as usual	Less than usual	Much less than usual
6. -	been managing as well as most people would in your shoes?	Better than most	About the same	Rather less well	Much less well
7. -	felt on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much less well
8. -	been satisfied with the way you've carried out your task?	More satisfied	About same as usual	Less satisfied than usual	Much less satisfied
9. -	been able to feel warmth and affection for those near to you?	Better than usual	About same as usual	Less well than usual	Much less well
10. -	been finding it easy to get on with other people?	Better than usual	About same as usual	Less well than usual	Much less well
11. -	spent much time chatting with people?	More time than usual	About same as usual	Less time than usual	Much less than usual
12. -	felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
13. -	felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much less capable
14. -	felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
15. -	felt you couldn't overcome your difficulties?	Not at all	Mo more than usual	Rather more than usual	Much more than usual
16. -	been finding life a struggle all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
17. -	been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual

Please turn over

HAVE YOU RECENTLY:-

18. - been taking things hard?	Not at all	No more than usual	Rather more than usual	Much more than usual
19. - been getting scared or panicky for no good reason	Not at all	No more than usual	Rather more than usual	Much more than usual
20. - been able to face up to your problems?	More so than usual	Same as usual	Less able than usual	Much less able
21. - found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
22. - been feeling unhappy and depressed	Not at all	No more than usual	Rather more than usual	Much more than usual
23. - been losing confidence in yourself?	Not at all	No more than usual	Rather more than usual	Much more than usual
24. - been thinking of yourself as a worthless person?	Not at all	No more than usual	Rather more than usual	Much more than usual
25. - felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much more than usual
26. - been feeling hopeful about your own future?	More so than usual	About same as usual	Less so than usual	Much less hopeful
27. - been feeling reasonably happy, all things considered?	More so than usual	About same as usual	Less so than usual	Much less than usual
28. - been feeling nervous and strung-up all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual
29. - felt that life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much more than usual
30. - found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much more than usual

THE CLINICAL INTERVIEW SCHEDULE

GENERAL MEDICAL HISTORY

Now I'd like to ask you about your previous health? Have you had any serious illnesses?

What about operations?

(Check the following)

Chronic chest condition? (e.g. bronchitis, asthma)

High blood pressure

Heart trouble?

Stomach or bowel trouble? (e.g. stomach ulcers, gastritis)

Jaundice?

Kidney or bladder disease?

Diabetes?

Any serious skin trouble?

Arthritis? (stiffness, pain in the joints)

Any kind of growth or tumour?

Anything else?

Do you suffer from any kind of ill-health now (apart from what you came to see Dr.....about)?

Have you ever had a nervous breakdown or suffered from bad nerves?

Were you ever a patient in a hospital for nerves (mental hospital)?

Did anyone in your family suffer from nervous trouble?

- or have treatment in a hospital for nerves (mental hospital)?

How long has Dr. ..... been your doctor now?

(If a new episode)
When was the last time you saw him, before this recent trouble?

What was that for?

(If not new episode)
How long have you been seeing him for this trouble?

During the past year, have you been under any other doctor?

- have you been in hospital, or attended hospital?

ADDITIONAL NOTES ON MEDICAL HISTORY
(including any special points from patient's medical notes)

ANY SPECIAL COMMENTS ON MEDICAL HISTORY BY PATIENT'S G.P.

Have you noticed anything else wrong with your health apart from the things you have already told me?

(Anything else?)

In the past week, have you been troubled with headache?

or indigestion?

If the rater suspects that psychological mechanisms may be implicated in any of the somatic symptoms described, elicit more details as follows:

How long have you had this trouble?

Does it seem to get worse when your nerves are bad?

How much does it upset you?

How often have you had it in this past week?

SOMATIC SYMPTOMS 4 3 2 1 0

ALL PATIENTS:- Are you at all worried about your health at the moment?

Do you find yourself thinking a lot about your health, or about the working of any part of your body?

Do you ever worry about having cancer? - or heart disease?

(The following Part 2 rating may be made at this point if the rater wishes)

EXCESSIVE CONCERN WITH BODILY FUNCTIONS 4 3 2 1 0

Have you noticed that you get tired easily?

Or that you seem to be lacking in energy?

-If the patient's replies indicate excessive fatigue or lethargy, go on as follows:

How long have you noticed this?

Do you feel tired the whole time, or just now and then?

What sort of things do you find most tiring?

Do you feel completely tired out in the evening?

How has it been this past week?

- Has it stopped you from doing anything you've wanted to do?

FATIGUE 4 3 2 1 0

What about your sleep?

If reply indicates difficulties, ask for details:

Do you have difficulty dropping off?

Are you restless at night?

Do you wake early?

Have you lost any sleep in the past week?

If the patient's replies indicate loss of sleep in the past week, go on as follows:-

How long have you had this trouble?

Have you any idea why you can't sleep?

How many nights in the past week have you lost sleep?

How many hours sleep do you think that you miss on a bad night?

SLEEP DISTURBANCE 4 3 2 1 0

ALL PATIENTS:

Do you take any sleeping pills?

If YES, go on to ask:

Do you get them from your doctor?

Do you know what they are called?

Do you take them every night, or just now and then?

How many have you had in the past week?

HYPNOTICS 2 1 0

Do you find that you are easily upset or irritable with those around you?

If the patient's reply indicates irritability, go on as follows:

How long have you been like this?

Are you like it all the time, or just occasionally?

What sort of things upset you?

How has it been in the past week?

Have you had any rows with anyone in this past week?

Are there still any hard feelings?

IRRITABILITY 4 3 2 1 0

Do you find it difficult to concentrate?

Do you get muddled or forgetful?

If replies indicate impairment, go on as follows:

How long have you noticed this trouble?

Do you notice it all the time, or just now and then?

Has it caused any difficulty? at home?

or at work?

Can you concentrate on a newspaper or on a play on TV?

How bad has it been in this past week?

- has it stopped you from doing anything?

- how many of your activities are affected?

LACK OF CONCENTRATION 4 3 2 1 0

How have you been feeling in your spirits in the past week?

Have you had spells of feeling sad or miserable?

If the patient's replies indicate despondency or sadness, go on as follows:

Have you felt low the whole time, or just occasionally?

Does it seem connected with anything that happens?

How bad does it get?

Do you ever get weepy?

Can you snap out of it?

Do you sometimes feel hopeless?

Have you felt like making an end to it all?

DEPRESSION 4 3 2 1 0

If indicated, ask the following questions for the Part 2 rating of depressive thoughts:-

Do you ever blame yourself for being like this?

Do you ever find yourself feeling guilty?

Do you sometimes feel inferior to other people?

How do you feel about the future?

DEPRESSIVE THOUGHTS (Part 2 rating) 4 3 2 1 0

Would you say that you are a highly strung or nervous person?

Do you ever find that you get anxious or frightened for no good reason? —

Do you worry a lot about things?

If the patient's replies indicate anxiety and worrying, go on to ask more:

What sort of things do you chiefly worry about?

Have you always been like this, or is it something that has only started recently?

Do you worry all the time, or only now and then?

Do you find your self worrying more than you need about little things?

Have you been very upset by worries in the past week?

Are there any special things or situations that you find frightening or upsetting?

What about being alone in the house?

- going out by yourself?

- travelling on buses or trains?

- animals? insects? heights? the dark?

If patient's replies indicate any phobias, go on to elicit details, viz:

How severe is this?

Do you get it all the time, or just now and again?

How bad has it been in this past week?

Do you have to go out of your way to avoid - or alter your usual activities in any way?

Do you ever find that you have to do things over and over to make sure that you've done them right?

Or that you keep having unwelcome thoughts that you can't get rid of?
(If patient asks what is meant: Well, any sort of unpleasant thought that comes into your mind against your will.

Do you find it hard to make decisions?

If the patient's replies indicate possible obsessions or compulsions, ask appropriate questions from the following:

(CHECKING)

How many times do you find yourself checking your work?

Do you check it even though you know that it's right really?

Are there any other things you find yourself having to do a number of times?

(UNWELCOME THOUGHTS)

Can you describe them to me?

(DIFFICULTY WITH DECISIONS)

Is this something that you've always had, or is it something new?

Is it just over important issues, or does it affect trivialities as well?

ALL PHENOMENA

Do you try and struggle against it?

Is it very distressing?

Does it take up much of your time?

How bad has it been in this past week?

OBSESSIONS AND COMPULSIONS 4 3 2 1 0

Do you ever get the feeling that you're not really there? Or that everything around you seems unreal?

If patient's replies indicate possible depersonalisation, go on to elicit details, viz:

Can you describe the feeling?

Do you find it unpleasant or frightening?

Do you get it every day, or just now and again?

How long does it last when you get it?

How bad has it been just lately? (in this past week)?

DEPERSONALISATION 4 3 2 1 0

Is there anything else to do with your health that you think might be important?

- or anything I haven't asked you about?

FAMILY'S PSYCHIATRIC HISTORY

BRIEF PERSONAL AND SOCIAL HISTORY

PART TWO RATINGS: Evidence for Psychiatric Disturbance Noted at Interview

Name of Rating:	Reason for Morbid Rating:	Rating Assigned:
SLOW, lacking spontaneity		4 3 2 1 0
SUSPICIOUS, defensive		4 3 2 1 0
HISTRIONIC		4 3 2 1 0
DEPRESSED		4 3 2 1 0
ANXIOUS tense AGITATED		4 3 2 1 0
ELATED, euphoric		4 3 2 1 0
FLATTENED INCONGRUOUS		4 3 2 1 0
DELUSIONS Misinterpretations THOUGHT DISORDER		4 3 2 1 0
HALLUCINATIONS		4 3 2 1 0
INTELLECTUAL IMPAIRMENT		4 3 2 1 0
The following ratings may already have been made:		
EXCESSIVE CONCERN with BODILY FUNCTIONS		4 3 2 1 0
DEPRESSIVE THOUGHTS		4 3 2 1 0

Interviewer's Notes:

Summary and Formulation:

Assessment of the Reliability of the Information:

GOOD / FAIR / POOR

I.C.D. DIAGNOSIS:

Principal Diagnosis: .....

Ancillary Diagnosis: .....

OVERALL SEVERITY RATING: 4 3 2 1 0

Appendix 2: Clinical Vignette.

A. is a thirty year old Irishman who works as a clerk in the civil service. His chronic active hepatitis was discovered eighteen months prior to treatment following his donation of blood.

His father died two years ago from cirrhosis of the liver. His mother is a fifty-eight year old housewife who is alive and well and supportive to the patient. A. is the sixth of eleven children. He has quite a lot of contacts with his siblings which he finds generally rewarding and satisfying. His father was an alcoholic and one brother has been diagnosed as having antisocial personality disorder. There is no family history of phobias.

A.'s birth and milestones are normal. He was a bedwetter until age 12. His childhood was unhappy due to parental discord and separation when he was nine years old. He attended school between four and fifteen years and had a series of unskilled jobs until he obtained his current position as a clerk. A has his own flat and a good social network. He is homosexual and has been with his current boy-friend for two years.

At the start of the study A. described himself as being happy, easygoing and knowing what he wants out of life. There was no previous psychiatric history.

At the initial interview A.complained of fatigue and moderate concern about his health. His CIS score was 9. After two weeks of alpha-interferon treatment he complained of increased fatigue, sleep disturbance, lack of concentration and mild depression. His CIS score was 15, which made him a 'case'. Twelve weeks after starting treatment he had similar complaints but had also become phobic of pigeons six weeks previously. When seen he completely avoided pigeons and would cross the road when he noticed any in his path. This made his life quite difficult, as for example, he would have to cross the road several times between the underground station and the hospital. His CIS score was 15. He had also developed psoriasis, which is a known complication of interferon treatment.

Six weeks following cessation of alpha-interferon treatment his pigeon phobia had completely disappeared. His other complaints of poor concentration, depression and sleep disturbance had also ceased. He complained of mild irritability and his psoriasis was still a problem. His CIS score was 2.

Addendum 1: The Relationship Between CIS Score and Social Support

Co-variate	Co-efficient	Beta	Std. error	T-value	Sign.
Social support	-1.11	-0.45	0.36	-3.06	0.004

The regression co-efficient between the total CIS score and the social support score was -1.11. For a unit increase in the Social Support score there was thus a corresponding decrease of -1.11 on the CIS score. A t-test was performed by dividing the co-efficient by the associated standard error. The significance of this was tested by dividing by the standard error. This gave a t value of --3.065, which was significant at the 0.004 level, indicating that the result was unlikely to have occurred by chance.

The 95% confidence intervals for the regression coefficient are -1.84 and -0.38. This means that the true rate of decline in the CIS score for a unit change in Social Support may be as large as 1.85 or as small as 0.38 (thus for a change of 1 s.d. on the Social Support score the expected reduction in the CIS may be as large as 4 points).