

The Effect of Gluten-Free Diet on Urinary Peptide Excretion and Clinical State in Schizophrenia

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Introduction

This study is based on three different but possibly related observations: 1) That schizophrenia is rare where gluten intake is rare (Dohan 1966, 1980; Dohan et al 1984), 2) That dietary gluten seems to have toxic effects and behavioural effects in some schizophrenics (Dohan and Gras-berger 1973; Singh and Kay 1976; Rice et al 1978; Vlissides et al 1986; Jansson et al 1984), and 3) That there is an increased urinary excretion of glyco-protein-bound and benzoic acid precipitable bioactive peptides in schizophrenia (Hole et al 1979; Reichelt et al 1981; Reichelt et al 1985). The increase in a group of peptides with the same bioactivities has been confirmed in serum (Drysdale et al 1982).

The incidence of schizophrenia in the families of coeliacs is higher than the expected rate (Dohan 1980,1983). Psychiatric symptoms are furthermore common in coeliac patients, both in childhood (Asperger 1961) and in adults (Hallert et al 1966).

Intracranial injections of partial hydro-lysates of wheat gliadin induces abnormal behaviour in rats (Dohan et al 1978). Forced feeding of cats with gluten and gliadin induced changes in CNS monoamines and decreased dopamine beta-hydroxylase activity (Thibault et al 1988). However, several negative dietary clinical trials have been published (Potkin et al 1981; Vlissides et al 1986).

Ten relatively chronic schizophrenic patients, rather unresponsive to neurolept

tics, were assessed by urinary profiles.

We also related these profiles to the DSMIII classification and the description of Crow (Crow 1982). The effect of a gluten free diet was followed by urinary profiles and various ratings scales run blind. An open clinical evaluation was used, and IgA and IgG antibodies to some food proteins were also measured.

An effect of diet on peptide excretion was quite clear, but it took twenty-eight weeks to normalize the urinary patterns. A weak but uncertain, effect on blind ratings was also observed. Open evaluation indicated a positive effects in four and probable in three patients. Increased levels of IgA antibodies to milk proteins and gluten was more frequently observed than expected.

Patients and Methods

Patients

Eleven male schizophrenics with a mean duration of illness of 4.9 years (range 3.5 to 7) were diagnosed according to the DSMIII criteria (ES and JL). They all gave informed consent. Exclusion criteria were serious somatic illness, lack of ability to cooperate, and drug or alcohol abuse during the last year. One patient dropped out at once. The age of the remaining 10 ranged from 22 to 38 years.

For subdivision into hebephrenic and paranoid subgroups the description of Langfeldt (1965) was used, and also that of Crow (1982) into type 1 and 2 (NB! Our type 1 urinary pattern corresponds to type 2 in Crow's terminology). Some patients had periods in which they presented mainly hebephrenic/-catatonic features, and other periods in which paranoid symptoms dominated. They could thus satisfy the cri-

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teria for different subtypes at different times. Therefore, in table 1 we have given both the diagnosis stated in the patient's record (usually given several years earlier) and the diagnosis based on the state of the patient at the start of this study.

At the start of the trial, all patients were on neuroleptics, and it was intended to keep medication unchanged. However, patient A2 stopped taking medication on his own accord, and had to be re-medicated. Patient A5 had extremely high doses of neuroleptics which had to be halved. Patient B1 had his neuroleptic dose reduced because of somatic side effects that became apparent during the diet period.

Prior to the trial five patients were inpatients at different wards in the hospital. Five (A1, A2, A4, B4 and B5) were staying in half-way houses outside the hospital, but supervised by the hospital staff. It may be important to note that these five patients to a large extent made their own meals, which by their own description were relatively rich in gluten.

Design

At the start of the trial, the patients were transferred to an open research ward. After 1 week to equilibrate to their new surroundings the patients were randomly divided into two equal groups, A and B.

Group A was given a gluten free diet for eight weeks and switched to ordinary diet for the next eight weeks. Group B the other way around. After 16 weeks, the patients were returned to their original wards or places of residence. Those wanting to, continued diets supervised by dietician. This included from week 16 to 28 patients A1, A3, A4, B2 and B3, and from week 28 to 56 A1, A3, B1, B3 and B4. The gluten-free diet was the hospital standardized diet for coeliacs, guided by nutritionist.

Patient B3 had to be transferred from open to closed ward early in the study, but diet shifts were carried through as planned. Several breaks in diet were noticed (eg. beer drinking, especially for B5). Initially patients A2, A5 and B2 had occasional breaks in their diets. B2 and B3 were the most severely ill patients and rating scales proved impossible to procure initially. Interestingly both could be tested during periods

on diet.

Clinical Assessment

Ratings of patients were carried out independently by two MD's who did not know the dietary status of the patients. The following instruments were used: 1) The Comprehensive Psychopathological Rating scale (CPRS; Aasberg et al 1978), 2) A subscale of CPRS designed for schizophrenia (Jacobsen et al 1978), and 3) The Whitaker Index of Schizophrenic Thinking (WIST; Whitaker 1980) translated into Norwegian by J. Landmark. NOSIE-30 was rated non-blindly by the ward attendants. In addition, clinical assessment was performed non-blind by the psychiatric staff and ward attendants at the end of each trial interval. Interrater reliability had been assured before the start of the experiment and was satisfactory.

Urine Analysis

Twenty-four hour urines were collected under supervision and numbered from 1 and up at weeks 0, 16, 28 and 56. Average volume was 1666 ± 729 mL. The urines were stored frozen until analyzed, then thawed and the pH adjusted to 4.3 with HCl. Benzoic acid precipitation, ethanol wash with methylisobutyl-ketone containing ethanol and gel chromatography have been described elsewhere (Reichelt et al 1985; Saelid et al 1985; Reichelt et al 1986; Hole et al 1988).

On G-25 gel filtration besides the void volume, two main peak areas are obtained. The first from 600-900 mL is made up of glycoprotein-peptide-benzoic acid complexes and hence retarded.

The benzoic acid coats the glycoprotein-peptide complexes like a mini-detergent. The late peak from 1100-1500 mL is similarly made up of glycoprotein-purine-peptide complexes (Reichelt et al 1985; Reichelt et al 1986, Saelid et al 1985).

Material corresponding to the first of the retarded peaks of each patient (600-900 mL Fig. 1) was rotavapored and redissolved in 1M acetic acid and fractionated on Biorad P2 gels in 0.5 M acetic acid as described (Reichelt et al 1985; Reichelt and Edminson 1985).

10% aliquots of each fraction were dried overnight at 150° C. The content of hydrolysis

released ninhydrin groups was measured after alkaline hydrolysis in 2M KOH and ninhydrin staining (Reichelt and Kvamme 1973; Reichelt and Edminson 1985). Using this procedure ammonia is driven off, urea reduced and many amines other than amino acids are destroyed. The acetate-cyanide buffer used has the advantage of a close to equimolar absorption coefficient at 570 nm for each amino acid (Reichelt and Kvamme 1973). Thus an estimate of released amino acids in micro-moles is possible. About half of the peptides pass through a Dowex 50 cation exchange resin in the H⁺ form at pH 2 and are therefore N-substituted (Reichelt and Edminson 1985). This has also been confirmed by pyrogluopeptidase action on these peptides (Reichelt et al in prep.). The amino acid nature of the material has been checked by amino acid analysis before and after hydrolysis (Reichelt and Edminson 1985).

The obtained chromatograms were compared to previously run samples from psychiatric patients (Reichelt et al 1981 and 1985), and could on this basis be classified into two main types:

Type 1 is characterized on G25 by a relatively large and strongly retarded late peak (1100-1500 mL) with a frequently stepwise increase (Fig. 1). Total area under the UV 280 nm curve is larger than that of the 600-900 mL peak which is often pseudo-normal. Type 1 has been found mainly in patients with catatonic traits and hebephrenic types of schizophrenia (Fig. 1).

Type 2 is characterized by an insignificant or totally absent late peak, whereas the 600-900 mL peak is very large, and sometimes extremely large. This type is found mainly in paranoid schizophrenics and in those with more acute onset, regardless of type (Fig. 1) (Reichelt et al 1985; Cade et al 1989).

On the P 2 gels the material from the 600-900 mL peak results in a complex pattern with more retarded peaks than found in depression (Reichelt et al 1985). The type 1 in general contains twice as much low MW material as the type 2 (Reichelt et al 1987) in the urine. These retarded peaks, that disappear or are reduced on diet, indicate either lower MW than in depression or more aromatic interaction with the gel. The previously found elution peak maxima expressed as Kav

values, where Kav is defined as $V_e - V_o / V_t - V_o$, are used to describe the individual chromatograms. V_e is the elution volume of any given peak, V_o the void volume and V_t the total volume of the column.

From previous study of schizophrenics (Reichelt et al 1985) the peak characteristics of 63 patients were as follows (Kav values are given with frequency of occurrence in parenthesis). For type 1: 0.20 (5/34), 0.41 (14/34), 0.61 (21/34), 0.68 (20/34), 0.76 (28/34), 0.84 (27/34), 0.93 (24/34), 1.15 (20/34) and 1.25 (15/34). Type 2 schizophrenics typically had the following Kav values (n = 29): 0.46 (10/29), 0.53 (12/29), 0.61 (17/29), 0.69 (22/29), 0.77 (27/29), 0.85 (20/29), 0.93 (19/29), 1.03 (17/29), 1.26 (11/29) and 1.35 (2/29). The considerable microheterogeneity of these complex peaks should be obvious also chemically.

The method has false positives in approximately 7% of the normals, and false negatives in about 5% (unpublished data). Neuroleptics decreases the level of peptide excreted. Monthly measurements in a single schizophrenic patient over two years showed an average level of 48 ± 5.1 (n = 24) micromoles.

Evaluation of diet induced changes was based on changes in the G25 pattern. Type 1 showed a reduction of the most retarded peak and generally also in the 600-900 mL peak. Type 2 a reduction in the middle peak (600-900 mL) on G25 and a slight increase in the usually absent late peak.

On P2 chromatograms the Kav peaks larger than urea, from 0.76 to 1.25 were the ones that mainly decreased or disappeared, but there was also a decrease in overall micromoles of hydrolysis released amino acids in all peaks.

Using these criteria to assess diet-induced alterations we only missed one change, in patients (A-5). This is probably due to his medication being reduced to half. Reduction in neuroleptic dose increases urinary peptide levels (unpublished data).

When possible, CT was performed on the patients (Table 2).

Antibodies to dietary antigens: The enzyme-linked immunoassay (ELISA) used has been described in detail (Scott et al 1985a). Briefly, Costar EIA microplates (no 3590) were

coated with antigens at concentrations found to be optimal (0.001 -0.01 g/1 for different antigens) and the patients sera tested for IgA and IgG activity at 1:400. The following antigens were used: crude gluten (ICN Pharmaceuticals, Cleveland, Ohio, USA), a gluten fraction called Glyc-gli (Douglas 1976), casein, alpa-lactalbumin, beta-lactoglobulin and ovalbumin (Sigma Chem Corp., St. Louis, Mo, USA). Based on previous studies (Scott et al 1985b) the following optical density (OD) values for various specificities were taken as the upper normal ranges: Glyc-gli and Gluten, IgG = 1.7 and IgA = 0.4; Alpa-lactalbumin, IgG =1.6 and IgA = 0.3; Betalactoglobulin and ovalbumin, IgG = 1.8 and IgA = 0.4; and casein IgG = 1.8 and IgA = 0.8.

Statistical Evaluation

Because of the low number of patients and the fact that two chromatographic subtypes could be seen, nonparametric tests were used. The Wilcoxon paired ranking test (McCall 1980). The enormous difference in micromoles excreted and rating scores, which varied with a factor of almost 10, made some normalization of the data mandatory. Per cent change of the initial value for each test interval and patient was chosen. Otherwise the enormous spread of data would obscure even large real changes.

The Mann Whitney U test was also used for nonpaired comparisons. Because of frequent use some t values are also given.

Results

The relation of the blind urinary classification to the clinical evaluation is given in table 1. Our type I urinary pattern fitted Langfeldt's (1965) description of hebephrenic with or without catatonic traits. Type 2 pattern fitted the paranoid schizophrenic subtype. Crow's (Crow 1982) type 2 fits our type I reasonably closely, and his type 1 our type 2. Table 1 gives the DSMIII classification from the records and from direct observation. Effect of diet is based on open clinical evaluation. CNS atrophy was expected to render diet less effective.

Fig. 1 illustrates the two different schizophrenic types and also the normal pattern on G25 (Reichelt et al 1985).

Clinical Course in Relation to Diet Periods

In Table 1 the open evaluation of the experiment is seen. Eight of the patients have asked to continue the diet beyond the experimental period because of subjective well being on diet.

The behavioural scores can be seen in Table 2. When n is smaller than *the* total population this is caused by incomplete data. Using Mann Whitney U test the alterations from period to period do not show any significant differences between patients with or without diet. For Nosie at 56 weeks a $p < 0.05$ was found. The Wilcoxon paired ranking test was significant for the late observation points however (Table 2). If we normalize the scores in percent of the first value for each interval (Table 3), the differences obtained for the different time intervals are significant as indicated using the Wilcoxon paired ranking test. A weak but probable effect on behavioural scores seems a reasonable conclusion. This is also indicated by the statistically significant worsening in the dietary group in their NOSIE ratings for week 0 to 8, which was expected by the initiators of the experiment due to abstention phenomena, but not conveyed to the attendants scoring the patients. In agreement with these data are the fact that B2 and B3 could only be tested during diet periods. Even in coeliac disease 8 weeks is far too short to catch long lasting coeliac changes in the gut (Kumar et al 1979), therefore most emphasis should be on the late scores (week 16 and especially 28 and 56) (see discussion) when the urinary patterns were normalized.

Alterations in Urinary Patterns

The change on and off diet is given in Table 2 and the percentual change for type 1 pattern patients in Fig. 2 and type 2 in Fig. 3. The intervals compared are given in the tables. With a difference in initial micro-moles per 24 h varying from 134.1 to 6.0 micromoles for the 600-900 mL peak fractionated on P2 gels; it was obvious that percentual comparison was more correct. Again it is clear that the late periods showed the highest statistical significance with p values < 0.01 for 16-28 and 28 to 56 weeks.

Using the scores directly in the Mann Whitney U test the last two periods are also significantly different on diet from no diet with $p < 0.01$. It is believed that some of the change in the first 8 weeks may be obscured by the fact that patients from halfway houses who prepared their own food probably had a very large gluten intake relative to inpatients. Comparing B4 and B5 to B1, B2 and B3 we find as decrease in peptide levels in the outpatients of 51 micromoles while the inpatient group had a decrease of 3.5 micromoles in the first 8 weeks.

In Fig. 4 the G-25 pattern changes is shown for one type 1 to the left and one type 2 to the right. In Fig. 5 and 6 the changes in hydrolysis released ninhydrin-colourable groups can be seen. Normal patterns and amounts were only obtained after 56 weeks. Normal 24 h secretion in the G 25 peak from 600-900 mL is 7.9 ± 2.3 micromoles ($X \pm 1$ SD $n = 75$) (Reichelt et al 1985). Assessing the curves blind we missed only A5 once when he had his neuroleptic dose halved; this always increases the peptide levels found (unpublished data). For type 1 disorders the micromoles amino acid equivalents in the most retarded G25 peak was at 56 weeks (A1, A3 and B4) 2.3 ± 2.5 compared to the initial value 35.5 ± 9.5 micromoles.

The late (high K_{av}) peaks of material eluting after urea decreased the most on P2 gel filtration of the 600-900 mL peak from G25 runs. For K_{av} peaks later than urea the following changes were found: The K_{av} 0.68 peak decreased during the 28-56 week span by 4.0 ± 3.1 micromoles ($n = 4$), and off diet the same peak increased to 8.5 ± 8.8 ($n = 4$) micromoles ($p < 0.01$). Likewise for the interval 0-56 weeks the decrease in the late P2 peaks (eluting after urea) on diet was 22 ± 15.7 micromoles ($n = 4$), while off diet an increase of 8.2 ± 10.6 ($n = 4$) micromoles was found.

The results of the measured levels of IgA and IgG antibodies to dietary antigens can be seen in table 4. Slightly raised antibodies to gluten was found in two and to glyc-gli in one. Increased IgA activities to cow's milk casein and lactoglobulin were found in three. This result conforms to data recently published (Lindstroem et al 1989).

Discussion

Our data seem to indicate that the abnormally high peptide levels found in schizophrenia could be changed by dietary intervention, with a tendency to reappear when a normal diet is resumed. We have never before seen such changes in patients followed over a two year period. We have not studied the effect of gluten free diet in normal persons, but as they have a rather low secretion of peptides compared to schizophrenics, one would not expect very marked changes. The more so as acid soluble peptides excreted in urine do not reflect diet in normal persons and animals, but endogenous protein metabolism (Hanson and Ansorge 1967; Ansorge and Hanson 1967; Noguchi et al 1982).

Manifest coeliac disease with psychic symptoms show G25 and P2 patterns very similar to schizophrenics but on P2 gels more high MW peptide peaks are found (Reichelt et al in prep.). This agrees with other observations showing increased py-roglu peptide secretion in coeliacs (Wauters and Vande Kamer 1978; Kowlessar et al 1970).

We have elsewhere shown the composition of the material analyzed (Reichelt et al 1981; Reichelt et al 1985; Saelid et al 1985; Reichelt et al 1986). That amino acids are the surviving amines after alkaline hydrolysis has been shown by amino acid analysis. The recovery of bioactive and also synthesized peptide from such urine material has been found (Reichelt et al 1984).

The peptides excreted are probably not an epiphenomenon as various bioactivities have been isolated that mimic some symptoms similar to those of schizophrenia in animals (Hole et al 1979; Drysdale et al 1982; Reichelt et al 1985). Urinary peptide increases with retained bioactivity have also been found in autism (Reichelt et al 1981; Reichelt et al 1986) and again confirmed with independent techniques (Israngkun et al 1986).

There may be several reasons why an excess of urinary peptides are found in schizophrenics. It could be that more peptides were formed in the gut and because of peptidase insufficiency taken up across the gut wall, thus increasing the level of opioid peptides in blood and

spinal fluid as found (Drysdale et al 1982; Linstroem et al 1986). Unpublished data have shown that neuroleptics tend to decrease the peptide levels as seen in patient A5 in this study also.

So far we have not shown that schizophrenics produce more peptides from gluten in the intestinal tract. However, it has been shown that powerful exorphins can be produced from gluten at duodenal pH by the action of trypsin, chymotrypsin and pepsin (Zioudrou et al 1984; Huebner et al 1984). Also MIF I can thus be formed (Mycroft et al 1982) and from casein caseo-morphins have been shown to be made in duodenum in vivo (Svedberg et al 1985). Peptides are taken up across the gut wall (Gardner 1983; Webb 1986; Alpers 1986; Takaori et al 1986) especially after peptidase inhibition (Mahe et al 1989). Peptides taken up may have a direct pharmacological effect but more importantly may inhibit extensively the breakdown of endogenous peptides. Peptide inhibition of peptide breakdown is well documented (LaBella et al 1985). It should be noted that the regulation of releasing factor activity in the hypothalamus is regulated by endocrine feedback onto critically localized peptidases that terminate peptide activity (Griffiths 1975). Disturbances in the hypothalamic-pituitary functions should therefore be expected. Peptidase insufficiency compounded by endocrine changes acting on peptidases could therefore easily be seen as the pathophysiological precondition for the disorder. Interestingly neuroleptics stimulate the N-terminal amino peptidase in vivo (Traficante and Turnbull 1982). Neuroleptics also changes the central neurotensin metabolism in vitro (Davis and Culling-Berglund 1987). Although no direct proof of any relationship between peptidase activation and antipsychotic effect is known, it is interesting that the sedative effects appear fast while the antipsychotic effects of neuroleptics appear generally much later.

Genetically caused peptidase deficiency regularly leads to peptiduria (Wright et al 1979; Blau et al 1988; Myara et al 1984; Lunde et al 1986). Also experimental inhibition of peptidases may cause peptiduria (Griffiths and Meister 1984). Pyro-glu-peptides like some of those we find

increased in schizophrenics (Reichelt and Edminson 1985) are also found increased in urines of coeliacs (Wauters and Vande Kamer 1978; Kowlessar et al 1970). Evidence for peptidase defects in schizophrenia has been found by several groups (Arregui et al 1979; Davis et al 1983; Schoemaker and Davis 1984; Reichelt et al 1987; Wie-gant et al 1988).

Some of the peptides in the urine may also be endogenous and it is interesting that intracranio-ventricularly injected low MW peptides may be found unchanged secreted mainly in the urine (Ziesler et al 1984). Especially if their breakdown are inhibited by exogenous peptides (LaBella et al 1985) this should be expected.

It is also relevant to our discussion that some coeliac children show profound psychiatric symptoms (Asperger 1961).

Fragments of gluten have been found in brain (Hemmings, 1978) and are taken up from the gut (Woodley et al 1980) as are phosphorylated and peptidase resistant peptides from casein (Mellander and Isaks-son 1950). In coeliac children provocation with gluten after diet causes an alarmingly high frequency of EEG changes that persist up to a year (Paul et al 1985). In adults neurological symptoms have been described in relation to coeliac disease (Cooke and Smith 1966) and motor end plate changes as seen in psychosis (Cooke et al 1966). Psychiatric problems are quite common to coeliac patients (Hallert et al 1982). Also immunological tests designed for coeliac disease are frequently positive in schizophrenics (Askenazi et al 1979). Food antibodies in psychosis have been found by several groups (Dohan et al 1972; Rix et al 1985; Sugeran et al 1982). Our data (table 4) may indicate increased permeability of the mucosa to immunologically active fragments of the proteins shown in 4 out of 11 patients. The pathogenic factors in coeliac disease seems to be peptidic (Bronstein et al 1966; Wieser et al 1984; Cornell 1988) and are taken up across the gut wall.

Immunoreactive bovine beta-lactoglobulin is found in human milk (Axelsson et al 1986; Stuart et al 1984) and immunoreactive gliadin (Troncone et al 1987). Insomnia (Kahn et al 1985) and infantile colic are both caused by passage of cow's

milk antigens to the infant (Lothe et al 1982). This clearly demonstrates that peptide uptake from the gut with bioactive consequences is a reality. The role of caseomorphin in post-partum psychosis (Lindstroem et al 1984) clearly demonstrates the possibilities inherent to our concept.

In Conclusion

Some relationship of gluten to the increased urinary secretion of a family of peptides seems probable. A weak but significant effect is possibly seen also by ratings scales for the late changes. The late normalization of the urinary patterns and the simultaneous late appearance of statistically significant changes of the behaviour tests, are probably not accidental. Slow changes are typical for coeliac disease (Davidson and Bridges 1987) also on provocation with gluten (Kumar et al 1979) and in cases of gluten induced dermatitis herpetiformis (Fry et al 1973). Open clinical assessment is that four patients find the treatment useful and three have probably effects, in this rather chronic group of patients.

The most important conclusion is that short trials are of very little relevance, and could be the cause of the confusing results obtained in other studies. This is clearly seen in Fig. 4 and 5 where completely normal peptide pattern was only found at 56 weeks. This of course does not preclude faster changes especially in more acute cases.

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Figure 1. Shows the UV trace at 280nm obtained by gelfiltration of the benzoic acid precipitate described in methods. The range of normals to date and a typical type 1 (mainly hebephrenic-catatonic trait) and type 2 (mainly paranoid) types can be seen (Reichelt et al 1985). The 600-900 mL peak consists of glycoprotein-peptide-benzoic acid complexes and the late peaks of purines mainly uric acid complexed to glycoprotein-peptide complexes (Reichelt et al 1986; Reichelt et al 1985).

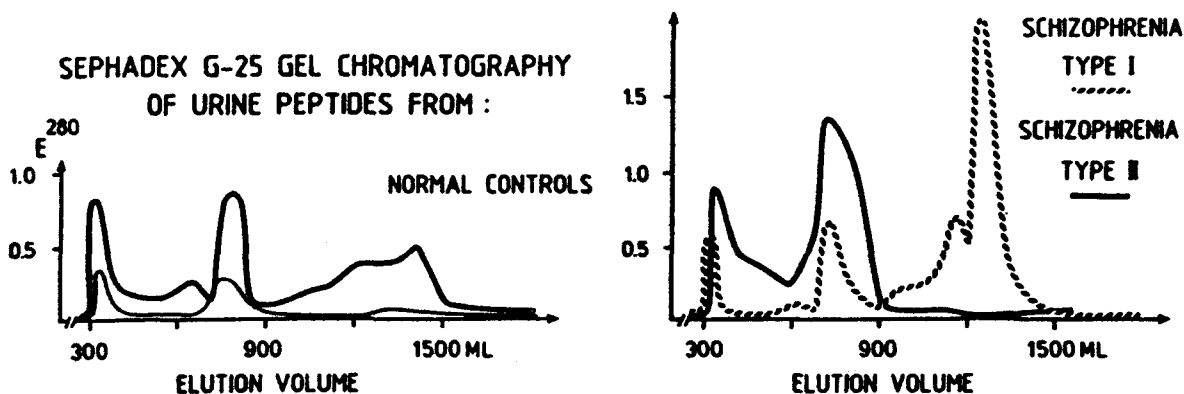


Figure 2. Shows the percent for the 600-900 mL peak of the type 1 patients in percent of initial values. From week 28 to 56 all patients were returned to their original place of living, but with dietary supervision. Note A-4 was on diet from week 28 to 50 and then went off diet, which would probably decrease his off diet levels artificially. B-1 was off diet from week 28 to 43 but then returned to diet because of upcropping acute paranoid ideation and hallucinations that motivated him to continue. On diet these were rapidly lost. B3 had the most frequent breaks in diet (beer) during the period 6 to 16 weeks. The decrease in A4 and A2 from week 8-16 and the increase in A4 from 16-28 could well be carry over effects.

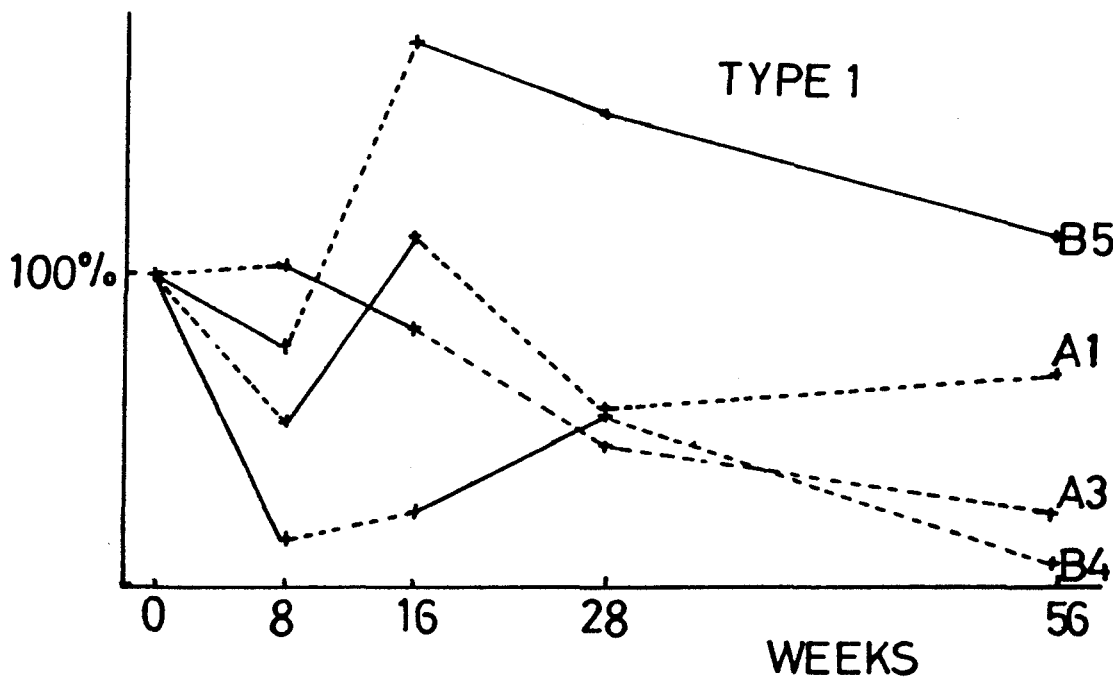


Figure 3. Shows the percentage change for type 2 patients as in Fig. 2.

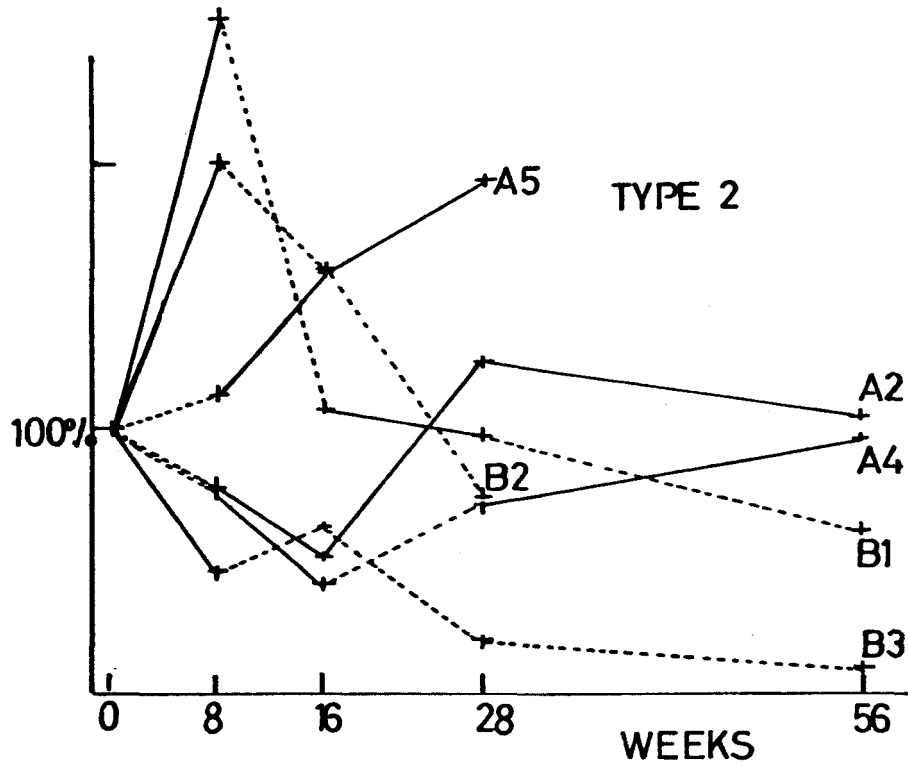


Figure 4. Shows a type 1 and a type 2 patient followed through periods on and off diet by the G-25 UV280 trace. The type 2 patient was on diet from week 8 to 16. The type 1 was on diet from week 0 to 8 and off diet from 8 to 28. The large drop in the type 2 pattern could be due to admission from single household diet to hospital diet (see text).

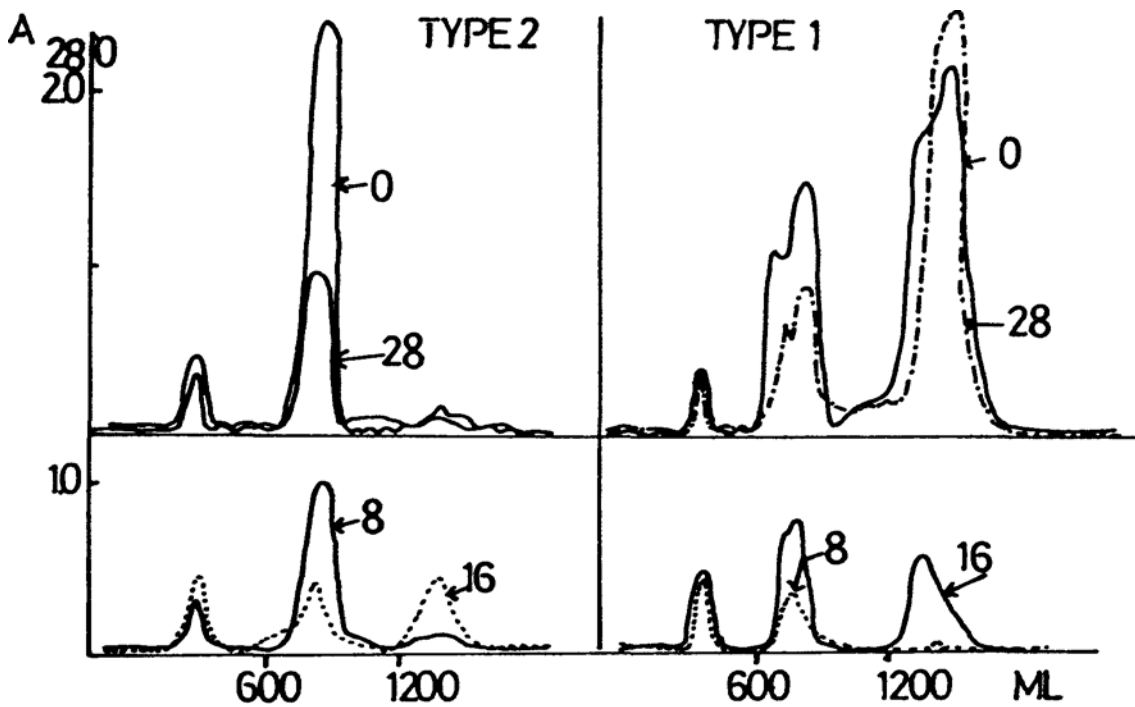


Figure 5. The P2 gel filtration pattern changes are shown for the 600-900 mL peak for two patients. The P2 column separates out peptides with MW < 200 Daltons. The ninhydrin colour is shown after alkaline hydrolysis obtained by a method that yields an equimolar absorption coefficient for the different amino acids (Reichelt and Edmison 1985). Dotted lines are periods on diet and solid lines periods off diet. Note that the pattern only becomes normal at 56 weeks.

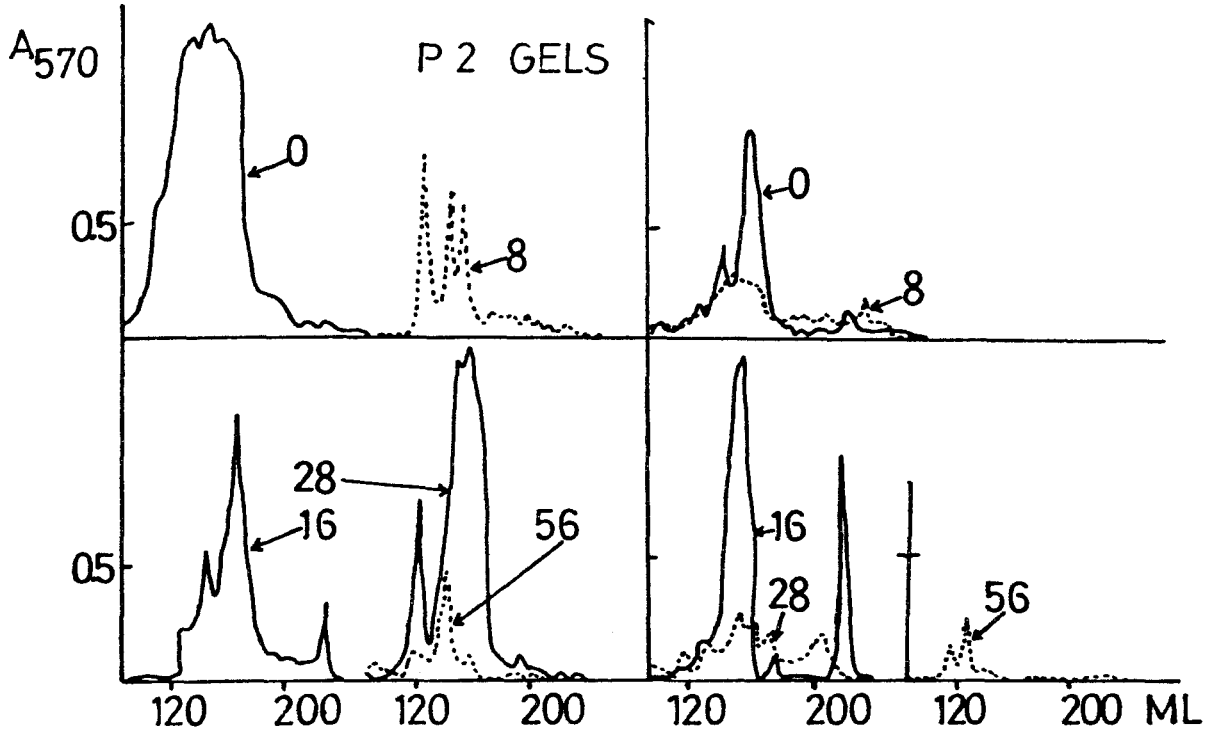


Figure 6. The P2 peptidogram of the 600-900 mL peak of another type 1 patient. Note the normalization after 56 weeks.

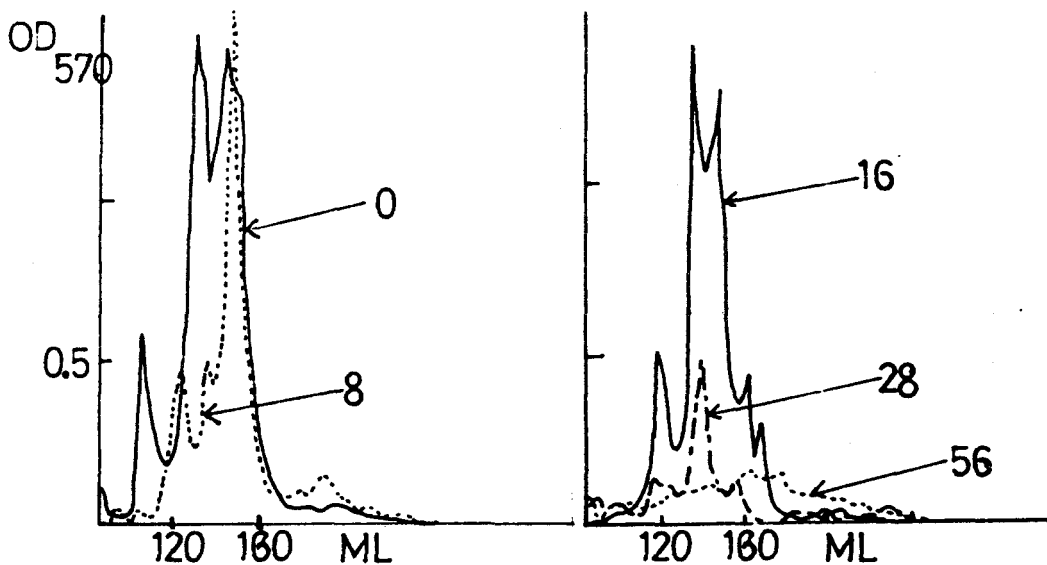


Table 1
Patient Characteristics

Patient	A1	A2	A3	A4	A5*	B1	B2	B3	B4	B5	Drop Out
Duration of disorder	4	6	5	4.5	5	7	4.7	4.7	3.5	5.5	8
Diagnosis from journals	295.1	295.9	295.9	295.3	295.1	295.9	295.1	295.1	295.1	295.1	295.1
Diagnosis on observations	295.1	295.9	295.1	295.9	295.3	295.3	295.3	295.9	295.1	295.1	295.1
Urinary pattern	1	2	1	1	2	2	2	2	1?	1	1
Crow's criteria	2	1	2	2	1	1	1	1	2	2	2
Hereditary factor	+	—	(+)	—	(+)	(+)	+	—	+	—	+
CT scan	N	N	A	—	A	A	—	—	N	—	—
Effect of diet	+	—	(+)	+	—	+	+	(+)	(+)	—	drop out

Table 1 shows the DSM III diagnosis before observation in the ward and after, and the urinary patterns (fig. 1) found in the different disorders. Hereditary load when + means that the patient had close relatives with schizophrenia. -: means no known relatives. (+): indicate relatives with undiagnosed psychotic states. B4 had a cousin suffering from coeliac disease. CT-scanning with atrophy is designated A. Normal is marked N and not performed -.

* A5 had enormous doses of medication on entry into the hospital and this was after a few weeks halved. This caused a more certain diagnosis to be made (more productive symptoms).

Table 2
Changes in Average Scores of the Different Monitoring System, ± Standard Deviation

System	Initial Score X ± SD	Diet	Week 0 - 8	Week 8- 16	Week 16-28	Week 28 - 56	Week 0 - 56
C.P.R.S.	26.8 ± 4.2(n=5)	+	— 9.8 ± 11.0 (n=5)	— 2.0 ± 4.7 (n=3)	+ 2.3 ± 1.5 (n=3)	— 4.0 ± 3.1 (n=4)**	— 22.0 ± 15.7 (n=4)*
	29.0 ± 17.5(n=3)	—	— 8.0 ± 10.0 (n=3)	— 8.0 ± 9.5 (n=3)	— 4.5 ± 6.6 (n=4)	+ 8.5 ± 8.8 (n=4)	— 8.2 ± 10.6 (n=4)
C.P.R.S. Sub scale	17.6 ± 4.1(n=5)	+	— 5.4 ± 6.3 (n=5)	+ 0.7 ± 4.5 (n=3)	+ 1.3 ± 1.5 (n=3)	— 3.0 ± 5.0 (n=4)*	— 15.8 ± 12.1 (n=4)*
	22.3 ± 12.5(n=3)	—	— 8.0 ± 11.4 (n=3)	— 1.6 ± 12.3 (n=5)	— 8.2 ± 11.5 (n=5)	+ 5.2 ± 9.5 (n=4)*	— 5.5 ± 7.5 (n=4)
W.I.S.T.	20.6 ± 8.6(n=5)	+	— 7.0 ± 3.9 (n=5)	— 0.3 ± 3.3 (n=4)	0	— 1.8 ± 6.6 (n=5)*	— 14.0 ± 21.8 (n=5)*
	37.3 ± 41.5(n=5)	—	— 12.5 ± 21.7 (n=4)	— 1.0 ± 3.6 (n=5)	0	+ 3.2 ± 5.5 (n=4)	— 5.7 ± 6.4 (n=4)
NOSIE	20.2 ± 22.0(n=5)	+	+ 4.0 ± 3.2 (n=5)*	— 23.0 ± 17.1(n=5)	+ 13.7 ± 8.9 (n=3)	— 5.5 ± 5.3 (n=4)	— 11.8±16.0 (n=4)
	49.0 ± 32.0(n=5)	—	— 21.2 ± 16.6 (n=5)	— 2.4 ± 2.9 (n=5)	+ 8.8 ± 10.2 (n=6)	— 9.0 ± 10.9 (n=4)	+ 18.2 ± 8.3 (n=5)
A.U.C. (cm ² under UV 280 trace)	28.8 ± 19.0(n=5)	+	— 10.6 ± 10.9 (n=5)	— 7.9 ± 7.2 (n=4)	— 2.6 ± 13.8 (n=5) *	+ 12.8 ± 34.4 (n=5)*	+ 8.6 ± 25.5 (n=5)*
	31.8 ± 18.5(n=5)	—	— 16.4 ± 24.9 (n=5)	— 2.2 ± 4.9 (n=5)	+ 18.9 ± 19.6 (n=5)	+ 67.0 ± 32.7 (n=3)	+ 47.7 ± 22.0 (n=3)
Micromoles 600-700 ml G25 peak	24.1 ± 13.6(n=5)	+	— 5.7 ± 6.9 (n=4)	+ 0.4 ± 18.0 (n=4)	— 14.6 ± 13.0 (n=5) *	— 18.7 ± 25.7 (n=5) **	— 49.4 ± 49.0 (n=5)*
	55.1 ± 51.0(n=5)	—	— 26.5 ± 54.0 (n=5)	— 0.6 ± 11.0 (n=5)	+ 9.1 ± 19.0 (n=5)	— 4.6 ± 9.6 (n=3)	+ 2.3 ± 2.4 (n=3)

Week 8-16 patient B-5 is known for severe breaks in *diet (beer)*. Therefore not *included* week 8-16.

* Statistically significant at the $p < 0.05$ level, two tailed using Wilcoxon ranking test.

** Statistically significant at the $p < 0.01$ level, two tailed using Wilcoxon ranking test.

For the schizophrenia subscale and period 0-56 weeks Wobs, (df = 7), = 0, $p < 0.01$ and for the period 0-28 weeks Wobs (df = 7) = 0, $p < 0.01$ (Wilcoxon). Using the usual t-test period 0-56 weeks, tobs= 1.45, n = 7,ns. For the period 28-56 weeks tobs = 2.16, df = 7, $p < 0.05$ directional. CPRS week 28-56, tobs = 2.68, f = 7, $p < 0.05$ now directional. NOSIE period 0.56, tobs = 5.6, df = 6, $p < 0.01$.

Table 3
Percent Change ± S.E.M. for the Critical Monitoring Systems

System	X±SD	Diet	Week 0 - 8	Week 8 -16	Week 16 - 28	Week 28 - 56
	Initial Score					
C.P.R.S.SZ	17.6 ± 4.1(n=5)	+	— 29.2± 6.7 (n=5)	+ 10.4 ± 8.9 (n=3)	+ 28.3 ±10.0 (n=3)**	— 39.3 ±13.1(n=4)**
Sub scale	22.3 ±12.5(n=)	—	— 9.4± 9.7 (n=3)	— 10.3 ±14.9 (n=5)	— 24.2 ±12.9 (n=5)	+ 109.5 ±17.2 (n=4)
W.I.S.T.	20.6 ± 8.6(n=5)	+	— 33.2± 2.1(n=5)	— 7.0 ± 4.9 (n=4)	0	— 2.5 ± 5.6 (n=5) *
	37.3 ± 41.5(n=5)	—	— 16.5± 5.7 (n=4)	— 1.0 ± 6.7 (n=5)	0	+ 16.1 ± 8.4 (n=5)
NOSIE	20.2 ± 22.0(n=5)	+	+ 42.4± 8.8 (n=5)*	— 4.8 ± 6.9 (n=5)	+ 129.3 ±14.0 (n=4)	+ 11.9 ± 9.1(n=5)
	49.0 ±32.0(n=5)	—	— 37.6± 4.6 (n=5)	— 8.5 ± 3.3 (n=5)	+ 39.6 ±99.0 (n=6)	+ 25.9 ±10.2 (n=4)

* p < 0.05

** p < 0.01 Using Wilcoxon's paired ranking.

Note the increase in NOSIE 30 scores for week 0-8. The percent change for each interval for each patient has been calculated from the start score for each interval. Using T-test and the probably most relevant, schizophrenia subscale: Period 8-16 weeks, t = 2.15, (df = 7), p < 0.10 nondirectional and < 0.05 directional. For the period 16-28 weeks, t = 5.97, (df = 7) and p < 0.01 nondirectional. For the period 28-56 weeks t = 13.8, (df = 7), p < 0.001 nondirectional. For WIST from week 28-56, t = 4.13 (df = 7), p < 0.01.

Table 4
Median Elisa Values (OD at 405 nm) for Serum Activity to Different IgA and IgG Levels Against Food Proteins
in 10 Schizophrenic Patients Before Start of a Gluten-Free Diet

A	Type	Glyc-gliadin		Gluten		Lactalbumin		Lactoglobulin		Casein		Ovalbumin	
		IgG	IgA	IgG	IgA	IgG	IgA	IgG	IgA	IgG	IgA	IgG	IgA
A-1	1	0.25	0.18	0.28	0.32	0.42	0.15	0.77	0.14	1.24	<u>1.57</u>	0.85	0.23
A-2	2	0.14	0.19	0.16	0.29	0.00	0.06	0.21	0.07	0.03	0.27	0.19	0.12
A-3	1	0.05	0.05	0.08	0.16	0.02	0.32	0.00	0.00	0.08	0.09	0.03	0.03
A-4	1	0.59	0.22	0.51	<u>0.44</u>	0.07	0.05	0.52	0.08	0.48	0.07	0.96	0.17
A-5	2	0.52	<u>0.62</u>	0.45	<u>0.62</u>	0.09	0.01	0.48	0.03	0.81	0.16	1.07	0.14
B-1	2	0.29	0.14	0.26	0.29	0.02	0.02	0.02	0.05	0.29	0.09	0.10	0.26
B-2	2	0.68	0.09	0.55	0.17	0.00	0.02	0.06	0.00	1.13	0.49	1.01	0.13
B-3	2	0.67	0.08	0.78	0.15	0.04	0.01	1.00	0.02	1.18	0.49	1.00	0.07
B-4	1?	0.58	0.21	0.54	0.33	0.02	0.01	0.97	0.03	1.10	0.55	0.91	0.04
B-5	1	0.68	0.31	0.66	0.32	0.06	0.14	1.28	<u>1.57</u>	1.22	0.63	0.85	0.20
Drop. out 1		0.31	0.15	0.29	0.23	0.10	0.07	1.15	<u>0.83</u>	0.91	0.31	0.55	0.10
Upper normal limit		1.70	0.40	1.70	0.40	1.60	0.30	1.80	0.40	1.80	0.80	1.80	0.40

* Median average of 3 measurements, optical density units at 405 nm is given in the table. All units are in arbitrary OD units from Elisa assay of specific antibodies. Increased levels are underlined.