

UMEÅ UNIVERSITY MEDICAL DISSERTATIONS
New Series No. 940, ISSN 0346-6612, ISBN 91-7305-803-3

From Medicine and Family Medicine
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Umeå University, SE-901 85 Umeå, Sweden

Cobalamin Communication in Sweden 1990 – 2000

Views, knowledge and practice among Swedish physicians

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Umeå 2005
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ISBN *91-7305-803-3*
ISSN *0346-6612*

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Printed in Sweden by Landstingstryckeriet, Umeå, 2005

*To my granddaughter Emelie,
Who links the past and the present together.*

Abstract

Cobalamin (vitamin B12) is one of several essential micronutrients needed by the human organism. Other important micronutrients, which interplay with vitamin B12, are folate and iron. Deficiency of these micronutrients can lead to different types of disorders. During the last ten years, the attention has been drawn to different forms of neurological disorders supposed to be caused by vitamin B12 deficiency. Vitamin B12 deficiency states are common among elderly patients in primary health care and sometimes in hospital care, especially in geriatric practice.

This is a study to define the cobalamin treatment traditions, among Swedish physicians in the period 1990 – 2000. The period was distinguished by an intense debate on the issue by the physicians, an increase of cobalamin consumption, and a shift from parenteral therapy towards oral high-dose therapy.

For long, it had been known that symptoms of cobalamin deficiency could start in the nervous system. This old knowledge was reinforced by the application of homocysteine (Hcy) and methyl-malonic acid (MMA) in deficiency diagnosis. The introduction of homocysteine and MMA in deficiency diagnosis changed the view on deficiency prevalence, by identifying persons at risk to develop B12 deficiency prior to established symptoms.

In this study, Swedish physicians are regarded mainly as receivers of scientific communication about the markers homocysteine and MMA, and deficiency states of cobalamin and folate. The main senders were four teams of scientists, from North America, Norway, Denmark, and Sweden.

This study sets the senders and the receivers of cobalamin communication on a collegial level and quantifies and evaluates the feed-back from the receivers. The receivers in this case, general practitioners and geriatricians, appeared to be familiar with old knowledge and frontier concepts in the field. Thus, it is suggested that the increase of B12 prescriptions in Sweden 1990 – 2000 reflected an increased awareness of B12-associated clinical problems among the physicians managing the majority of deficiency patients, although a possible overconsumption of pharmaceutical drugs must be kept in mind.

Key words: Cobalamin, folate, iron, homocysteine, MMA, vitamin B12 deficiency, therapy tradition, drug epidemiology, communication, receivers, senders.

List of original papers

This dissertation consists of the following original papers:

I: M Nilsson, B Norberg, J Hultdin, H Sandström, G Westman, J Lökk. Medical intelligence in Sweden: Cobalamin – oral versus parenteral? Postgraduate Medical Journal 2004 (in press).

II: Lökk J, Nilsson M, Norberg B, Rudolphi O, Sandström H, Westman G. Controversies around vitamin B12 in Sweden. Attitudes and values behind clinical decision-making in primary health care 1996. Hematology 1997; 2:341-50.

III: Lökk J, Nilsson M, Norberg B, Hultdin J, Sandström H, Westman G. Shifts in B12 opinions in primary health care of Sweden. Scand J Public Health 2001; 29: 122 - 128.

IV: Lökk J, Nilsson M, Norberg B, Hultdin J, Sandström H, Westman G. Vitamin B12 in primary health care and geriatrics. Attitudes, knowledge, competence. Int J Ger Psych 2001; 17: 987 - 992.

V: Nilsson M, Lökk J, Norberg B, Hultdin J, Sandström H, Westman G. Sex differences in cobalamin (vitamin B12) opinions of Swedish physicians. Nord J Psychiatry 2002; 56(4): 299-303.

The papers will be referred to by their Roman numerals I-V.

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CONTENTS

1. INTRODUCTION	9
1.1 Preface	9
1.2 Background	9
1.2.1 Historical background	9
1.2.2 The function of iron, pyridoxine, folate and cobalamin	12
1.2.2.1 Iron	12
1.2.2.2 Pyridoxine (vitamin B6)	12
1.2.2.3 Vitamin B12 (cobalamin) and folate	13
1.2.2.4 Homocysteine (Hcy) and Methylmalonic Acid (MMA)	15
1.2.2.5 Senders of homocysteine/MMA messages	15
1.2.2.6 Statistics of Sweden	16
1.3 Aims of the dissertation	17
2. MATERIAL AND METHOD	17
2.1 Administrative organisation and tradition areas	17
2.2 Sales and prescriptions of cobalamin	19
2.3 Calculations and basic assumptions for B12 consumption	20
2.4 Questionnaire studies	20
2.5 Statements probing cobalamin knowledge	21
2.6 Statements probing cobalamin communication	21
2.7 Ethical considerations	22
2.8 Statistical considerations	22

3. RESULTS AND SPECIFIC DISCUSSIONS	26
3.1 Cobalamin context in Sweden 1990 – 2000 (I)	26
3.2 Prescription pattern during 2000 (I)	27
3.3 Statements probing knowledge (II – V)	28
3.4 Results of statements probing knowledge	28
3.4.1 Statement 3	28
3.4.2 Statement 4	28
3.4.3 Statement 5	29
3.4.4 Statement 6	29
3.4.5 Statement 7	30
3.4.6 Statement 11	30
3.4.7 Statement 14	31
3.4.8 Statement 15	31
3.4.9 Statement 16	32
3.4.10 Statement 17	33
3.4.11 Statement 18	33
3.4.12 Statement 19	34
3.4.13 Statement 20	34
4.3.14 Statement 21	34
3.4.15 Statement 22	35
3.4.16 Statement 23	36
3.4.17 Statement 24	36
3.5 Results of communication statements	36
3.5.1 Statement 1	37

3.5.2 Statement 2	37
3.5.3 Statement 8	38
3.5.4 Statement 9	38
3.5.5 Statement 10	38
3.5.6 Statement 12	39
3.5.7 Statement 13	40
4. GENERAL DISCUSSION	40
4. 1 Summary	45
5. ACKNOWLEDGEMENT	45
6. REFERENCES	46

1. Introduction

1.1 Preface

During the spring 1996, a group of medical scientist contacted me. This research group was asking me, if I, as a statistician, could help them to perform a questionnaire study among a sample of Swedish general practitioners (GPs). At that time, one of my work assignments was to serve as a statistical consultant in relation to different occupational and research groups in the County Council of Västerbotten.

My first task for the research group was to adjust statements and evaluation scales for future databases and analyses. At that time, during the spring 1996, my work was mainly to provide the research group with practical help; sending out and taking care of incoming questionnaires, checking addresses, keep record of incoming answers, sending out reminders, collecting data into a database and processing the data. Another of my tasks in the beginning was to provide the group with charts and diagrams, and do the statistical computations needed by the research group.

Since my contributions to the first study (II) exceeded the duties of my basal service, the state of co-author was offered to me. Thus, the follow-up studies 1998 provided more service and increasing responsibilities (III-IV); “good service is rewarded by more service.” In a stimulating multidisciplinary interplay with tutors, co-workers, and other scientists, the chance emerged to extend the primary questionnaire studies to a dissertation on cobalamin communication (I – V). No such study has previously been performed; however, a few rudimentary investigations (Lederle 1991 & 1998) and a few letters (Berlin 1968, 1978, Herbert 1996, 1998, Elia 1998) were previously published.

Besides my professional involvement, the topic gained a personal interest, when my mother had a vitamin B12 deficiency diagnose in 1999 and was prescribed treatment with hydroxycobalamin injections. Later on, she switched to oral cyanocobalamin treatment. At the start of symptoms, my mother was close to 70 years of age, a typical age of deficiency debut (Sandström 1996, Björkegren 2003).

1.2 Background

1.2.1 Historical background

Vitamin B12 (cobalamin) is one of several essential micronutrients needed by the human organism. Folate, iron and possibly vitamin B6 (pyridoxine) are important even nowadays in Western countries as well as in the rest of the world. Deficiency of these micronutritients can lead to different types of disorders. During the last ten years, the attention has been drawn to different forms of neurological disorders, supposed to be caused by vitamin B12 deficiency (Hoffbrand 1996, Asselt et al 2001).

Vitamin B12 deficiency states are common among patients in primary health care and sometimes in hospital care, especially in geriatric practice. In studies among elderly people, 10 to 20 percent of the investigated population was found to have vitamin B12 deficiency (Björkegren

2003, Johnson et al 2003). Anaemia is the classical sign of deficiency of the micronutrients, macrocytic anaemia for lack of cobalamin and/or folate with mean corpuscular volume (MCV) above 100 fL, microcytic anaemia for lack of iron, MCV less than 78 fL. The prevalence of deficiency disorders differs widely, especially when Western countries are compared with developing countries (Bevan 2004).

In a historical light (Wintrobe 1993, Engstedt 1998), the function of the blood has been a secret until the last 200 - 300 years. The knowledge about the blood as a necessity for life is ancient. In many religions, the blood has played an important role; for example, the kosher slaughter in Jewry and the atonement by blood sacrifice in Jewry and Christianity (Lev 17, Matt 26:17-30). When the clotted blood is examined in a glass vessel, it is possible for the naked eye to recognise different layers. The ancient doctrine of “cardinal humors” (black bile, sanguis, phlegma and yellow bile) is thought to be derived from observations on such blood layers (Wintrobe 1993).

In the year 1674, Anton van Leeuwenhoek from Holland made a description of the red blood corpuscles (red cells, erythrocytes). This was done in the work “Philosophical Transactions of the Royal Society” in London. Leeuwenhoek constructed a microscope and used it to study his own blood. In the following two centuries, routines developed to determine the number (erythrocyte particle concentration, EPC), volume (haematocrit, erythrocyte volume fraction; EVF) and haemoglobin contents (B-Hb) of the blood; especially the haematocrit value had a good reputation for periods (Wintrobe 1993, Engstedt 1998).

Among the blood diseases, the first that was treated in an effective way was chlorosis (from the Greek word for green, *χλωρός*), which originated from deficiency of iron. Johannes Lange first described the disease in 1554. During the last decades of the 1900th century, this anaemia occurred mainly among girls, 14 - 17 years of age. The incidence of chlorosis declined, and after 1910, the cases were rare (Lee 1993a).

Thomas Addison (1855) first described the blood disease anaemia perniciosa. The pernicious anaemia was a mystery for the physicians up to 1920. This anaemia, a result of the bone marrow failure to produce sufficient numbers of red blood cells, is due to a lack of vitamin B12. The disease leads in most cases to death within a limited time, often 1 – 2 years. Sometimes, the victims of the disease also had neurological and mental symptoms (Lee 1993b, Wintrobe 1993). Nowadays, it is known that a patient with advanced anaemia perniciosa often suffers lack of leukocytes (leukopenia), thrombocytes (thrombocytopenia), mucosal cells, other fast-growing cells, and lesions in the myelin sheaths of nerve cells (Reilly & Cawley, 1996).

In the year 1900, Karl Landsteiner from Austria, discovered the ABO blood group system. Landsteiner described the serologic differences between red cells from different persons, and was then able to classify individuals in four groups according to blood type (Schroeder & Rayner 1993a). This opened the opportunity to treat the anaemia with blood transfusions. On some occasions, the treatments led to a remission, probably due to micronutrients in the transfusion (Schroeder & Rayner 1993b, Engstedt 1998).

George Whipple discovered another treatment for anaemia perniciosa in 1918. He found that dogs with experimental anaemia recovered faster on a liver diet than dogs on other diets. Due to these findings, two other Boston doctors, William Murphy and George Minot, started to treat an anaemia patient with 200 – 300 grams raw liver on a daily basis, with a remission of the anaemia as a result. Later liver extracts for oral and parenteral treatment were developed. The

initial documentation was made possible by the development of the reticulocyte count. The Nobel Prize of medicine 1934 was given to Whipple, Minot and Murphy for their discovery (Lee 1993a, Engstedt 1998).

The importance of folate deficiency was discovered 1931 by Lucy Wills and co-workers. Folates were extracted 1941 from spinach and from liver in 1943 (Lee 1993 b). Furthermore, vitamin B12 was isolated and the structure clarified by the British biochemist Dorothy Crowfoot Hodgkin 1955, published 1956 (Hodgkin 1956), a discovery awarded with the Noble Prize in chemistry 1964. Professor Gunnar Hägg, Member of the Royal Academy of Sciences said in his presentation speech: *"Professor Hodgkin. You have for many years directed your efforts towards the determination of crystal structures by means of X-ray diffraction techniques. You have solved a large number of structural problems, the majority of great importance in biochemistry and medicine, but there are two landmarks, which stand out. The first is the determination of the structure of penicillin, which has been described as a magnificent start to a new era of crystallography. The second, the determination of the structure of vitamin B12, has been considered the crowning triumph of X-ray crystallographic analysis, both in respect of the chemical and biological importance of the results and the vast complexity of the structure"* (Hägg, 1972).

Clinical routine lingered behind the scientific discoveries for years and decades. Liver therapy had first been oral, then parenteral. Since liver preparations also contained folate and iron, most concomitant deficiencies were also cured (Lee 1993 b). The first clinical trial with oral cyanocobalamin, 1 mg daily, was published in 1960 (McIntyre 1960).

In the period 1950 - 1970, there was confusion about the route and mode of B12 therapy. Patients with pernicious anaemia in relapse were plenty, and provided a model for clinical trials. A single oral dose of 3 mg of B12 was given to five patients in a study 1950 (Ungley 1950). The patients were reported to have a maximal haematological response within the first 15 days of observation. Ungley continued with an extended study and presented results from 38 patients, treating them with oral vitamin B12, in doses ranging from 0.5 to 3 mg daily. The daily dose of 0.5 mg gave a positive response during 15 days. Single oral doses between 1 and 3 mg also gave positive haematological responses (Ross et al 1954).

In another study, a single oral dose of 5 mg vitamin B12 gave a complete remission (Conley 1951). In the same study, single oral doses of 1 or 2 mg gave rise to detectable but incomplete remissions. In this study, parenteral B12 for maintenance therapy was used. In a third centre, eleven patients with pernicious anaemia in relapse were treated with oral B12 dose in one to four weeks. The patients involved in the study were monitored for three to twenty-one months (Unglaub & Goldsmith 1955).

McIntyre and co-workers found that managing pernicious anaemia with 1 mg of oral cyanocobalamin daily was an optimal, safe and reliable regime (McIntyre 1960). About the same time, Ragnar Berlin and co-workers started to treat patients with pernicious anaemia with 0.5 or 1.0 mg of oral cyanocobalamin daily. The Berlin group found that 1 mg of oral cyanocobalamin daily was a safe and reliable treatment of B12 deficiency, both for remission and maintenance therapy. Lower doses, 0.5 mg daily, was associated with high incidence of therapy failure (Berlin 1968), in fact 50 – 80 percent failures as deemed from their Figure 8.

In clinical practice, however, the predominant treatment for vitamin B12 deficiency was parenteral during the period 1960 - 1970. In Sweden, as in the rest of the world (even today), there was a hesitation for oral treatment. As an amendment for the anxiety among Swedish physi-

cians, Berlin and co-workers recommended that a remission treatment could start with 2 mg of oral cyanocobalamin twice a day during one month (Berlin 1968).

With a single oral dose of 2 mg cobalamin, the absorbed quantity of B12 does not exceed the transport capacity of transcobalamin and haptocorrin from bowel to body tissues. As with parenteral therapy, the surplus oral cobalamin is spilled into the urine. As for safety, an oral dose of 100 mg was found to be non-toxic. In the range 2 – 100 mg, the pharmacokinetics of oral single doses of cyanocobalamin approached that of 1 mg parenteral cyanocobalamin. In 1978, the Berlin group verified that 1 mg of oral cyanocobalamin daily fills the body stores as effectively as intramuscular injections (Berlin 1978).

Since about 1970, oral treatment for vitamin B12 deficiency has gained the confidence of the Swedish physicians. The reason for this is probably complex. One influence might be the “7-crown reform”, (Shenkin 1973, Carder & Klingberg 1980). With the reform, it became financially neutral to choose between oral or parenteral treatment for vitamin B12 deficiency in Sweden. This neutrality was thought to concern all parts, patient, physician, producer and financer (the Swedish society). However, other scientists have also argued that oral treatment is more favourable for public finances than parenteral treatment in a Western society (Lederle 1991 & 1998, Walraven 2001, Nyholm 2003)

1.2.2 The function of iron, pyridoxine, folate and cobalamin

Iron, pyridoxine (vitamin B6), folate and cobalamin (vitamin B12) are micronutrients essential for the human body. The micronutrients provide main parts in monocarbon metabolism (e.g. the methionine cycle), in DNA synthesis, in cell growth, and in cell function. Anaemia and neuropathy are conspicuous correlates of advanced micronutrient deficiency (Bevan 2004, Macleod & Mumford 2004).

1.2.2.1 Iron

Iron is essential in the transportation of oxygen from lungs to body tissues. The body store of iron is mainly found in erythrocytes and muscle cells. Iron deficiency can arise from lack of iron from foods (food with highest content of iron is given in Table 1). Other causes of iron deficiency are chronic gastritis, lack of hydrochloric acid, celiac disease, ulcers and cancers in stomach and bowel. Excess of iron can lead to tissue damage and fibrosis caused by, for example, repeated blood transfusions and hereditary haemochromatosis (Lee 1993a, Pippard 1996).

In the present dissertation, two statements of the questionnaire studies address the role of iron deficiency as a confounder in the diagnosis and treatment of cobalamin deficiency (see Tables 2, statements 15 and 16).

1.2.2.2 Pyridoxine (vitamin B6)

Although vitamin B6, the therapy form pyridoxine, is an important coenzyme for many reactions in the human body, deficiency states are thought to be rare in Western countries, and fall outside the scope of routine health care in Sweden (Lee 1993b, Rosenberg et al 2004). There is,

though, an ongoing discussion about vitamin B6 and its influence on dementia (Jansson 2002, Seshadri 2002, García & Zanibbi 2004, and Rosenberg et al 2004).

The recommended daily intake of vitamin B6 is 1 to 3 mg/day. Since many foodstuffs in Sweden today are rich in vitamin B6, or even enriched with vitamin B6 (Table 1), the danger of deficiency appears negligible for most citizens. Overdoses may produce neurological disorders. The toxicity of vitamin B6 can partly be avoided by simultaneous supplementation with folate and vitamin B12, which are supposed to compensate for the leakage of methyl groups from the system (Lee 1996b, Hultdin 2003). Vitamin B6 is, in any case, outside the scope of the present dissertation.

1.2.2.3 Vitamin B12 (cobalamin) and folate

Folate and vitamin B12 (cobalamin) are connected by a series linkage in the human metabolism. The classical symptom of folate and/or B12 deficiency is macrocytic anaemia, which is due to an inhibition of the DNA synthesis in the bone marrow. The deficiency is due to lack of vitamin B12 and/or folate. Vitamin B12 deficiency also causes neuropathy, which can be severe (Hoffbrand 1996, Asselt et al 2001).

In the 1970'ies, the analysis of serum B12 became routine in Sweden. The oral cyanocobalamin treatment and new laboratory techniques had a medical and social impact. Diagnosis and adequate treatment came earlier in the course of deficiency. Patients with pernicious anaemia are rare in a Western society today (Norberg & Palmblad 1998). In the Kuzminski study of oral versus parenteral treatment, only two out of thirty-nine patients had overt anaemia (Kuzminski et al 1998).

A further development in the early diagnosis of deficiency occurred during the 1990'ies, when new markers such as homocysteine (Hcy), methylmalonic acid (MMA), gastrin and pepsinogen A, were introduced. The laboratory parameters of vitamin levels in the intravascular compartment could miss deficiency in the cells (Hoffman 1996, Nilsson 2000).

Vitamin B12 is considered to be Nature's most beautiful cofactor (Stubbe 1994). It was isolated 1948 by Smith, Rickes and co-workers. Hodgkin and co-workers made a description of the molecular structure 1955 (Hodgkin et al. 1956). The vitamin consists of a central cobalt atom, surrounded by corrin rings with a side chain of bezimidazole. To the cobalt atom, there is a linkage to different radicals (Hodgkin 1964). Variants of cobalamin are formed due to replacement oxidation or reduction of the cobalt nucleus, for example; methylcobalamin, hydroxycobalamin, adenosylcobalamin and cyanocobalamin (Nilsson 2000). The human body is unable to synthesise cobalamin and the contribution of vitamin B12 is mainly from animal proteins (Hoffbrand 1996).

As a matter of curiosity, the articles of food with the highest content of micronutrient per 100 g are listed in Table 1. It is conceivable that some of these foods may be found as ingredients in prefabricated food e.g. meatballs and hamburgers.

Table 1. The five foodstuffs with the highest content of essential micronutrients.

	1	2	3	4	5
Iron	Pig blood	Cattle blood	Blood bread	Special K	Black pudding
B6	Special K	Oatmeal gruel	Dry yeast	Wheat-germ	All bran regular
Folate	Fried chicken liver	Yeast	Chicken liver	Black eye beans	Mung beans
B12	Fried cattle liver	Fried cattle liver coated	Cattle liver	Rein-deer liver	Lamb liver

Source: Swedish National Food Administration.

The daily requirement of vitamin B12 is 1 - 3 µg/day for adults (Hoffbrand 1996). For children to the age up to 10 years, the recommendation is in the interval 0.3 - 1.4 µg/day according to Swedish National Food Administration (www.slv.se). Beside the food listed in Table 1, good sources of folate and vitamin B12 are milk and dairy products. Arkbåge found that fermentation of milk, during manufacturing of six fermented dairy products and storage for 14 days in +4°C, reduced vitamin B12 content by 40 to 60 percent, while the folate content increased. On the other hand, when making hard cheese, the vitamin B12 content increased by a factor 4 - 7 (Arkbåge 2003).

For vitamin B12 to be useful for the organism, it has to be released from the food proteins with the help of hydrochloric acid and peptic hydrolysis in the stomach. In the acid environment of the normal stomach, the released B12 binds to haptocorrin. In the alkaloidal environment of the duodenum, cobalamin binds to intrinsic factor (IF). Lack of this factor, especially among elderly, provides a major cause of vitamin B12 deficiency. The B12-IF complex is bound to receptors of the epithelial cells in the distal part of ileum, transported across the bowel wall, and bound to transcobalamin (25 percent) and haptocorrin (75 percent) in blood: transcobalamin is the active transport protein with fast kinetics (Lee 1996b, Schneede 1996, Hultdin 1998).

It should be emphasised that the nomenclature has changed with time. Transcobalamin was formerly called “transcobalamin II”, haptocorrin was called “transcobalamin I” and/or transcobalamin III, or “R binders” (Gueant 1990). The receptor for the B12-IF complex on the luminal side of the epithelial cells in the distal part of the ileum is defined, and has the name “cubilin” (Andrés et al 2003).

Lack of IF is usually due to atrophic gastritis, sometimes to gastric surgery. The down-stream transport of vitamin B12 may also be disturbed by pancreatic insufficiency, celiac disease, cubilin deficiency due to inborn genetic defects or surgery, genetic defects of B12-binding proteins in the blood. Vitamin B12 may be inactivated by nitrous oxide (“laughing gas”) in surgery, dentistry, or abuse. The main symptoms of cobalamin/folate deficiency include anaemia, polyneuropathy and mental disturbances (Schneede 1996, Engstedt et al 1998, Lökk 2002).

The Norwegian Erik Magnus showed 1986 that approximately one third of all patients with B12 deficiency had neurological symptoms at the start (Magnus 1986). The Magnus study was confirmed by Lindenbaum and co-workers (Lindenbaum 1988 et al), who studied 141 patients with a vitamin B12 deficiency. Among these, 40 did not show a traditional anaemia perniciosa

or macrocytic anaemia. These 40 patients instead showed symptoms such as dementia, cognitive symptoms, ataxia, and other neuro-psychiatric disorders. After treatment with vitamin B12 alone, the levels of MMA and homocysteine were drastically reduced: the health of the patients also improved.

1.2.2.4 Homocysteine (Hcy) and Methylmalonic Acid (MMA)

The correlation between homocystinuria, a rare inborn error of metabolism, hyperhomocysteinemia and thrombosis was known from the 1950's. The patients often have a plasma homocysteine at the level of 350 mmol/L or more (Hankey & Eikelboom 1999, Nygård et al 1999). Cox and White (1962) appears to have been the first to suggest that homocysteine might be used in the diagnosis of cobalamin/folate deficiency, in which homocysteine values usually range between 20-100 mmol/L (Cox & White 1962). The American group of scientists around Lindenbaum, Allen and Stabler documented homocysteine and MMA for deficiency diagnosis (Lindenbaum et al 1988, 1990).

For long, it had been known that symptoms of cobalamin deficiency could start in the nervous system (Videbaek 1961, Magnus 1986). This old knowledge was reinforced by the application of homocysteine and MMA analysis in deficiency diagnosis (Lindenbaum 1988). During the 1980's, homocysteine analysis became available for the leading clinical researchers of Sweden (Brattström 1988, Regland 1991). The introduction of homocysteine and MMA in deficiency diagnosis changed the view on deficiency prevalence. The Skutskär study suggests that every second citizen suffers from cobalamin/folate deficiency during some period of her/his last ten years of life (Björkegren 2003).

1.2.2.5 Senders of homocysteine/MMA messages

During the period 1990 – 2000, Swedish physicians are regarded mainly as receivers of messages about homocysteine, MMA, and deficiency states of cobalamin and folate. The main senders of messages were four teams of scientists, the American group around John Lindenbaum, Robert Allen and Sally Stabler (Stabler et. al, 1986, 1988, 1996, Lindenbaum 1988, 1990), the Norwegian group around Per Magne Ueland, Helga Refsum and Jörn Schneede (Refsum et. al 1989, Ueland & Refsum 1989, Schneede 1996), the Danish group around Karsten Rasmussen, Ebba Nexö, and Jan Möller (Nexö et al 1994, Rasmussen et al 1990) and the Swedish Brattström group (Brattström 1988).

The clinical chemists of Sweden were gradually convinced that homocysteine and MMA contributed to early diagnosis and treatment of cobalamin/folate deficiency. For personal and logistic reasons, the revivalism for new markers grew with varying velocity in different parts of the country (Table 2). Not all parts of Sweden had access to homocysteine and MMA analysis in the clinical routine of their own county council in 2000, the end of the period of the present studies.

Table 2. The spreading of homocysteine (Hcy) and methylmalonic acid (MMA) from basic clinical research on homocystinuria to clinical routine for the diagnosis of cobalamin/folate deficiency was slow, as illustrated by method development in the leading laboratories of university hospitals in Sweden.

<i>University hospital</i>	<i>Hcy (year)</i>	<i>MMA (year)</i>
Lund	1986 ^a , 1992	1997
Gothenburg	1988 ^a , 1990 ^b	1995
Linköping	1990 ^a , 1998 ^c	1994
Umeå	1993 ^b	-

^a Amino acid analysis

^b HPLC (high pressure liquid chromatography)

^c IMX

Basic data, courtesy of the staff in charge of laboratory service at the sites mentioned.

Simultaneously with the discussions of the clinical chemists, the clinicians of Sweden also reviewed old traditions and new methods. A major debate took place in the Journal of the Swedish Medical Association (Läkartidningen) in 1992, Table 3.

Table 3. Contribution to the Swedish vitamin B12 debate in the Journal of Swedish Medical Association (Läkartidningen, LT) 1992.

Brattstöm L et al. LT 1992;89(7): 467 - 9
Mååge L, et al. LT 1992;89(12): 984 – 6
Nilsson-Ehle H, et al LT 1992; 89(17):1453 - 4
Borch K. LT 1992; 89(17):1459
Nordén et al LT 1992; 89(21):1870 – 3
Norberg et al LT 1992; 89(22): 2011 – 2
Lindstedt et al LT 1992; 89(23): 2083 – 4
Regland B, Gottfries C-G. LT 1992; 89(25): 2736 - 7
Gräsbäck R et al LT 1992; 89(41): 3377 - 80

The controversy was mainly a battle between senders who expressed their different views. Nobody appeared to be interested in the impact on the receivers. What ideas did the receivers accept? What ideas did the receivers reject? The questionnaire studies of the present dissertation addressed the general practitioners and geriatricians (II-V). During the work, it became evident to us that the Swedish tradition of oral high-dose cobalamin is unique in the world. Furthermore, the consumption of cobalamin appeared to be high in Sweden, at least compared with other Scandinavian countries. Thus, it was hypothesised that the prescription pattern of cobalamin by Swedish physicians might reflect their evaluation of the messages received during the period 1990 – 2000.

1.2.2.6 Statistics of Sweden

The population statistics and the official databases of Sweden provide unique sources of information. Their values in the surveillance of health and drug safety are widely recognised by the pioneer works of Westerholm and co-workers (Böttiger & Westerholm, 1971, 1973a, Böttiger, Boman, Eklund & Westerholm 1980). In the present dissertation, such statistics defined the context of cobalamin communication among general practitioners and geriatricians during the period 1990-2000 (I).

The early computerising of the health care, and the personal code number, made statistical matching possible. This kind of scouting, “Medical intelligence”, had practical impact on clinical practice. However, it is crucial to pay attention on some pitfalls. When pooling different databases together, it is essential to make sure that the variables are collected on the same scales of measurement, and that the definition of the variables are the same in different databases (Sjöholm 1980, Nilsson & Eklöf 1983, Cassel 1985, Svensson 1993).

1.3 Aims of the dissertation

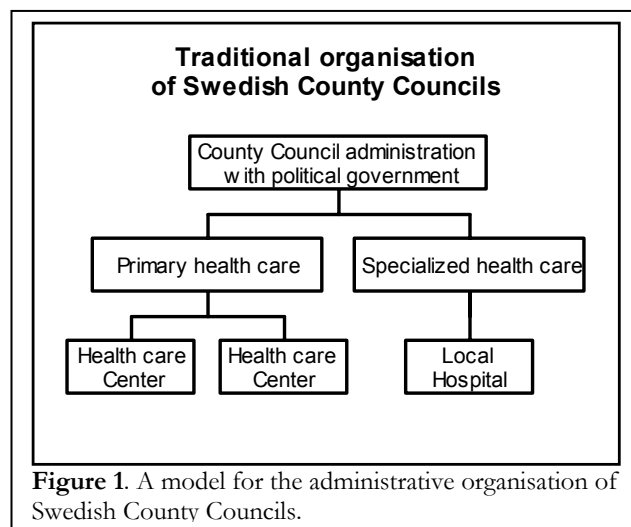
The aim of the present dissertation is to describe B12-associated views, knowledge and practice of Swedish physicians during the period 1990 – 2000. The material reflecting the physician practice was provided by sale/prescription statistics (paper I) for the period 1990 – 2000.

Views and knowledge were probed by two questionnaire studies 1996 and 1998 (paper II – V). The studied physician groups were general practitioners (GP’s), who made 95 percent of the prescriptions, and geriatricians, who provide a group of hospital physicians with wide experience of B12-associated problems.

2. Material and method

2.1 Administrative organisation and tradition areas

The county councils in Sweden are responsible for the health care of their residents. This organisation traces back to 1862, and was subject to formal legislation in 1928. In the period 1990 – 2000, there were 21 county councils, organised in six regions for expensive health care and education. Figure 1 gives an example of a structural model for the general organisation of the Swedish county councils. The regions are organized in an analogous structure.



The county councils are led by elected politicians and staffed with employed administrators. The financing of the county councils are from taxes (70 – 80 percent) and the rest from government transfers and patient charges (SoS report 1993:3).

The county council organisation has regularly been subject to criticism for rigidity and top-down management by business intelligence (Hamilton 1992, p 64):

*“People do not make great efforts: they fulfil only the technical function they are given, not taking into consideration whether it has a positive or negative effect on other functions or on their own activity.
 Flexibility is hampered or even non-existent. This applies to the functioning and qualities of the people working within the organisation as well as to the adoption of new techniques or the modification of old ones.
 Inter-relations between people inside the organisation are limited or non-existing.
 Information flow is primarily in one direction and is very slow to result in actions.
 Prestige and formal position disguise the performance of individuals as well as the organisation.
 Possibility of using social intelligence is limited although information sources exist within the organisation”.*

In contrast to the hierarchical administrative organisation, Hamilton gives the following idealized model for an autonomous network, Figure 2.

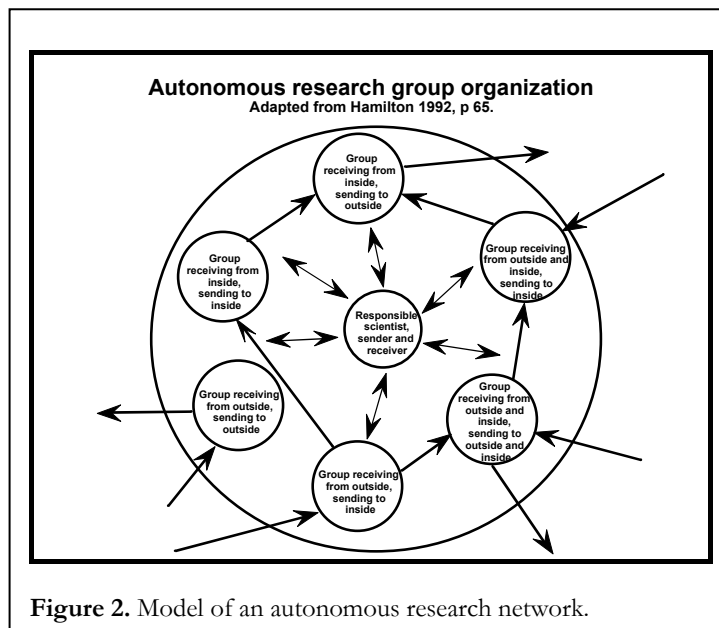


Figure 2. Model of an autonomous research network.

The size of each group is flexible, and the members chosen from their ability to perform their task (Hamilton 1992, p 66):

“Energy output per individual increases substantially through personal satisfaction and responsibility.

Management gains time to manage, i.e. to see to it that people function at their best and the organisation develops and uses its resources in the best possible way.

Flexibility is substantially increased.

Information flows auto-

matically in both directions.

Part of the knowledge and information available in the organisation is integrated in the Business Intelligence System in an efficient way.

Risk of self-deception, fraudulent behaviour, and secrecy negligence decreases”.

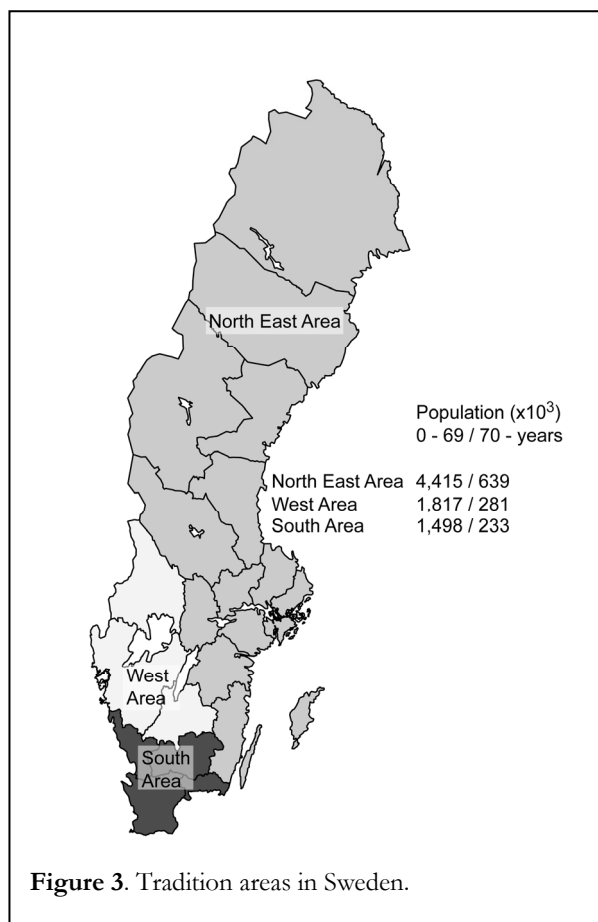
It should be emphasised that every loser has a reason to explain his fiasco and every winner has a need to explain his success. The Hamilton model does not exclude some constructive cooperation in the administrative system and some pitfalls of informal networks. Nor does the Hamilton model take into account such factors as “time” and “chance”, as formulated by an old cynic (Eccl. 9:11): *“The race is not to the swift or the battle to the strong, nor does food come to the wise or wealth to the brilliant or favour to the learned; but time and chance happen to them all.”*

In modern societies, there is an affluence of data. This huge amount of data does not automatically create information and knowledge, useful for planners and researchers, when needed. There are many facts, which are public and available, but can be difficult to collect in a way that gives a better understanding for the development of the society in general (Andersson 1984).

Stevan Dedijer was one of the first to realize the changes in the growing official statistic production in the beginning of the 1960'ies. He meant, that with the growing official statistic production and publication, "spying is dying" (Carlsson 1992, Piganiol 1992, Dedijer 2004). The

fact-finding, explained in terms of scouting, military intelligence, security intelligence, business intelligence or social intelligence was a tool for information gathering and perhaps new knowledge. In the same time period, Westerholm and co-workers reported the usefulness the databases of health care in e.g. the surveillance of drug safety (Böttiger & Westerholm 1971, 1973a); in analogy with social intelligence in general, the data mining in official health records could be called "medical intelligence".

In contrast to the county councils of Sweden, informal areas of slightly different medical traditions have emerged due to the history of the health care of the country; these tradition areas have been described in at least one previous report (Norberg 2001). The starting point of the tradition areas was the University hospitals of Uppsala-Stockholm, Lund-Malmö, and Gothenburg (Figure 3). It is reasonable to assume that similar tradition areas can be found in other countries as well.



2.2 Sales and prescriptions of cobalamin

The sales statistics of cobalamin originated from Swedish Pharmaceutical Data (Läke-medelsstatistik AB, Stockholm, Sweden) and Apoteket AB, (Stockholm, Sweden, the Swedish national supplier of drugs) throughout the period 1990 – 2000. The sales statistics covers prescriptions from the primary health care. The B12 prescription in hospital care and sales over the counter (without prescription) was negligible (2 – 3 percent). The population figures are from Statistics Sweden (www.scb.se).

2.3 Calculations and basic assumptions for B12 consumption

The calculation of the consumption of vitamin B12 uses the assumptions made by Apoteket AB for their national statistics. Thus, for injections 1 mg of vitamin B12 as hydroxycobalamin (approximately 80% of the market) or cyanocobalamin is assumed to correspond to 50 defined daily doses (DDD) of parenteral therapy. For tablets (cyanocobalamin), the DDD of oral high-dose vitamin B12 is assumed to correspond to 1 mg (one tablet, brands Behepan, approximately 80% of the market, and Betolvex). One patient year is the number of DDD's (tablets and injections) divided by 360. These approximations apply in paper I. It should be emphasised that the measure of cobalamin consumption in previous studies (II-V) were based on other assumptions and sale profits. The conversion to patient years and official assumptions makes present cobalamin figures comparable over time (I).

2.4 Questionnaire studies

The data for papers II – V originates from two inquiries accomplished 1996 and 1998. The questionnaires comprised 24 statements inquiring knowledge and communication on vitamin B12 deficiency. From the two inquiries, studies were made concerning the time course (i.e. differences between GPs 1996 – 1998), primary health care versus hospital care (as reflected among GPs and geriatricians, 1998), and finally influence of gender.

The questionnaires consisted of two types of statements, one questioning mainly knowledge of the responder, one probing primarily cobalamin communication within the health care and the society of Sweden. We tried to elucidate the stability of opinions, the acceptance of new knowledge, the interaction between senders and receivers in cobalamin communication in Sweden during the period 1990 – 2000. The questionnaires also contained some basic questions about the responder (age, sex duration of formal competence for up to three medical specialities).

In the 24 statements questionnaire, the respondent was asked to mark her/his personal position on an 11 grade visio-analogue scale ranging from 0="I reject it entirely" to 10="I agree completely". In constructing the scale, position 5 is in the middle to serve as a "neutral" answer. If the respondent had to think more than 10 seconds, the instruction was to leave the statement without evaluation. This was done with the purpose to get the respondents immediate view/knowledge on the statement.

There were two ways to handle the internal missing values. In the tables (paper II-V), they are referred as missing values, while in statistical tests they were handled as "neutral" in position 5 of the scale. The rationale was that the position "five" on the scale was a "no decision" equivalent with decline to answer.

In 1996 (paper II), 506 general practitioners were randomly sampled from the whole Swedish register then comprising of 4,554 GPs. Swedish Pharmaceutical Data (Läkemedelsstatistik AB, Stockholm, Sweden) provided the stratified and randomised sample with addresses.

In the 1998 study all of the GPs that had been questioned in 1996 were excluded from the sample base. The population base was then 4,030 GPs. A random sample of 499 GPs was drawn from the database (paper III). Combined with the sample of 499 GPs there was a total investigation among the 629 doctors working in geriatrics.

2.5 Statements probing cobalamin knowledge

Table 4 lists the statements questioning the knowledge of vitamin B12 deficiency:

Table 4: Statements probing knowledge concerning vitamin B12 deficiency, analysis, and treatment.

Statement number in Questionnaire / Statement text

3	“Women in fertile age are a risk group for vitamin B12 deficiency!”
4	“Vegans are a risk group for vitamin B12 deficiency!”
5	“Anorectics are a risk group for vitamin B12 deficiency!”
6	“Persons above 70 years of age are a risk group for vitamin B12 deficiency!”
7	“In alcoholics, serum cobalamin is often normal despite a functional vitamin B12 deficiency!”
11	“Homocysteine in serum or plasma replaces entirely serum cobalamin and serum folate in the first laboratory screening of a suspected case of malnutrition or malabsorption!”
14	“Serum gastrin, fasting value, is cheaper and more easy to interpret than the Schilling test in cases of suspected vitamin B12 malabsorption!”
15	“Simultaneous deficiency of iron and deficiency of vitamin B12 may produce anaemia with normal MCV (mean corpuscular volume)!”
16	“Treatment with vitamin B12 may turn a macrocytic anaemia into a microcytic anaemia!”
17	“It is an error of the art to treat a macrocytic anaemia with folate only!”
18	“Functional vitamin B12 deficiency in cells and tissues may occur despite normal or high blood haemoglobin!”
19	“Functional vitamin B12 deficiency may occur despite normal or high serum cobalamin”
20	“There is no reason to substitute patients with atrophic gastritis with vitamin B12!”
21	“As a precaution, I prescribe vitamin B12 to all my patients with atrophic gastritis!”
22	“There is no reason to substitute patients with vitamin B12 after gastric surgery!”
23	“As a precaution I prescribe vitamin B12 to all patients with gastric resections!”
24	“It is still acceptable to treat a patient with obscure neuropathy with vitamin B12 during 6-36 months and evaluate treatment efficiency by clinical parameters (e.g. performance, walking distance, reappearance of vibration sense or reflexes, reduction of sensory loss, reduction of hair loss, reduction of muscular pain)!”

2.6 Statements probing cobalamin communication

Table 5 lists the statements probing communication of vitamin B12 deficiency:

Table 5: Statements of communication about vitamin B12 deficiency, analysis, and treatment.

Statement number in Questionnaire / Statement text

1	“Anamnesis and physical examination are essential in investigating and treating a case of suspected vitamin B12 deficiency!”
2	“Vitamin B12 deficiency is nowadays entirely a laboratory diagnosis!”
8	“A competent clinician does not need many laboratory tests to find his cases of vitamin B12 deficiency. Every fifth patient investigated for suspected vitamin B12 deficiency has, in fact, vitamin B12 deficiency!”
9	“Serum cobalamin and serum folate are valuable but, unfortunately, capricious markers for

many different sorts of malnutrition and malabsorption. It is acceptable that only every 10 th investigation demonstrates deficiency of vitamin B12!"
10 "Serum cobalamin and serum folate are valuable but, unfortunately, capricious markers for many different sorts of malnutrition and malabsorption. It is acceptable that only every 20 th investigation demonstrates deficiency of vitamin B12!"
12 "A meticulous clinician cannot do without serum methyl malonate when investigating a case of suspected vitamin B12 deficiency!"
13 "The clinical significance of the modern markers homocysteine and methyl malonate in cases of suspected vitamin B12 deficiency is overrated!"

2.7 Ethical considerations

The answers of the questionnaires were not possible to trace back to the sender. This ensured the anonymity of the respondent. The strategy had at least one drawback: it was not possible to update missing social information as gender, age and number of specialities. However, we felt that the advantage with this procedure was valued among the respondents. The respondent had the possibility to add her/his name on the questionnaire. About 90 percent of the respondents did fill in their name and addresses.

The prescription data was on individual basis. The data were unidentified, and classified into age groups and gender. Therefore, no unique individual was traceable.

2.8 Statistical considerations

The sales and prescriptions data in paper I represent a total account, not a sample, on sales/prescriptions, classified into County Council areas. An observed difference between two county councils is genuine, and should not be subject to any statistical tests. In contrast, the grouping of county councils into tradition areas might induce a bias. Therefore, the classification of county councils was tested to evaluate if an observed difference between areas is likely to be actual, or was due to chance, dependent on the grouping. Small probabilities might reflect difference in tradition.

Unbalanced analysis of variance (ANOVA) was used to test the internal consistency within the tradition areas (using comparison between the counties of each area) and the differences between the tradition areas. The use of unbalanced ANOVA is justified by the fact that the number of counties varies between traditions areas (McCullagh & Nelder 1983, Fleiss 1986, Montgomery 1991, Wolter 1985). In all the data analysis, SAS[®] software (version 8.2, SAS Institute, Cary, NC, USA) was used.

The 24 statements in the inquiry form is an 11 grade visio-analogue scale ranging from zero = "I reject it entirely" to 10 = "I agree completely". The number of possible alternatives is odd, with the position "5" as a "neutral-ambivalent-don't know" statement. At least we hoped that the respondent would interpret the alternative in that way. An even number of grades forces the respondent to choose side, either the rejecting or agreeing side. Because of the complexity of the statements, we had a desire to give the respondent a neutral alternative. The measurement scale of the statements is ordinal, due to the construction of the scale (Eaden 1999).

When measuring an event, object or individual, an assignment of a label to this object is desirable. If this label is distinguishing between two or more categories, this creates nominal or categorical data, which is the lowest level of measurement scaling. Examples of categorical data are the eye colour of a newborn infant, agree – not agree, yes – no, diagnosis (Stevens 1946, Svensson 1993).

If you can order the data i.e. by assigning numbers from zero =”I reject it entirely”, to 10 =”I agree completely”, the categorical measurements is defined as ordinal. Other examples are place in a slalom race - first, second, third; school mark in mathematics - failed, passed, excellent. On the ordinal level, the data remains invariant in transformations to preserving the order, if you multiply the numbered scale by 10 it is still the same ranking between ”I reject it entirely” and ”I agree completely”. It is important to note that the numerical label does not represent a mathematical value in a mathematical sense. The numerical value only represents a category, ordered in relation to other categories, and the intermediate distance between adjacent categories is varying (Stevens 1946, Svensson 1993).

If the data is quantitative, the numerals have a mathematical meaning. There is equidistance between adjacent numerals; the measurement is on an interval scale. Mathematical operations, like summations, are allowed on this measurement scale, and the data has a zero point of its own. It is important to note, that the ratio of two values depends on the measurement unit. The conversion of temperature from Celsius to Fahrenheit degrees is $^{\circ}\text{F} = 32 + (9/5) \cdot ^{\circ}\text{C}$. This gives that 32 $^{\circ}\text{F}$ is zero $^{\circ}\text{C}$, and 212 $^{\circ}\text{F}$ is 100 $^{\circ}\text{C}$: the quote $0/100 \neq 32/212$.

On the highest level of the measurement scale, the ratio scale, data is rank-ordered, equidistant, have equality of ratios, and absolute zero. Examples of data on this measurement level are income, blood pressure and price. If the price of a commodity is zero €, then the commodity is free of charge (Stevens 1946, Svensson 1993).

Statistical computations, like means and variances, are impossible to compute on nominal or ordinal data. For nominal data, possible computations are mode and range, and for ordinal data median and percentiles. Means, standard deviation and variance are only allowed on interval and ratio scale. Table 6 describes some of the properties, for different scales of measurement.

Table 6. Properties of scales of measurement.

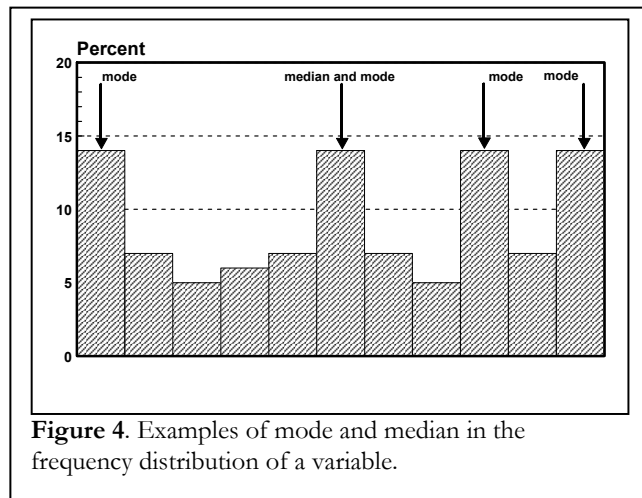
<i>Scale level</i>	<i>Rank</i>	<i>Property Equidistance</i>	<i>Zero point</i>
Nominal	No	No	No
Ordinal	Yes	No	No
Interval	Yes	Yes	No
Ratio	Yes	Yes	Yes

With the design of the two questionnaire studies, the sampling procedure of GPs resulted in two almost independent samples. Respondents participating in the 1996 study were withdrawn from the 1998 sample frame. This was done to avoid “learning effects” from seeing the questionnaires two times. There were also a question on the 1998 inquiry form sent to the GPs, asking if they had been participating 1996. A few (n=29) of the GPs participating 1996 did also answer the 1998 form. A guess is that they were answering for a college who did not feel that she/he had the time or knowledge to answer the questionnaire.

As mentioned before, the scale level of the questions is ordinal. Thus, nonparametric statistical methods have to be used in analyzing the questionnaire data in respect of differences between years, speciality and gender (Sprenst 1993).

Two such types of statistical tests were utilised, in order to compare the different subgroups. The first test is about central tendency in the material. In this case, either mode or median is usable. The mode is easy to use, but it has the disadvantage that there can be more than one mode in a distribution. The median gives the value where half of the respondents have a value below, and half a value above (Figure 4). The median, chosen in this analysis, is easier to interpret when comparing two populations.

In Figure 4, there are four mode values. The median and one of the mode values are in the bar in the middle. When comparing two distributions, use of the mode could be problematic, if there is more than one mode value in the distribution.



In paper III – V, the Mann-Whitney two-sample test for differences in median is used. The idea behind this test is as follows: If each of the two populations has the same median, one would expect the same number of observations below and above their common median. With help of the test, one tries to see if the two populations have the same, but unknown, median. In statistical terms, we formulate these simple ideas as follows.

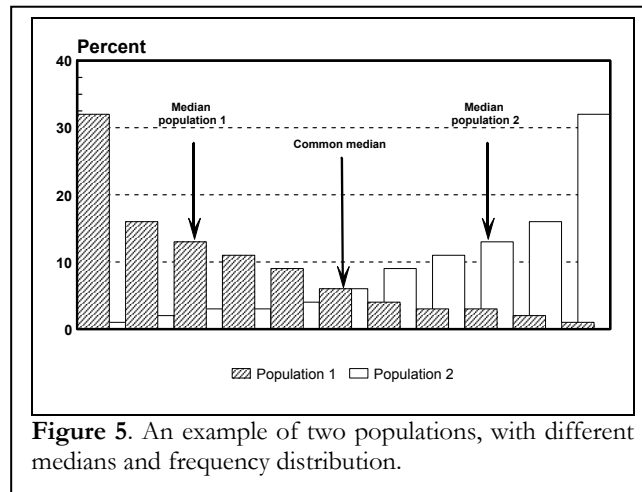
If the sample of m individuals comes from a population with unknown median θ_m , and a sample of n individuals from a population with unknown median θ_n , the hypothesis tested is:

$$H_0: \theta_m = \theta_n$$

Against the alternative (two-tail) hypothesis

$$H_1: \theta_m \neq \theta_n$$

The test investigates if an observed difference might be due to chance, or if the difference is non-random. Under the null hypothesis, a p-value < 0.05 is considered as significant, and the null hypothesis is rejected.



The Mann-Whitney test is easy to use and makes it easy to calculate confidence intervals for differences between the population medians (Sprent 1993). Figure 5 shows two distributions with $\text{median}_1 \neq \text{median}_2$. In this case, reject H_0 .

In Figure 6, $\text{median}_1 = \text{median}_2$. In this case, accept H_0 .

Besides the central tendency, in this case the median, also the shape of the frequency function and hence the cu-

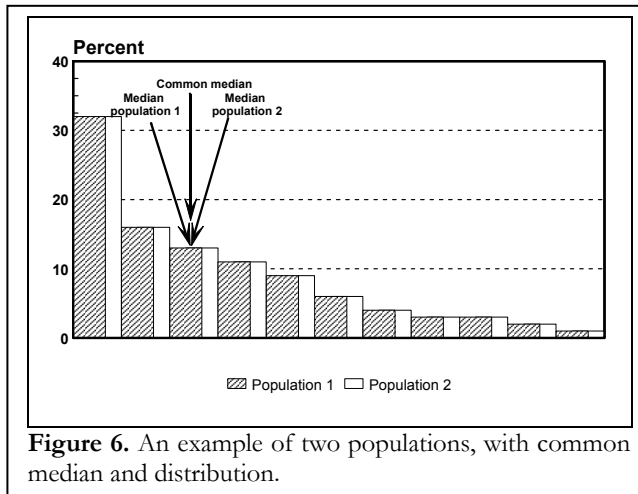


Figure 6. An example of two populations, with common median and distribution.

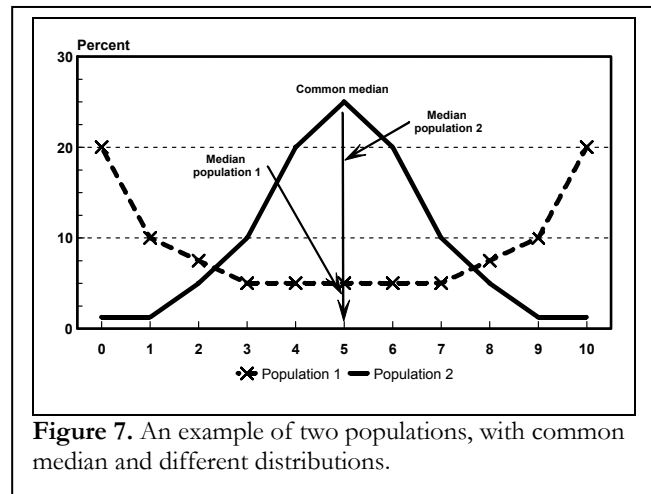


Figure 7. An example of two populations, with common median and different distributions.

Against

H_1 : the distributions are different

There are no additional assumptions about the nature of the possible differences (Sprent 1993).

In paper III-V, Cramér –von Mises test for differences in distribution shape is used. Under the null hypothesis, a $p\text{-value} < 0.05$ is considered as significant, and the null hypothesis is rejected. In Figure

mulative distribution function of the two populations is of interest. The shape of the distribution gives an idea of the spread of the data.

The question asked is as follows: Is the underlying distribution for the two populations the same? The hypothesis tested is then:

H_0 : the two samples originate from the same underlying distribution

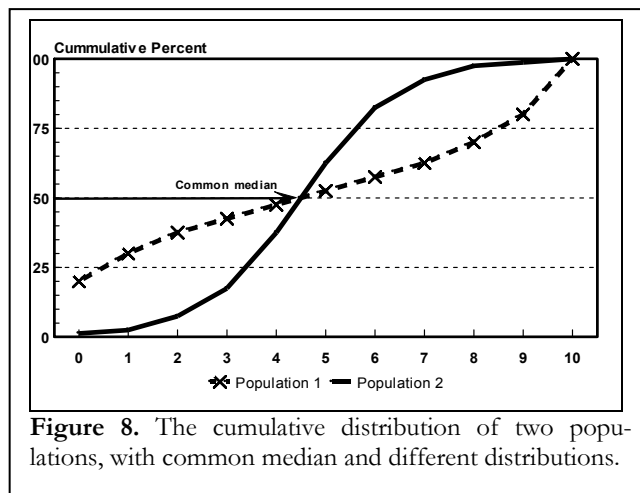
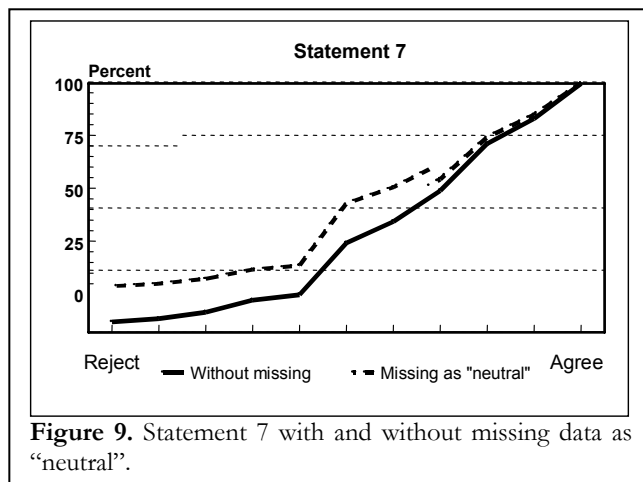


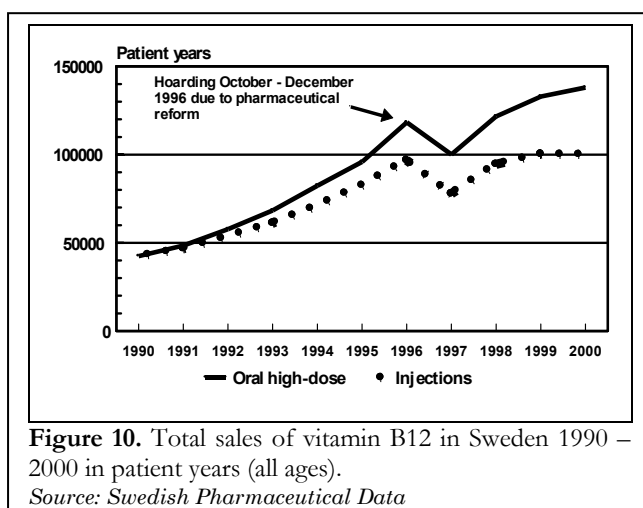
Figure 8. The cumulative distribution of two populations, with common median and different distributions.



because the desire to have the immediate reaction on the statement. In the statistical analysis of the statements, the internal missing values have been treated as a “neutral” or “no decision” value, and are recoded from missing to “neutral”. The statements with the highest number of recoded missing values are number 7, 10, 14 and 16. Figure 9 shows an example of the cumulative distributions for the statement with and without missing as “neutral”. The eventual impact of treating missing as neutral is given for statement 7 in the results.

Some of the statements are connected, i.e. if the respondent agrees on one statement she/he should probably agree to another. To determine internal validity among some of the statements, Cronbach’s alpha (α) have been used, and a Cronbach’s alpha greater than $|0.6|$ is in this case satisfactory. The rank correlation between the variables should also be $>|0.5|$ (Cronbach 1951, Bland & Altman 1997).

3. Results and specific discussions



5, the frequency distributions are different. In Figure 6, the frequency distributions have the same shape. Figure 7 shows the case where the medians are common, but the distribution of the variables differs. If plotting the cumulative distribution of Figure 7 the following picture is seen, Figure 8.

In the instructions to the questionnaire, the respondents were instructed to move to the next statement if they not could give an answer after ten seconds. This was

3.1 Cobalamin context in Sweden 1990 – 2000 (I)

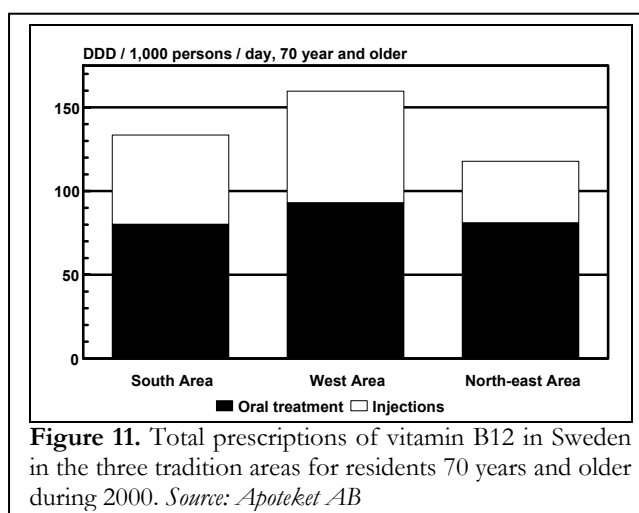
Swedish cobalamin context 1990 – 2000 was characterized by increasing oral therapy and stagnant parenteral therapy. Physicians in Sweden had gradually gained confidence in oral vitamin B12, since its introduction to the Swedish market in 1964. It is evident

from Figure 10 that by 1990 oral vitamin B12 therapy was as common as parenteral vitamin B12 therapy. Since then, the balance between the different forms of therapy has changed towards the tablets. The total experience of oral high-dose vitamin B12 in Sweden during the period 1990 - 2000 corresponds to approximately one million patient years and for parenteral therapy approximately 750,000 patient years. The increase of vitamin B12 sales from 1990 to 2000 could not be explained by an increase of elderly people; residents aged 70 or over only increased by 6% during the same period (Paper I).

The possibilities to make large population studies in Sweden are a result of the vital statistics, originating in 1749. In Sweden, every person has her/his own personal code number, which contains date of birth in six digits (year – month – day) and a three digit “serial number” ranging from 001 to 999, even for women and odd for men. The last digit is a control number. Every person in Sweden has a unique personal code number. This personal code was introduced in Sweden 1947 (with nine digits), and extended to ten digits 1967. This was to make it easier to computerize the national registration (Swedish National Tax Board 1999). This makes it possible to track prescription data on a population basis.

3.2 Prescription pattern during 2000 (I)

Data for the year 2000 were calculated from the prescription statistics of Apoteket AB, combined with the population statistics of Statistics Sweden. It is estimated that 13% of the residents aged 70 years and over were treated with vitamin B12, two out of three with oral high-dose vitamin B12. In the age group below 70, only one percent of the individuals were treated with vitamin B12, with an equal distribution between tablets and injections.



It is evident from Figure 11 that vitamin B12 prescriptions and sales differed in the three tradition areas. The West Area had the highest prescription rate of both tablets and injections, the Northeast Area the lowest ($p < 0.001$). In the North-east Area, 69% of the total vitamin B12 therapy was oral, compared with 58% in the West Area and 60% in the South Area ($p < 0.001$). Among residents aged 70 years and over, the fraction treated with vitamin B12 was 12% in the North-east Area, 16% in the West Area, and 14% in the South Area ($p < 0.001$).

As seen from Table 7 that the differences observed could not be explained by differences in age and gender between the populations of the three tradition areas. Nor could any internal inconsistency (heterogeneity) in the tradition areas be shown ($p = 0.75$).

Table 7. Age and gender distribution in the three tradition areas (Female / male percent).

<i>Tradition area</i>	<i>0 – 44 year</i>	<i>45 – 69 year</i>	<i>≥70 years</i>
South	46 / 49	35 / 37	19 / 14
West	46 / 50	35 / 36	18 / 13
Northeast	46 / 49	36 / 37	18 / 13

Source: Statistics Sweden

The differences between “Tradition areas”, in contrast to counties, supported the description of these areas by a previous observer (Norberg 2002).

3.3 Statements probing knowledge (II – V)

In the following section, the results from paper II – V are described. The figures shows the results of the time course study in GPs 1996 - 1998, the comparison between GPs and geriatricians 1998 and the gender study in the total material 1996 - 1998.

3.4 Results of statements probing knowledge

The following statements were constructed to investigate the knowledge among Swedish GPs and geriatricians on cobalamin-associated problems. The results are presented as three figures (see appendix 1 for a complete description). For each of the papers II – V tests are performed and reported about difference in median (Mann – Whitney, MW, two sample test) and difference in distribution shape (Cramér – von Mises, CvM). The test is presented as p-values or as ns (=not significant). In the figures in appendix 1, the results are commented below each statement. “Md” is the abbreviation for median. It is important to remember that the results shown should be interpreted according to the knowledge that was predominant during the period 1996 – 1998.

3.4.1 Statement 3

The correct evaluation of the statement, “*Women in fertile age are a risk group for vitamin B12 deficiency*” is supposed to be that women in fertile age are a small but important risk group for vitamin B12 deficiency (Sandström 1996). However, this view was not widely spread or accepted among the physicians at the time of the study. Schneede and co-workers pays attention to pregnant women who also are vegans. The B12 deficiency due to the diet can cause several problems for both the mother and the child (Schneede et. al 1994).

The opinion of GPs was stable over the period studied, identical with that of the geriatricians 1998 and independent of the gender of the responder (see Statement 3, appendix 1).

3.4.2 Statement 4

The correct evaluation of the statement, “*Vegans are a risk group for vitamin B12 deficiency*”, is supposed to be that vegans are a risk group for vitamin B12 deficiency (Lee 1993b, Schneede 1994, Hoffbrand 1996, Bevan 2004).

The knowledge of the GPs on the issue was acceptable and increasing (MW, $p < 0.001$; CvM, $p < 0.001$). However, by 1998 geriatricians were slightly better than GPs (MW, $p < 0.03$) and

female doctors better than male doctors (MW, $p < 0.001$; CvM, $p < 0.01$) on this issue (see statement 4, appendix 1) One possible explanation might be that female doctors were in majority among geriatricians. Thus, a speciality difference could mimic a gender difference, see Figure 12.

3.4.3 Statement 5

The correct evaluation of this statement, "*Anorectics are a risk group for vitamin B12 deficiency*", appears to be that anorectics are a risk group for vitamin B12 deficiency (Lee 1993b, Weatherall 1996, Bevan 2004).

From this point of view, the knowledge of the physicians studied was acceptable, with extra credit to female doctors (MW, $p < 0.001$; CvM, $p < 0.01$), Figure 13, and geriatricians (MW, $p < 0.02$). The observed gender difference might be because female doctors are in majority among the geriatricians (see statement 5, appendix 1).

3.4.4 Statement 6

The correct evaluation of this statement: "*Persons above 70 years of age are a risk group for vitamin B12 deficiency*" appears to be that persons above 70 years of age are a risk group for vitamin B12 deficiency (Sandström 1996, Nilsson-Ehle 1998, Björkegren & Svärdsudd 1999).

Female doctors (MW, $p < 0.001$; CvM, $p < 0.01$), Figure 14, and geriatricians (MW, $p < 0.001$; CvM, $p < 0.01$), Figure 15, were a bit

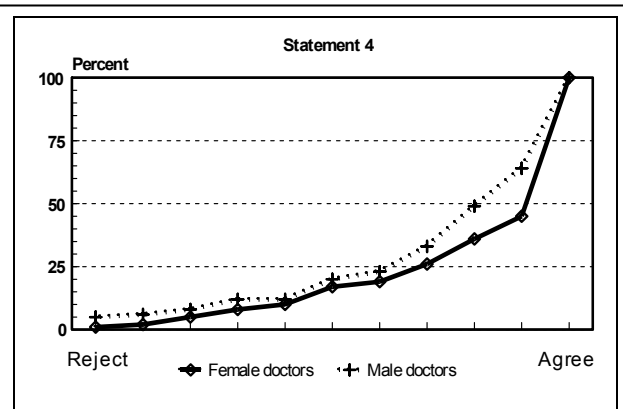


Figure 12. Cumulative distribution: Female and male doctors on statement 4.

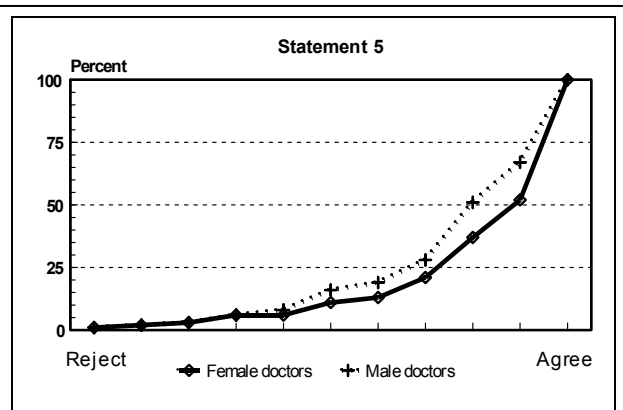


Figure 13. Cumulative distribution: Female and male doctors on statement 5.

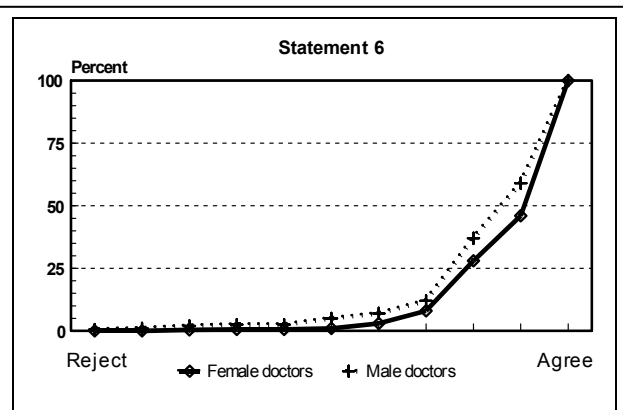
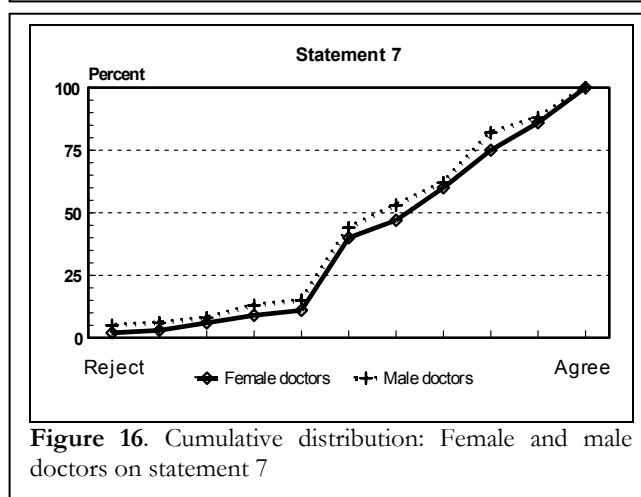
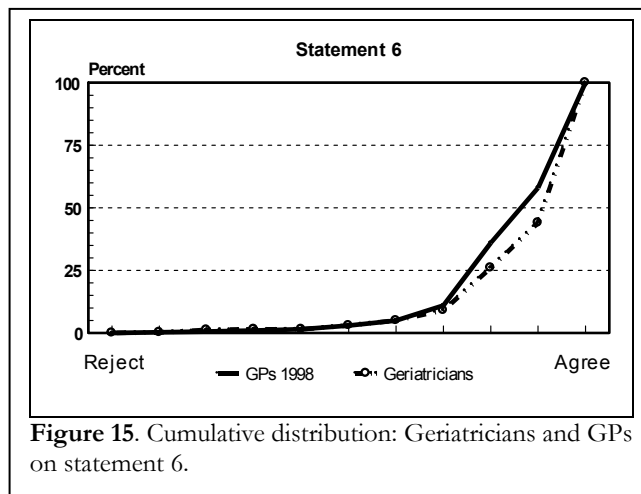


Figure 14. Cumulative distribution: Female and male doctors on statement 6.



more aware of the problem than GP's, but overall the knowledge was good (see statement 6, appendix 1). The observed gender difference might be because female doctors are in majority among the geriatricians.

3.4.5 Statement 7

Statement seven was formulated: "In alcoholics, serum cobalamin is often normal despite a functional vitamin B12 deficiency". The correct evaluation of this statement appears to be that serum cobalamin is often normal, despite a functional vitamin B12 deficiency, among alcoholics (Lee et al. 1993).

About one third of the doctors were uncertain about this statement, females least (see statement 7, appendix 1). Female doctors agreed more to this statement than their male colleagues did, Figure 16 (MW, $p < 0.001$; CvM, $p < 0.01$). This does probably reflect a gender difference, since there was no difference between specialities. The use of internal missing values as

"neutral" does not alter the results of the statistical analysis.

3.4.6 Statement 11

For the statement 11: "Homocysteine in serum or plasma replaces entirely serum cobalamin and serum folate in the first laboratory screening of a suspected case of malnutrition or malabsorption" the correct evaluation appears to be that homocysteine replaces cobalamin and folate in the first laboratory screening of a suspected case of malnutrition or malabsorption (Refsum 2002).

At the time, when the investigations were performed, not many laboratories had the equipment necessary to perform the modern tests (Table 2). The virtues of homocysteine in deficiency diagnosis of cobalamin and folate are evident from a glance at its key position of the methionine cycle. A lack of coenzyme (methylcobalamin) will raise the levels of homocysteine. A lack of substrate (5-methyltetrahydrofolate) will also cause elevation of homocysteine levels; and so

will a combined deficiency of both cobalamin and folate. Thus, homocysteine provides a sensitive marker for early stages of deficiency of cobalamin, folate, or both (Nilsson 2004).

The limitation of homocysteine as deficiency marker is a lack of specificity. Inborn errors of metabolism, impaired renal function (nephrosclerosis), impaired liver function, and several drugs hold back homocysteine levels in the presence of cobalamin and folate in physiological concentrations (Nilsson 2004).

At the time of the investigations, about 75 percent of the doctors were reluctant to accept the statement (see statement 11, appendix 1).

3.4.7 Statement 14

The correct evaluation the statement “*Serum gastrin, fasting value, is cheaper and easier to interpret than the Schilling test in cases of suspected vitamin B12 malabsorption*” is that serum gastrin is cheaper and easier to interpret than the Schilling test.

In many Western countries, the Schilling test is still the “golden standard” when evaluating suspected vitamin B12 deficiency (Andr s 2004). In Sweden today, the costly Schilling test is hardly used anymore: it has been replaced by more reliable and cheaper tests such as serum gastrin and serum pepsinogen A (Nilsson-Ehle 2003). At the time of the study, the Swedish clinical laboratories were at the crossroad between old and new markers for vitamin deficiency. Lindgren and co-workers (Lindgren 1998) focused on gastrointestinal causes to cobalamin deficiency in their studies.

Among the doctors, there were four out of ten that were uncertain, and the rest almost equally divided between rejections and acceptance (see statement 14, appendix 1). The GPs were closer to agreement than geriatricians were, Figure 17, (MW, $p < 0.01$; CvM, $p < 0.01$). The statistical test results were not changed with or without missing data as “neutral”.

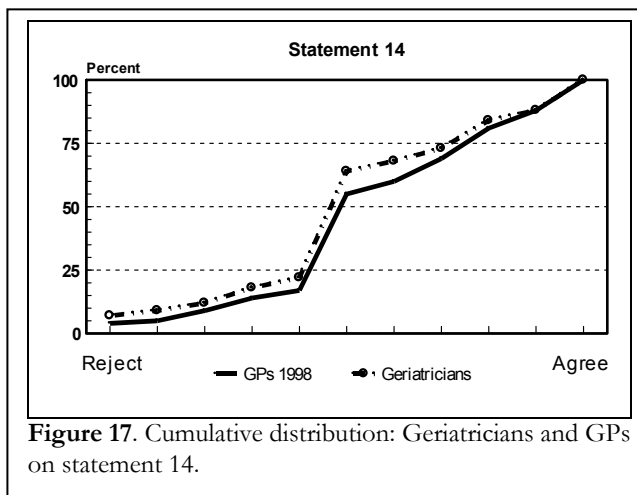


Figure 17. Cumulative distribution: Geriatricians and GPs on statement 14.

3.4.8 Statement 15

“*Simultaneous deficiency of iron and deficiency of vitamin B12 may produce anaemia with normal MCV (mean corpuscular volume)*”. The correct evaluation of this statement appears to be that simultaneous deficiency of iron and deficiency of vitamin B12 may produce anaemia with normal MCV.

The classical concept is “a dimorph picture”, with one fraction of small erythrocytes and one with large erythrocytes (c.f. Figure 5). Together they provide anaemia with normal MCV.

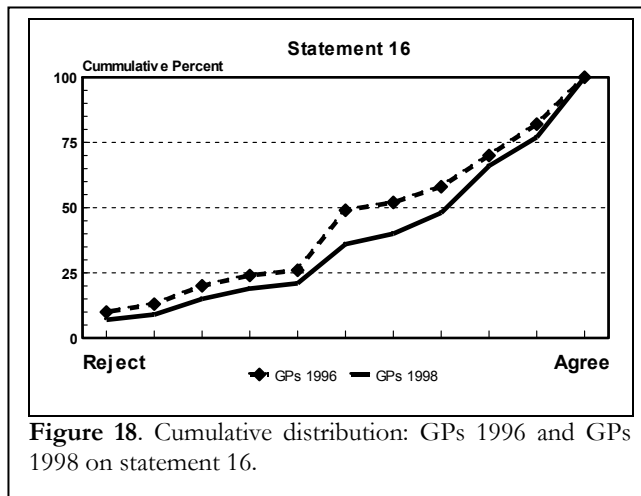


Figure 18. Cumulative distribution: GPs 1996 and GPs 1998 on statement 16.

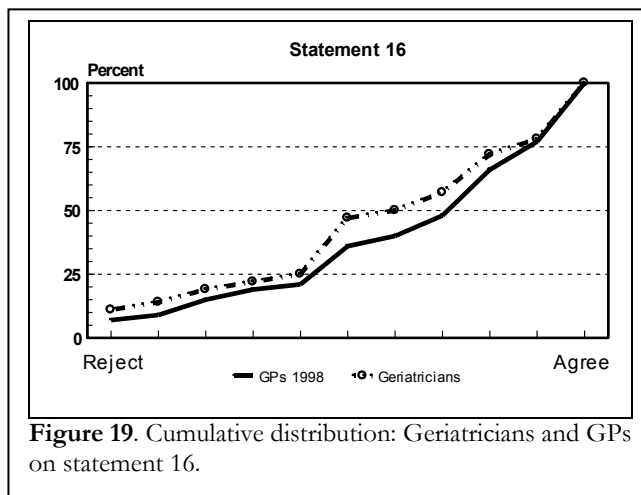


Figure 19. Cumulative distribution: Geriatricians and GPs on statement 16.

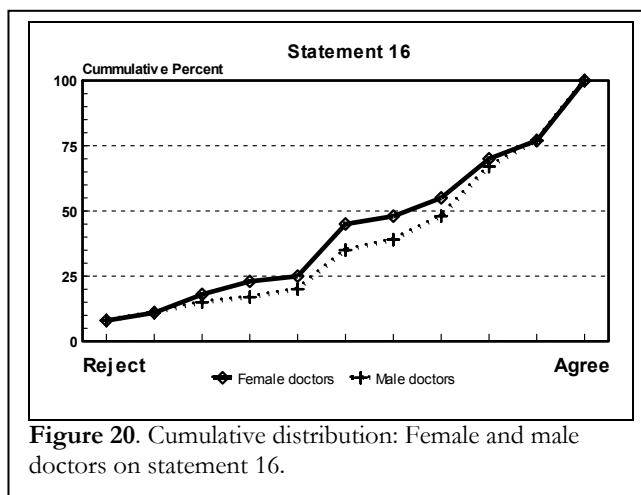


Figure 20. Cumulative distribution: Female and male doctors on statement 16.

The two-shape picture was known both 1996 and 1998, with a credit to the female doctors who seemed to agree a bit more (CvM, $p < 0.05$) than the male doctors did (see statement 15, appendix 1).

3.4.9 Statement 16

The correct evaluation of the statement “*Treatment with vitamin B12 may turn a macrocytic anaemia into a microcytic anaemia*” is that treatment with vitamin B12 only, can turn a macrocytic anaemia into a microcytic anaemia (Lee 1993c, Norberg & Palmblad 1998). If a patient, with a haemoglobin value below 110 g/L, is treated for vitamin B12 deficiency, this may deplete the body stores of potassium, iron and folate. Thus, it is advisable to substitute with potassium, iron and folate during the first treatment period for B12 deficiency.

Among the GPs, the insight that a macrocytic anaemia can turn into a microcytic anaemia had increased during the period 1996 – 1998, Figure 18, (MW, $p < 0.01$; CvM, $p < 0.01$). The GPs were also more aware about the problem than the geriatricians were, Figure 19, (MW, $p < 0.01$; CvM, $p < 0.05$). The observed opinions are compatible with the hypothesis that GPs meet younger patients, and had met the problem more often in their practice. Furthermore, male doctors seemed more aware about this than their female colleagues, Figure 20, (MW, $p < 0.04$; CvM, $p < 0.05$). Thus, the observed “gender

difference” might be explained by female overrepresentation among geriatricians (see statement 16, appendix 1).

3.4.10 Statement 17

For the statement, “*It is an error of the art to treat a macrocytic anaemia with folate only*” the correct evaluation is that it is an error of the art to treat a macrocytic anaemia with folate only. If a B12 deficiency is incipient, masked by folate treatment, no anaemia develops, while the B12 deficiency will continue to produce neuropathy. An alcoholic with low folate should be treated with both folate and vitamin B12. The S-co-balamin is probably a false normal value due to cirrhosis of the liver and raise in haptocorrin. An isolated folate treatment in this case might worsen the neuropathy (Lambert 1997, Carmel 2001).

Among the GPs the agreement decreased during the period, Figure 21, (MW, $p < 0.0$; CvM, $p < 0.01$), while the geriatricians seemed a bit more aware about this fact, Figure 22, (MW, $p < 0.05$; CvM, $p < 0.01$). There were no gender difference (see statement 17, appendix 1).

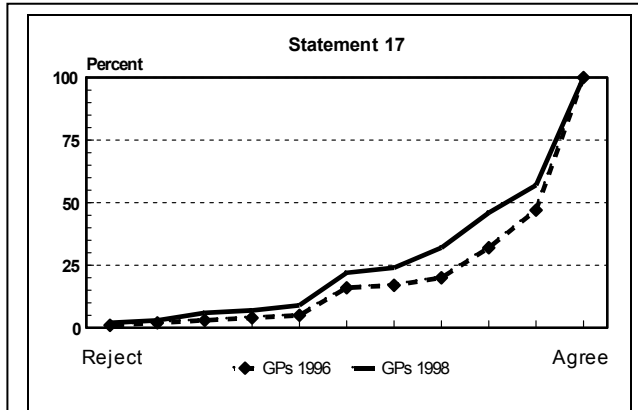


Figure 21. Cumulative distribution: GPs 1996 and GPs 1998 on statement 17.

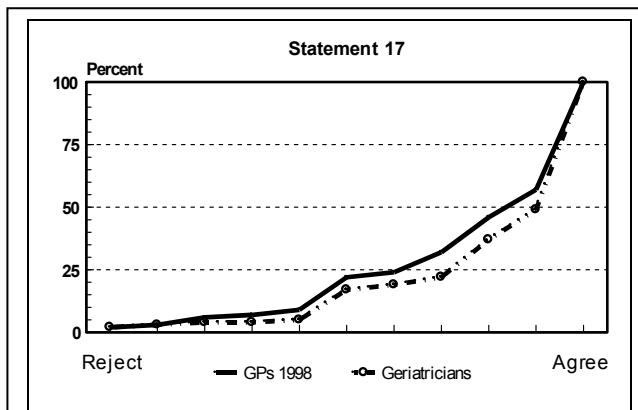


Figure 22. Cumulative distribution: Geriatricians and GPs on statement 17.

3.4.11 Statement 18

“*Functional vitamin B12 deficiency in cells and tissues may occur despite normal or high blood haemoglobin*”

The correct evaluation on this statement is that functional vitamin B12 deficiency in cells and tissues may occur despite normal or high blood haemoglobin (Lee 1993c, Norberg & Palmblad 1998).

The Swedish GPs and geriatricians were well informed on this topic at the time of the study with extra credit to female doctors, Figure 23, (MW, $p < 0.001$; CvM, $p < 0.0$), where a majority did fully agreed to the statement (see statement 18, appendix 1).

3.4.12 Statement 19

The correct evaluation of this statement “*Functional vitamin B12 deficiency may occur despite normal or high serum cobalamin*” is that functional vitamin B12 deficiency may occur despite normal or high serum cobalamin (Hultdin 1998). Only B12 that is bound to transcobalamin is accessible for the cells. About 70 – 80 percent of the measured B12 in blood is bound to haptocorrin. The GPs agreed to this both 1996 and 1998, as did the

geriatricians. The female doctors seemed a bit more convinced, Figure 24, (MW, $p < 0.01$; CvM, $p < 0.05$) than their male colleagues (see statement 19, appendix 1).

3.4.13 Statement 20

The statement “*There is no reason to substitute patients with atrophic gastritis with vitamin B12*” was rejected of three out of four doctors, i.e. the physicians accepted prophylactic treatment for patients with atrophic gastritis.

It is reasonable to assume that the “gender difference” that female doctors were more inclined to prophylactic treatment, Figure 25 (MW, $p < 0.01$; CvM, $p < 0.05$), is due to speciality difference, since males were overrepresented among GPs and females among geriatricians (see statement 20, appendix 1).

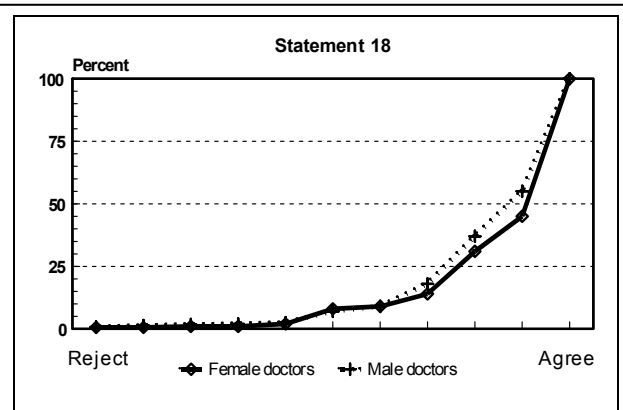


Figure 23. Cumulative distribution: Female and male doctors on statement 18.

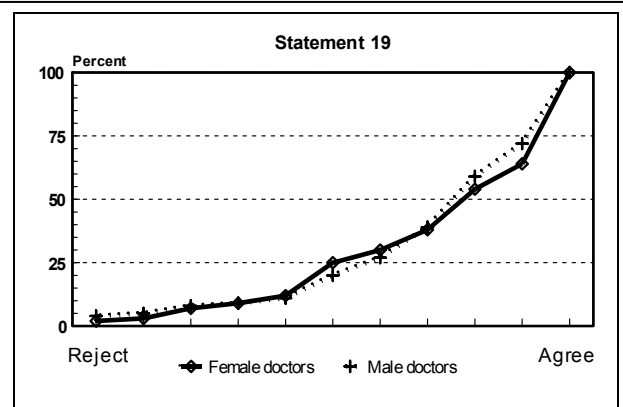


Figure 24. Cumulative distribution: Female and male

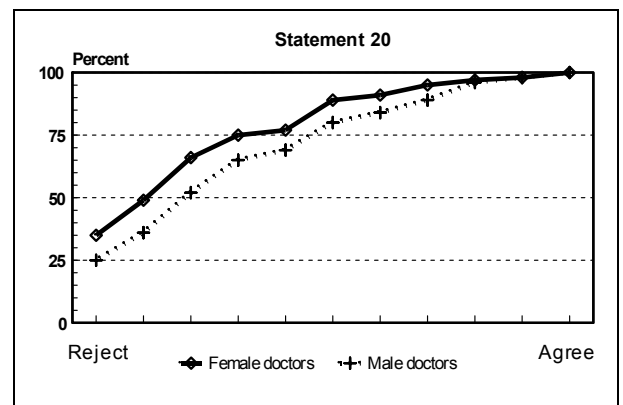


Figure 25. Cumulative distribution: Female and male doctors on statement 20.

4.3.14 Statement 21

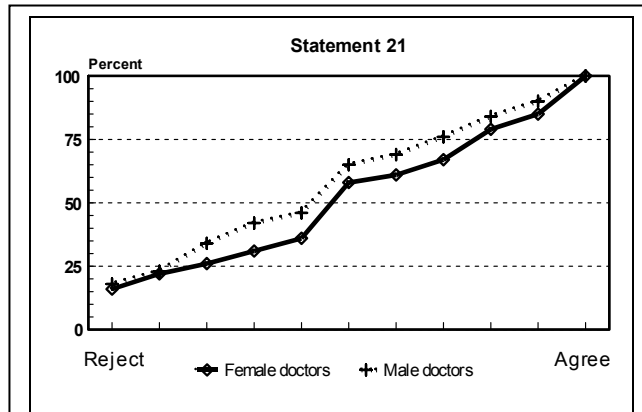


Figure 26. Cumulative distribution: Female and male doctors on statement 21.

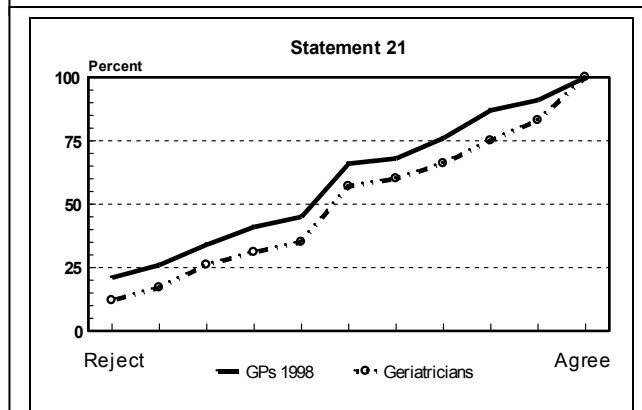


Figure 27. Cumulative distribution: Geriatricians and GPs on statement 21.

The statement “*As a precaution, I prescribe vitamin B12 to all my patients with atrophic gastritis*” is a corollary of previous statement (see statement 21, appendix 1).

The hesitation of the physicians reflected the difficulty of giving definite rules of thumb. It is reasonable to assume that the “gender difference”, Figure 26, (MW, $p < 0.01$; CvM, $p < 0.01$) reflected a speciality difference, Figure 27, (MW, $p < 0.01$; CvM, $p < 0.01$).

It should be emphasised that atrophic gastritis is a gradual process; the stage at which prophylaxis should be given is to some degree a matter of opinion, which could be discussed in terms of gastrin values and values of pepsinogen A (Lindgren et al 1997, 1998). In testing the internal consistency between some statements, the following hypothesis was tested with use of Cronbach’s α and rank correlation: Statement 20 and 21 are linked. If individuals

agree with statement 21, they should reject statement 20. In this case, $\alpha = -1.55$ and the rank correlation $\rho = -0.45$, which give support to the hypothesis.

3.4.15 Statement 22

A large majority of the doctors rejected the statement “*There is no reason to substitute patients with vitamin B12 after gastric surgery*”. Since surgery may interfere with cobalamin absorption, substitution is warranted (Wintrobe 1993, Oxford 1996, Rampton 1996).

It is reasonable to assume that the gender difference on this issue might reflect a reality, Figure 28, (MW, $p < 0.01$; CvM, $p < 0.01$), a credit to the female doctors; there were no demonstrable speciality differences (see statement 22, appendix 1).

3.4.16 Statement 23

To the statement, “*As a precaution I prescribe vitamin B12 to all patients with gastric resections*”, the doctors showed a dichotomy reaction, a concentration in both ends of the scale, with one out of four in the “uncertainty” position (see statement 23, appendix 1)

All four statements on atrophic gastritis and gastric surgery are akin. Such patients are prone to develop deficiency in the course of time (Lee 1993c, Rampton 1996, Reily & Cawley 1996). Thus, it is suggested that they should receive prophylaxis with the vitamins cobalamin and folate.

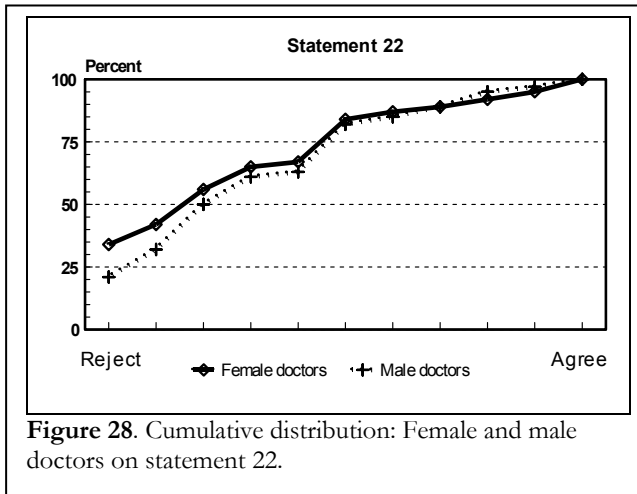


Figure 28. Cumulative distribution: Female and male doctors on statement 22.

To test the internal consistency between statement 22 and 23, the following hypothesis was tested with the help of Cronbach’s α and rank correlation: Statement 22 and statement 23 are also linked. If individuals agree with 23, they should reject 22. In this case, Cronbach’s $\alpha = -1.97$ and the rank correlation $\rho = -0.5$ support the hypothesis.

3.4.17 Statement 24

The correct evaluation of the last statement on the questionnaire is that “*It is still acceptable to treat a patient with obscure neuropathy with vitamin B12 during 6-36 months and evaluate treatment efficiency by clinical parameters*” (Magnus 1986, Schneede 1996, Kuzminski 1998).

This was well known among most GPs and geriatricians (see statement 24, appendix 1), although the GPs were a bit more convinced 1998 than 1996, Figure 29, (CvM, $p < 0.05$).

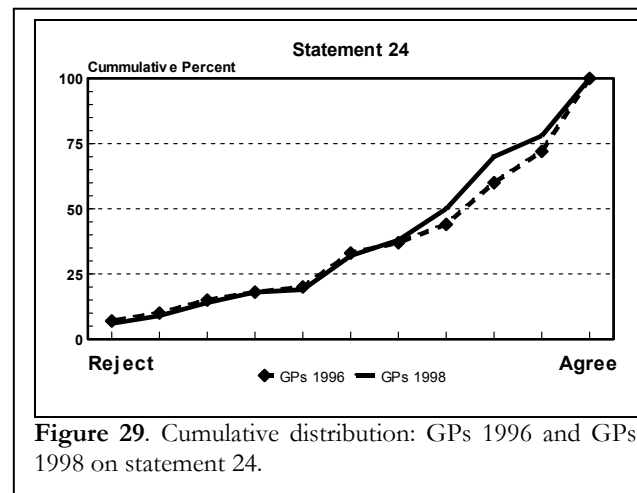


Figure 29. Cumulative distribution: GPs 1996 and GPs 1998 on statement 24.

3.5 Results of communication statements

The questions of communication are aimed to explore the impact of the debate on vitamin B12 deficiency problems during the period 1990 – 1996 and the debate that followed during the period 1996 – 1998. Many senders had sent their messages, and the receivers could choose

to accept or reject these messages. In Table 3, the contribution to the Swedish vitamin B12 debate in the Journal of Swedish Medical Association (Läkartidningen) 1992 is given. The senders could be colleagues, speakers at international/national meetings, the pharmaceutical and laboratory industry, patients and other lobby groups. Sometimes the receiver of a message later acted as sender (cf. Habermas 2003).

The results are presented as time course of opinion in the GP groups, GPs versus geriatricians 1998, and female versus male doctors 1996 - 1998. The differences in median and in distribution shapes were tested with the same methods, Mann – Whitney (for medians) and Cramér – von Mises (for distribution) as in the previous section.

3.5.1 Statement 1

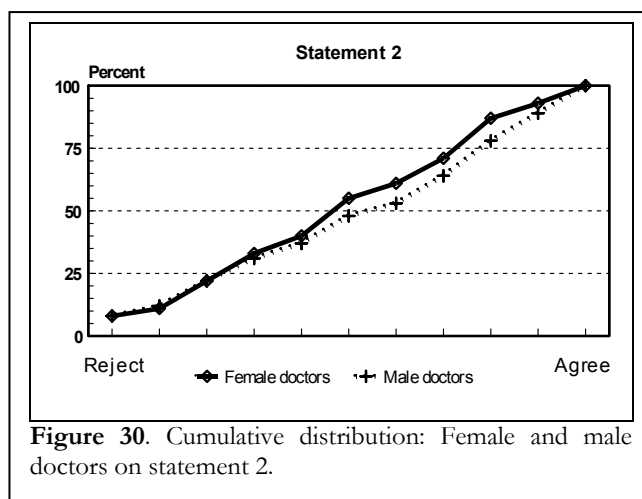
To the statement, “*Anamnesis and physical examination are essential in investigating and treating a case of suspected vitamin B12 deficiency*”, the doctor opinion was spread over the scale, although a majority was on the “agreeing” side.

B12 deficiency has many different symptoms, which makes it difficult to diagnose. The symptoms can be haematological, neuropsychiatric and others e.g. glossitis, infertility, and weight loss (Schneede 1996). It was important for the physician to make use of the normal “debugging” scheme in contact with the patient: case history, medication, heredity, physical examination, social status and present problems or ill health (see statement 1, appendix 1).

3.5.2 Statement 2

To the statement, “*Vitamin B12 deficiency is nowadays entirely a laboratory diagnosis*”, the female doctors were a bit more sceptical towards the statement, Figure 30, (MW, $p < 0.03$; CvM, $p < 0.05$) than their male colleagues (see statement 2, appendix 1) but the answers were quite evenly spread over the scale.

Both clinical diagnosis and laboratory diagnosis of cobalamin deficiency present pitfalls. In



interpreting serum cobalamin levels, the values can sometimes be falsely high (hiding a deficiency) or sometimes falsely low (imitate a deficiency). This is due to different causes. Falsely high values can occur due to abnormal serum binding proteins or an unreported cobalamin injection before the test occasion. Falsely low values might be due to, among other things, a folate deficiency, pregnancy or iron deficiency (Lee 1993b, c, Schneede 1996, Nilsson 2000).

It is reasonable to assume that the hesitation of the physicians in the evaluation of the preceding statement and present statement reflects the complexity of underlying realities. The back-

ground to deficiency depends on many processes - a slow onset over many years, a complex uptake and a normal body store that can last for many years.

3.5.3 Statement 8

The statement, “*A competent clinician does not need many laboratory tests to find his cases of vitamin B12 deficiency. Every fifth patient investigated for suspected vitamin B12 deficiency has, in fact, vitamin B12 deficiency*”, was rejected both 1996 and 1998. The portion of physicians who were hesitating was 25 percent (see statement 8, appendix 1).

The statement reflects the evaluation of clinical examination versus laboratory testing. The feeling of the responders was that less than every fifth suspect has indeed B12 deficiency. Sandström (1996) found that nine percent of analyzed serum samples had a cobalamin value <145 pmol/L. The investigating laboratory had a reference range of 130 - 670 pmol/L, the expected cut-off for deciles at the lowest values.

3.5.4 Statement 9

To the statement, “*Serum cobalamin and serum folate are valuable but, unfortunately, capricious markers for many different sorts of malnutrition and malabsorption. It is acceptable that only every 10th investigation demonstrates deficiency of vitamin B12*”, the reaction was the same as in the previous statement (see statement 9, appendix 1).

The evaluation of the statement is difficult. In a patient study from 1993, with serum cobalamin as sole marker, Sandström and co-workers found a hit ratio of approximately 1:10 in the specialities most familiar with cobalamin deficiency (Sandström 1996). In a population study with MMA as marker, Björkegren found that 10 percent of the examined had elevated values (Björkegren 2003).

3.5.5 Statement 10

This statement, “*Serum cobalamin and serum folate are valuable but, unfortunately, capricious markers for many different sorts of malnutrition and malabsorption. It is acceptable that only every 20th investigation demonstrates deficiency of vitamin B12*”, was rejected by a majority of the doctors; however, one out of four was again uncertain (see statement 10, appendix 1). The geriatricians, Figure 31, (MW, $p > 0.03$; CvM, $p < 0.05$) and the female doctors, Figure 32, (MW, $p < 0.01$; CvM, $p < 0.01$) rejected this statement more firmly.

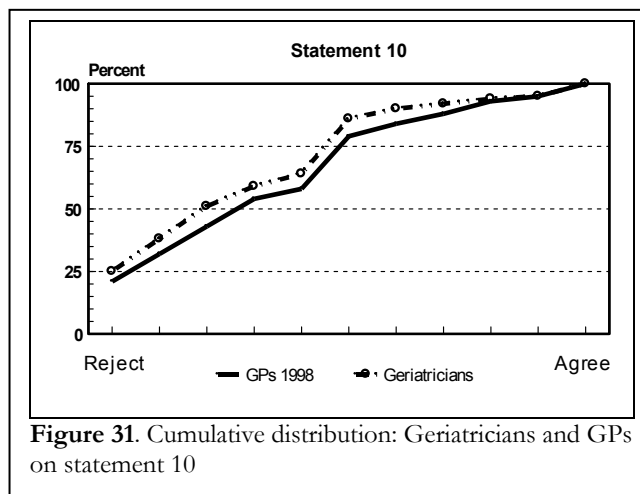


Figure 31. Cumulative distribution: Geriatricians and GPs on statement 10

In this case, there is no difference of the statistical tests if internal missing values is used as “neutral” or not. The comparison between female and male doctors is not altered either.

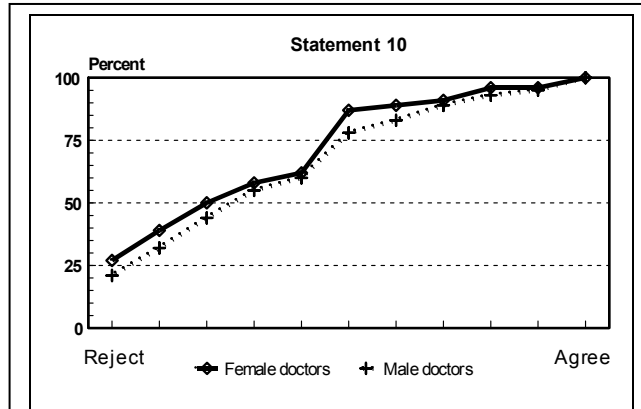


Figure 32. Cumulative distribution: Female and male doctors on statement 10.

It should be emphasised that the gender difference of opinion may, in fact, be a speciality difference. The grouping together of the total material will provide relevant information on gender difference only in case that there is no significant difference between GP's 1996, GP's 1998 and geriatricians 1998. The problems of the present studies (II – V) reflect a structure problem of Meta analysis.

The internal consistency between the statements 8, 9 and 10 tested with Cronbach's α and rank correlation gives the following hypothesis, and results: Suppose a grouping of statement 8, 9 and 10. There is, though, a possibility that a person could reject all three statements, but they should not agree completely with all three statements. When testing the consistency with all three statements together, the result where that they did not seem to be grouped, $\alpha=0.54$, which is not regarded as satisfactory (the same applies if statement 8 is tested with statement 9 or statement 10 separately). Comparison of statement 9 and 10 gives, $\alpha=0.80$, and the rank correlation is 0.66, which is better. To conclude: statement 8 does not seem to group with statement 9 or statement 10, but statement 9 and statement 10 seems linked together.

The internal consistency

3.5.6 Statement 12

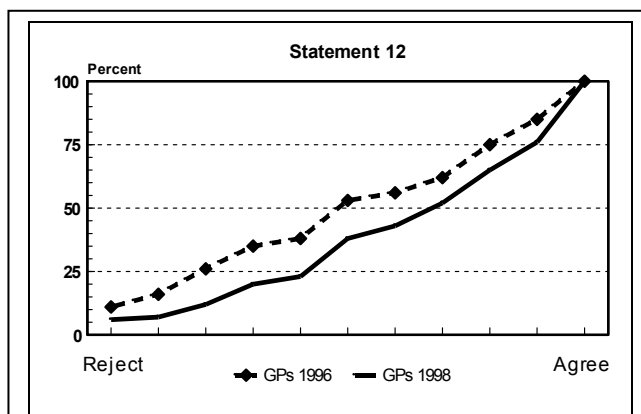


Figure 33. Cumulative distribution: GPs 1996 and GPs 1998 on statement 12.

The answers to the statement, “*A meticulous clinician cannot do without serum methyl malonate when investigating a case of suspected vitamin B12 deficiency*”, showed that the physicians seemed to accept the new marker MMA when investigating vitamin B12 deficiency (see statement 12, appendix 1).

During the period 1996 – 1998, the GPs gained in confidence, Figure 33, (MW $p<0.001$; CvM, $p<0.01$). This is remarkable, since MMA

could be analysed at few laboratories at the time of the investigations (Table 2). It is reasonable

to assume that the early Swedish studies with MMA as a tool of clinical research had paved the road for its acceptance (Brattström 1988, Regland 1991).

3.5.7 Statement 13

To this statement, “*The clinical significance of the modern markers homocysteine and methyl malonate in cases of suspected vitamin B12 deficiency is overrated*”, there was a significant shift in attitudes in favour of modern markers, Figure 34, (MW, $p < 0.001$; CvM, $p < 0.01$) among the GPs. Geriatricians also accepted the new markers (see statement 13, appendix 1).

However, the view is still highly controversial (Neuman 2003, Rosenberg et. al 2004).

First, elevated levels of MMA and homocysteine may be due to other causes than vitamin B12 deficiency (Bolander-Gouaille 2002). Second, the time of prophylaxis or therapy is subject to debate.

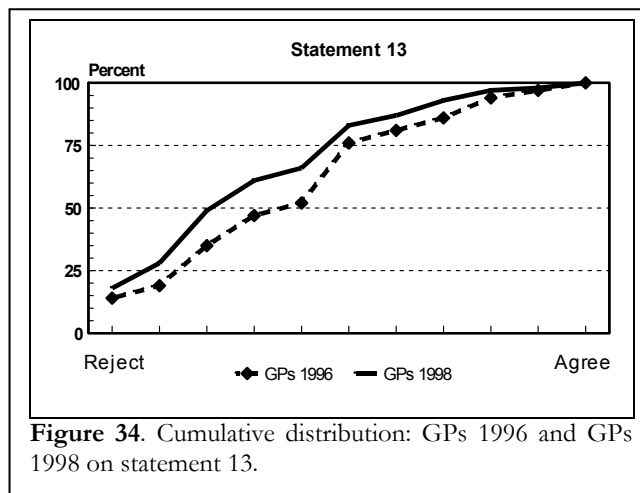


Figure 34. Cumulative distribution: GPs 1996 and GPs 1998 on statement 13.

The internal consistency between the statements 11, 12 and 13 tested with Cronbach's α and rank correlation gives the following hypothesis and results: Statement 11 and statement 13 were linked and so are statement 12 and 13. Individuals agreeing with statement 11 or statement 12 or both should always reject statement 13. When all three statements are included the $\alpha = -0.47$, with statement 11 and 13 the $\alpha = -0.02$ ($p = -0.01$) and statement 12 and 13 $\alpha = -1.38$ (and $p = -0.4$), which indicates that 12 and 13 are related, but 11 and 13 are not.

4. General discussion

The present study defined the practice of cobalamin treatment in Sweden in the period 1990-2000 (I). The Swedish tradition of B12 therapy has been thought to be unique in the world for a long time (Berlin 1968, 1978, Lederle 1991, 1998, Nyholm 2003). However, this is the first thorough study on the Swedish cobalamin tradition. The Swedish consumption of cobalamin was high, for instance, six times the Danish consumption (Andersen 2004).

One characteristic of the Swedish practice of cobalamin therapy is the use of oral high-dose medication. In the rest of the world, parenteral therapy dominates (Nyholm 2003). It is suggested from Figure 13 that a paradigm shift occurred in Sweden during the period 1990 – 2000. The physicians accepted the new markers for cobalamin deficiency, homocysteine and methylmalonic acid, and the focus changed from treating overt deficiency with clinical symptoms, to treating patients with preclinical stages of deficiency (patients at risk).

Furthermore, the present studies investigated views, knowledge and practice in two key groups of physicians, general practitioners and geriatricians in the period 1996-1998 (II-V). The knowledge of B12-associated problems appeared to be close to the state of the art in the physicians evaluated, as checked against the leading textbooks of the period as Wintrob's Clinical Hematology, Oxford textbook of Medicine and Axfords Medicine. A brief discussion of the observations, assumptions, and theoretical models behind the studies is warranted.

The population-based study of Björkegren (Björkegren 2003) suggests that every second citizen suffers from deficiency for some period during her/his last ten years. Although the symptoms are mild and reversible in most cases, it is reasonable to assume that a considerable gain in health and quality of life could be achieved by early diagnosis and treatment. Thus, it is still important to trace and treat cobalamin/folate deficiency.

Manifest pernicious anaemia is rare today, (Norberg & Palmblad, 1998). This observation is consistent with the hypothesis that competent GPs reveal and treat deficiency states at an early stage (II-V). The cost of this competence is a high consumption of B12, as compared with other countries (Hvas 2002, Andersen 2004). The risk for over-treatment, as manifested as toxic reactions from B12 consumption, seems to be negligible. The abundant vitamin B12 is eliminated via the urine (Berlin 1968).

In Sweden, patients with vitamin B12/folate deficiency have left the outpatient clinics of the hospitals and moved to the general practitioners of primary health care since about 1970 (Shenkin 1973, Carder 1980, Sandström 1996). An analogous trend appears to be in progress in other Western countries (Andrès 2003). In Western countries, deficiency is mainly due to gastrointestinal malfunction such as atrophic gastritis (Nilsson-Ehle 1988); a prolonged life span in the population might expand incidence and prevalence. In developing countries, the deficiency is mainly thought to be due to malnutrition (Andrès 2003).

With the development and more widespread use of new markers for vitamin B12/folate deficiency, the possibility to discover a deficiency in an early stage increased. From around 1970, bone marrow smears and serum cobalamin had innovated B12 deficiency analysis (Chanarin & Metz 1997). The new markers, homocysteine (Hcy) and methylmalonic acid (MMA) were introduced in the late 1980's (Lindenbaum et al 1988, 1990).

In Sweden, the technical basis for shifts of practice in cobalamin therapy was the estimation of serum cobalamin and serum folate in clinical routine from about 1970 and the introduction of homocysteine and methylmalonic acid in clinical routine in the period 1990 – 2000 (Table 2). In other comparable countries, classical methods as bone marrow smears and the Schilling test were still advocated (Lindgren 1997, Chanarin & Metz 1998, Andrès 2003). It is reasonable to assume that Swedish physicians were successful in the adaptation of new technique and new ideas due to a vivid cobalamin communication between different doctors (Engstedt et al 1998).

Homocysteine and MMA signal in an early stage for functional vitamin B12 deficiency, and are cheaper and more effective than the old Shilling test (Schneede 1996, Lindgren 1997). The Shilling test is almost exterminated in Swedish medical praxis today, but was still used around 1995. However, a slightly modified Shilling test is still seen as a standard test in other Western countries (André 2003).

In the process of spreading new information, for example about new markers for vitamin B12/folate deficiency, there is a complicated interaction between the sender of the new con-

cepts and the receiver of the message. For the receiver to obtain and interpret the new information, and transform it into useful knowledge she/he needs to be able to:

1. Receive data.
2. Have knowledge to interpret the data.
3. Have time to interpret the data.

The process could be formulated as the following functional model (Andersson et al 1984, Andersson 1984):

$$I=f(D, K, t) \quad (4.1)$$

Where

I= information; f=function; D= data; K= knowledge; t=time

The interaction between sender and receiver is a crucial step of communication (Andersson et al 1984, Andersson 1984). If the presentation of the data from the sender is imperfect, or if the receiver is lacking knowledge and/or time, the function of information transfer will be imperfect. The receiver of the information could ignore or misconstrue the message. These information exchanges need to be a two-way exchange in order to create communication between a sender and a receiver.

It is important to remember that information not necessarily is equal to new knowledge. The information needs to couple to a system of relationships that has been set up, and judged for their relevance and capability to either support or falsify the hypothesis of interest (Piganiol 1992).

In formula 4.1, the data can be presented in a variety of ways: it can consist of numbers or letters, a paper in a review, the speech on a conference. The knowledge consists of the receiver's knowledge and experience, and the way she or he can convert the data to information with this in mind. The time available for interpreting the data in relation to knowledge is also varying. Sometimes the receiver only has a short moment for interpretation, in other cases several days/years. A simple example is reading a text: you have to recognise the letters have the knowledge to interpret the meaning of the word, and the time to read the word.

In its simplest form, an act of communication is either a success or a failure, dependent on the receiver's response to the senders' assertion, either with affirmation or with refusal. The German philosopher Jürgen Habermas gives three fundamental types of validity claims raised by a sender in a speech act (Habermas 2003):

1. "A claim to the truth of what is said or is presupposed."
2. "A claim to the normative rightness of the speech act in the given context or the underlying norm."
3. "A claim to the truthfulness of the speaker".

In communication, the sender has different tools, e.g. reviews in scientific papers, meetings with the receivers, advertising brochures, and discussions. It should be emphasised, that a successful sender has to listen to qualified receivers in order to get their respect and their ears.

The GPs of Sweden see many patients with cobalamin/folate deficiency each year and develop considerable skill and knowledge in the field (Sandström 1996). In 1992, the main senders on cobalamin messages were involved in a major debate in *Läkartidningen* (Table 3). The senders were different kinds of “experts” such as basic researchers, clinical chemists, internists, haematologists, neurologists, psychiatrists, geriatricians. The main receivers of the message were various prescribers. It is reasonable to assume that the prescription pattern in Figure 13 reflects the impact of communication on GPs, since they prescribe about 95 percent of the cobalamin sales. The role of other actors such as pharmaceutical industry and laboratory industry remains to be elucidated.

The existence of different “tradition areas” in Sweden has previously provided some kind of “medical folklore”, (Norberg 2002), believed by some and denied by others. The sales and prescription study (I) demonstrated differences in cobalamin consumption between the postulated tradition areas, but not between the county councils of the administrative organisation of Swedish health care. The observation supports the view that tradition areas existed and maybe still exist to some degree. It is reasonable to assume that the phenomenon is worth further studies.

The Swedish use of oral high-dose (1 mg/day) treatment of vitamin B12 deficiency was considered “medicine’s best kept secret” (Lederle 1991, Vidall-Alaball & Butler 2003). Two out of three patients with B12 deficiency were treated with tablets in Sweden, during the year 2000. The Swedish experience of oral high-dose treatment was more than one million patient years during the period 1990 – 2000 (paper I).

The first oral high-dose preparation was introduced to the Swedish Market 1964. It gradually gained the confidence of Swedish physicians. The B12 uptake by intrinsic factor and cubilin is thought to be restricted to approximately 1 microgram daily. One or two micrograms more may be absorbed by diffusion, mainly in the upper part of the small bowel (Berlin 1968, 1978, Kuzminski 1998). Approximately 1% of oral cyanocobalamin is absorbed by such diffusion, i.e. 10 microgram from a 1 mg tablet. This regimen is calculated and proven sufficient for most patients, who are able to comply. In demented persons and alcoholics, compliance failure is to be expected; such patients should have parenteral therapy.

For the patient, the oral high-dose treatment has led to advantages – freedom from consultations and injection pain, avoidance of tiredness at the end of an interval between two injections. Such features may seem as convenient to the post-modern human (Singer 1993, Tännsjö 2001) as to the traditional “old Adam”.

With the introduction of the “7-crown reform” in Sweden 1970, a large group of hospital physicians had their payment changed from capitation per patient treated to a monthly wage (Shenkin 1973, Carder 1980). The treatment of parenteral vitamin B12 deficiency was at that time handled among these specialists mainly. With the introduction of oral high-dose treatment of B12 deficiency, the workload for the doctor was reduced, since the patient, normally healthy in other aspects, reduced the number of yearly visits from 4 – 16 to one or two. Thus, with a monthly wage that was not dependent of number of patients treated, the tablets might have been a labour-saving measure. In Sweden, the oral treatment is financially neutral to the

patient, the producer and the prescribers. However, other scientists have argued that oral treatment saves society many costs, compared with parenteral therapy (Hvas 2001, Nyholm 2003 and Andr  s 2004).

Most Swedish patients with B12 deficiency were handled by general practitioners in primary health care in the beginning of the 1990'ies. In our first study (Paper II) it was found that the GPs were familiar with the biochemical, pathophysiological and social problems associated with vitamin B12 deficiency.

The first study (II) led to more discussion and resulted in a debate book "Controversies around vitamin B12" (Engstedt et al 1998). In order to evaluate the stability, a new study was performed two years later (III). The main finding when comparing these two years was that the GPs had improved their professional knowledge and competence in B12-related clinical and laboratory problems. The shifts were marginal: "from brightness to brightness", although statistically significant. The shape of the sale statistics curve suggests that the paradigm shift from treatment of clinical deficiency to prophylaxis of clinical deficiency took place during the period of the questionnaire studies 1996 – 1998 (I –V).

Since approximately 95 percent of the cobalamin prescriptions originate from GPs (I), it was desirable to compare their skill and competence with that of hospital-based physicians (IV). The geriatricians were chosen as a contrast; cobalamin/folate deficiencies are common among geriatric patients (Sandstr  m 1996, Bj  rkegren 2003). There were marginal but significant differences of opinion between GPs and geriatricians. Some of the divergence in views and knowledge might be explained from differences of patients managed; other might reflect the physicians' gender. Among the geriatricians, there were almost 60 percent female doctors, in contrast to 40 percent among GPs.

The Meta analysis (paper V) was designed to elucidate whether there were differences of opinion between female and male doctors. Our findings were compatible with the hypothesis that there are gender differences in the attitudes of doctors toward B12-associated problems; the differences were marginal, although statistically significant on some statements. Our findings are consistent with the observations of gender differences in other fields of doctoring (Andersson 1995, Risberg 2004). A tentative hypothesis could then be formulated: a female doctor seems to be more observant to clinical findings, and a male doctor to laboratory findings.

The stability of B12-related opinions within the group of general practitioners in the period 1996-1998 was remarkable (III). The absolute shifts were generally small, although the statistical significance often was high. The observation is consistent with the hypothesis that most physicians were aware of the state of the art. However, it should be emphasised the knowledge, competence and opinions are a matter of continuous training and communication. The state of the professional skill 1996-1998 cannot be projected to 2004; it is suggested that present state should be defined by present studies.

The population statistics of Sweden is unique (I). In the present context, these statistics implies a possibility to define the full extent of the Swedish experience with oral cobalamin therapy, parenteral cobalamin therapy, folic acid therapy, and the possible side effects of different regimens. Such future studies provide an opportunity of international interest (cf. B  ttiger & Westerholm 1973, 1980).

4. 1 Summary

This is the first study to define the context of contemporary B12 tradition in Sweden during the period 1990 – 2000. The period was distinguished by an intense debate on the issue by the physicians, an increase of cobalamin consumption, and a shift from parenteral therapy towards oral high-dose therapy. The Swedish experience with oral high-dose cobalamin (cyanocobalamin, 1 mg daily) comprised approximately one million patient years. In the same period, the experience with parenteral cobalamin comprised 750,000 patient years.

In a communication model, the physicians were mainly receivers of messages from basic researchers and clinicians with special interest in the field. The findings suggested that the clinical introduction of the new B12 deficiency markers homocysteine and methylmalonic acid produced a shift in paradigm, from treatment of clinical deficiency to treatment of threatening deficiency (prophylaxis).

This study is the first to set the senders and the receivers of cobalamin communication on the same level, quantify, and evaluate the feedback from the receivers. The receivers, general practitioners and geriatricians, appeared to be familiar with both knowledge and frontier concepts in the field. Thus, it is suggested that the increase of vitamin B12 prescriptions in Sweden 1990 – 2000 reflect an increased awareness of B12-associated clinical problems among the physicians managing the majority of patients.

5. Acknowledgement

I thank my scientific advisers, Johan Lökk, Bo Norberg, and Göran Westman, for constructive criticism, my former employer, County Council of Västerbotten, for a generous redundancy, the material basis for two post-doctoral years of research, my trade union, JUSEK, for strength, skill, and solidarity in the negotiations, which led to the redundancy mentioned, my friends and co-workers for inspiration and support in crisis, my loyal family. My most cordial Thanks!

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Appendix

A 1 Statement 1

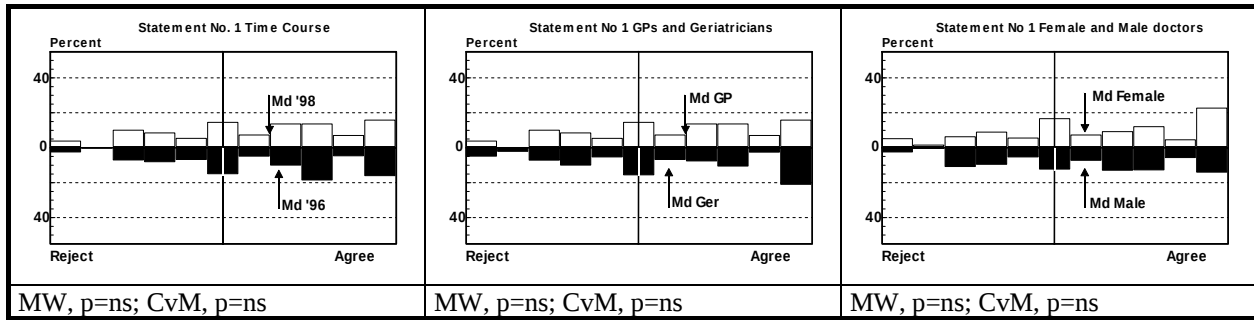


Figure A1. “Anamnesis and physical examination are essential in investigating and treating a case of suspected vitamin B12 deficiency”

A 2 Statement 2

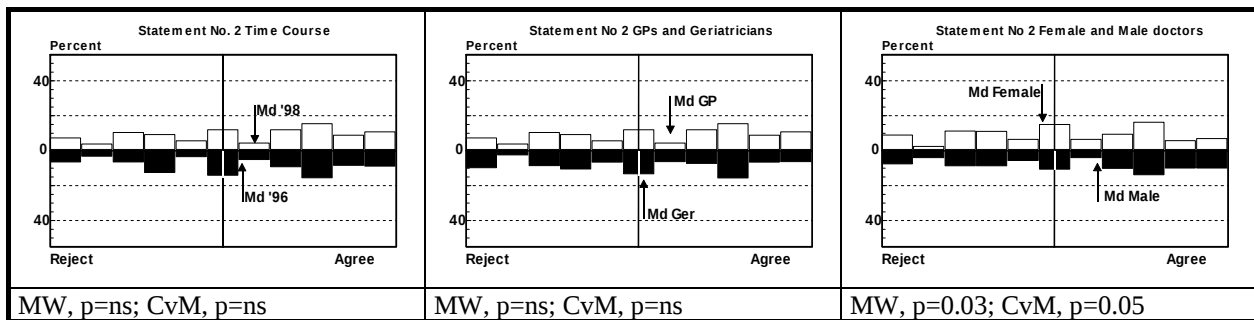


Figure A2. “Vitamin B12 deficiency is nowadays entirely a laboratory diagnosis”

A 3 Statement 3

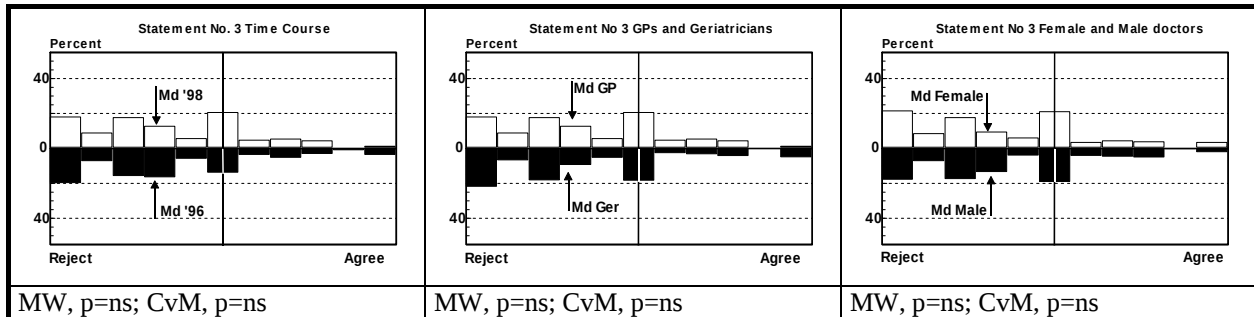


Figure A3. “Women in fertile age are a risk group for vitamin B12 deficiency”

A 4 Statement 4

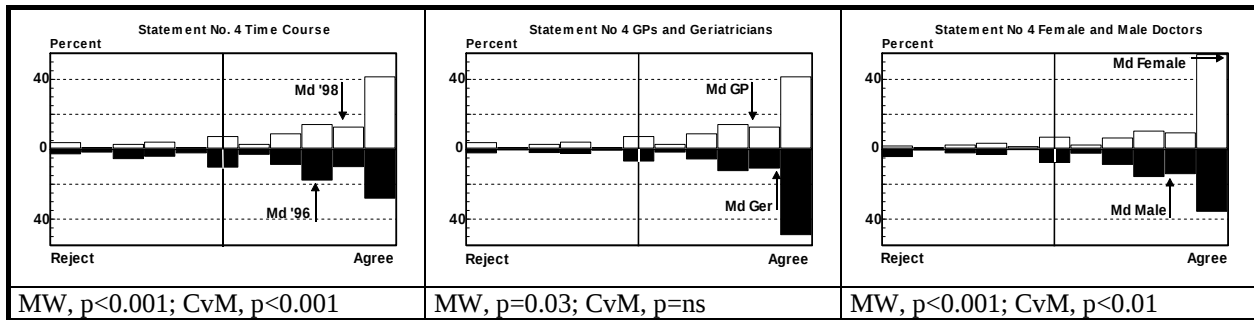


Figure A4. “Vegans are a risk group for vitamin B12 deficiency”

A 5 Statement 5

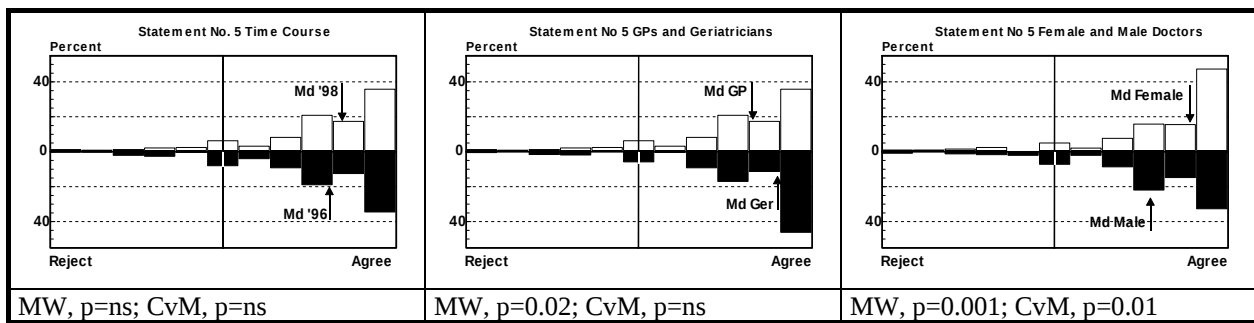


Figure A5. "Anorectics are a risk group for vitamin B12 deficiency"

A 6 Statement 6

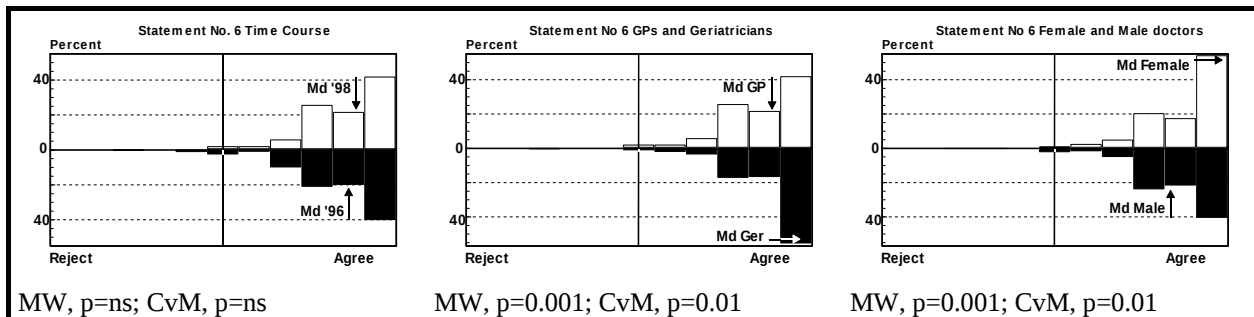


Figure A6. "Persons above 70 years of age are a risk group for vitamin B12 deficiency"

A 7 Statement 7

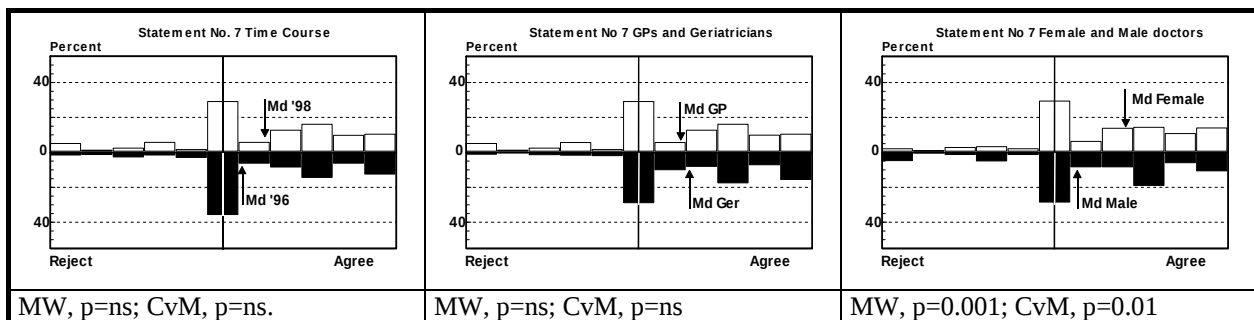


Figure A7. "In alcoholics, serum cobalamin is often normal despite a functional vitamin B12 deficiency"

A 8 Statement 8

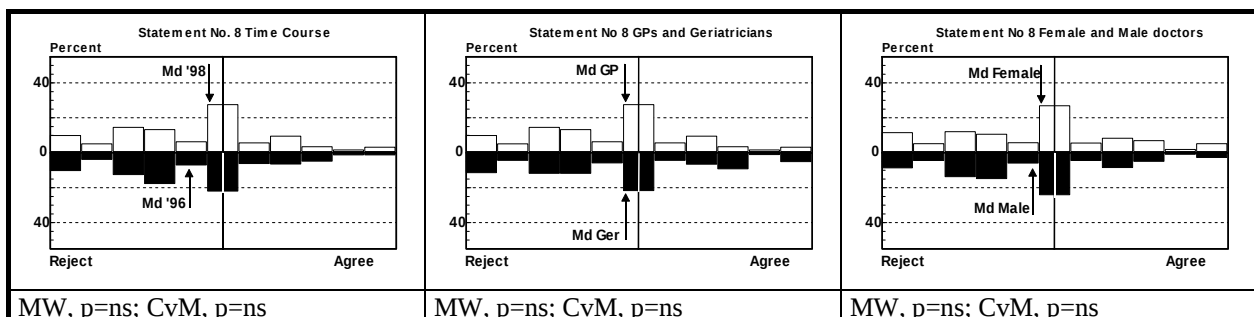


Figure A8. "A competent clinician does not need many laboratory tests to find his cases of vitamin B12 deficiency. Every fifth patient investigated for suspected vitamin B12 deficiency has, in fact, vitamin B12 deficiency!"

A 9 Statement 9

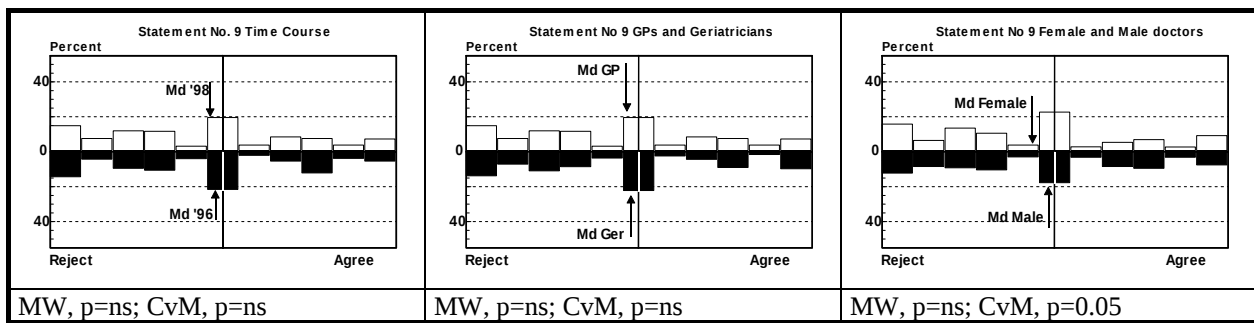


Figure A9. “Serum cobalamin and serum folate are valuable but, unfortunately, capricious markers for many different sorts of malnutrition and malabsorption. It is acceptable that only every 10th investigation demonstrates deficiency of vitamin B12”

A 10 Statement 10

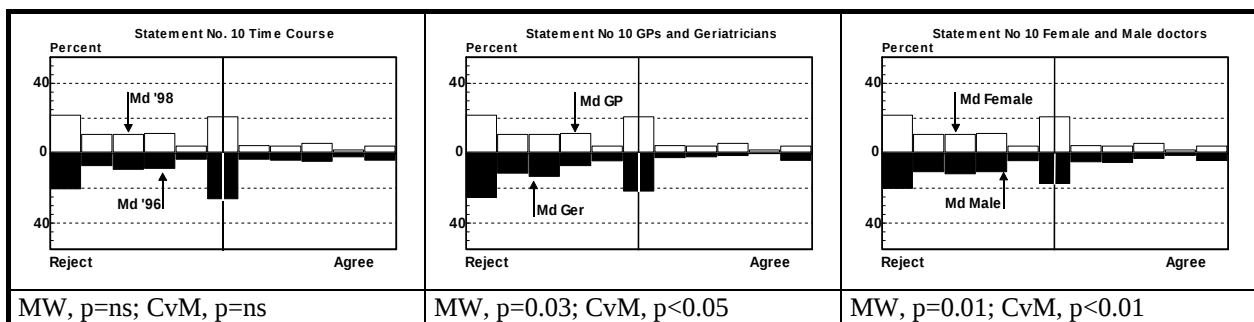


Figure A10. “Serum cobalamin and serum folate are valuable but, unfortunately, capricious markers for many different sorts of malnutrition and malabsorption. It is acceptable that only every 20th investigation demonstrates deficiency of vitamin B12”

A 11 Statement 11

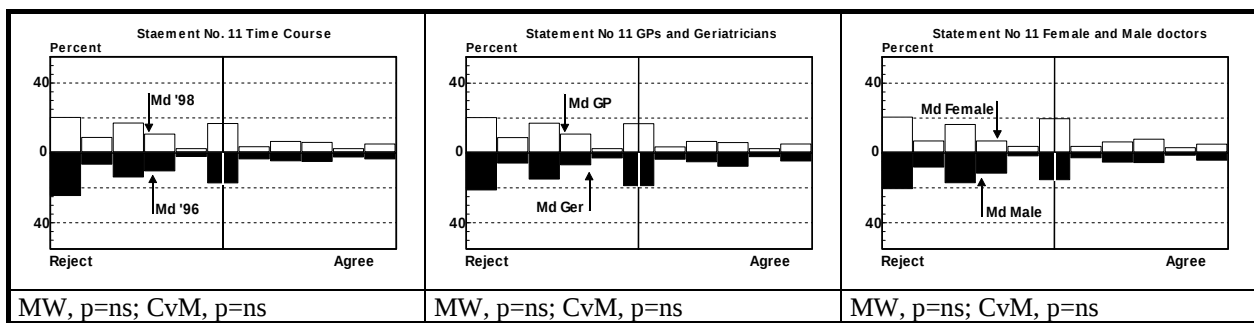


Figure A11. “Homocysteine in serum or plasma replaces entirely serum cobalamin and serum folate in the first laboratory screening of a suspected case of malnutrition or malabsorption”

A 12 Statement 12

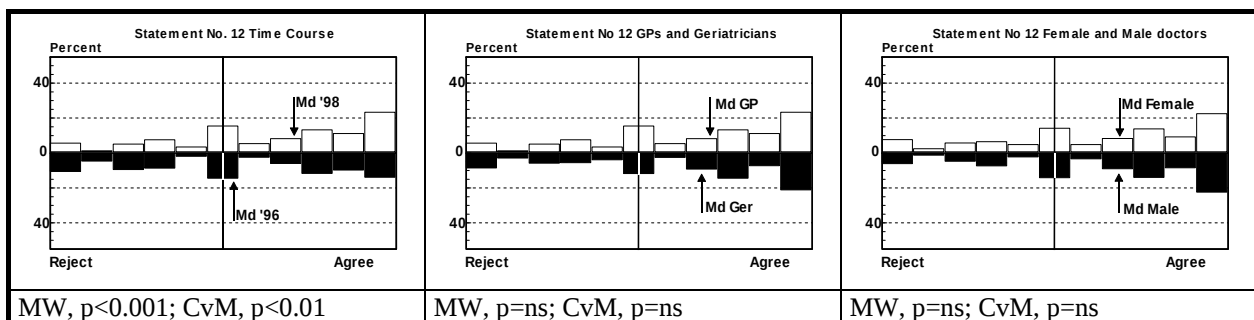


Figure A12. “A meticulous clinician cannot do without serum methyl malonate when investigating a case of suspected vitamin B12 deficiency”

A 13 Statement 13

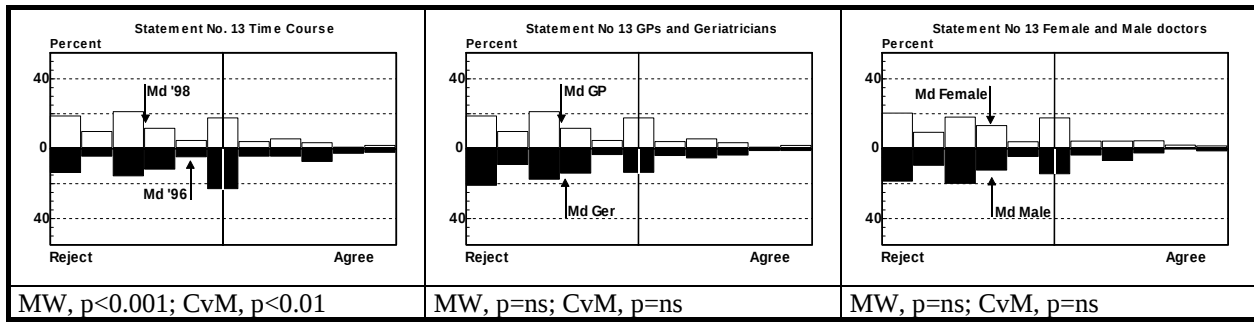


Figure A13. “The clinical significance of the modern markers homocysteine and methyl malonate in cases of suspected vitamin B12 deficiency is overrated”

A 14 Statement 14

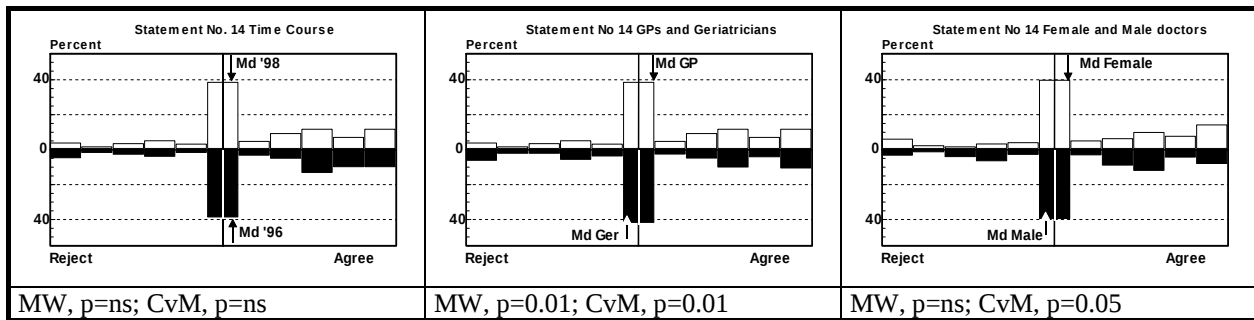


Figure A14. “Serum gastrin, fasting value, is cheaper and easier to interpret than the Schilling test in cases of suspected vitamin B12 malabsorption”

A 15 Statement 15

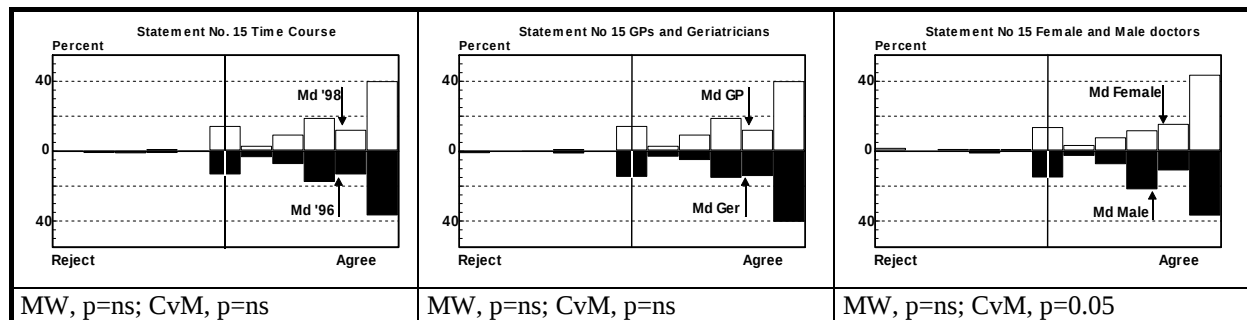


Figure A15. “Simultaneous deficiency of iron and deficiency of vitamin B12 may produce anaemia with normal MCV (mean corpuscular volume)”

A 16 Statement 16

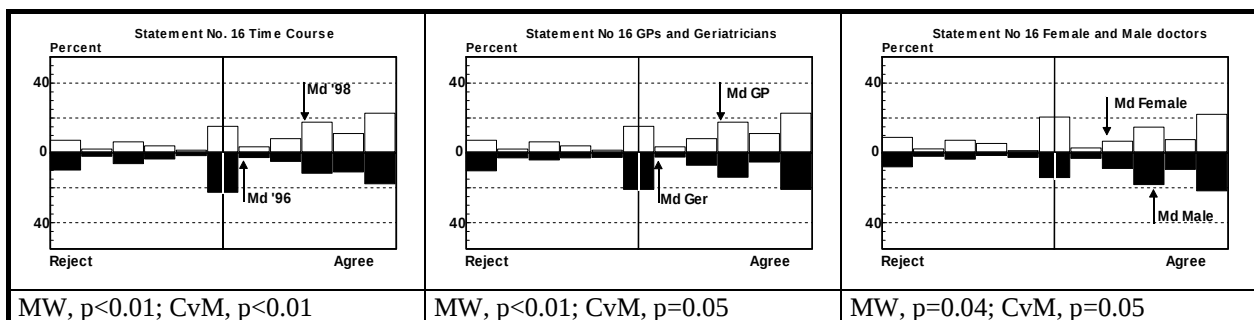


Figure A16. “Treatment with vitamin B12 may turn a macrocytic anaemia into a microcytic anaemia”

A 17 Statement 17

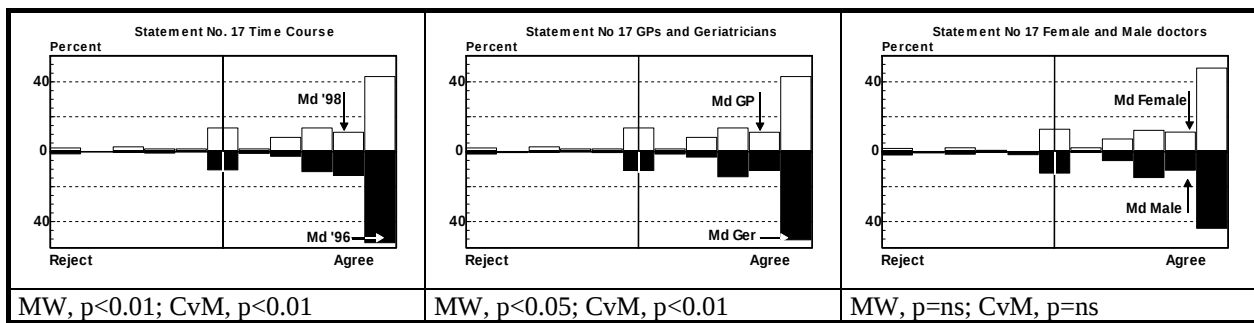


Figure A17. It is an error of the art to treat a macrocytic anaemia with folate only”

A 18 Statement 18

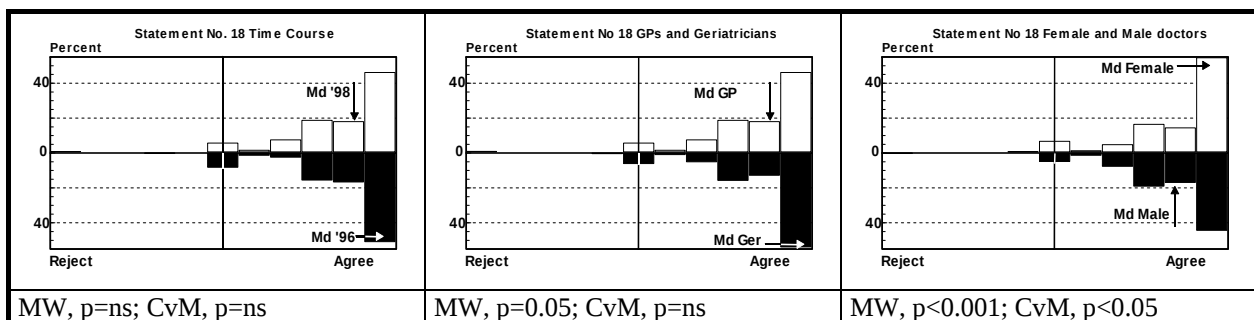


Figure A18. “Functional vitamin B12 deficiency in cells and tissues may occur despite normal or high blood haemoglobin”

A 19 Statement 19

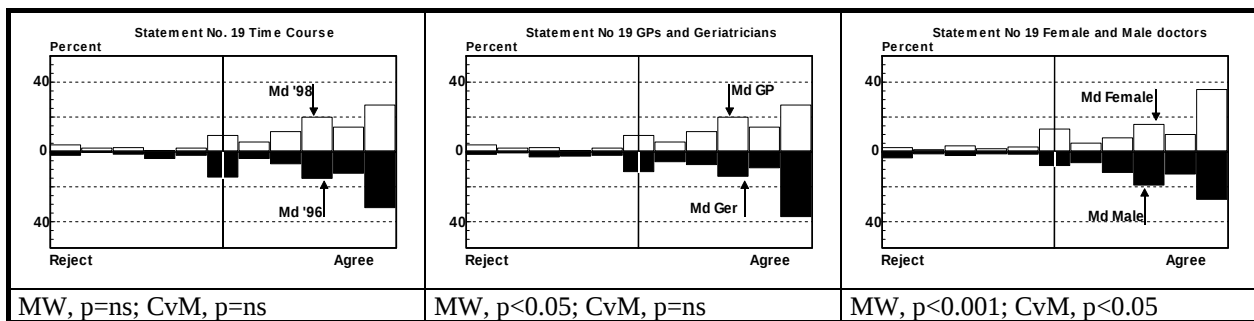


Figure A19. “Functional vitamin B12 deficiency may occur despite normal or high serum cobalamin”

A 20 Statement 20

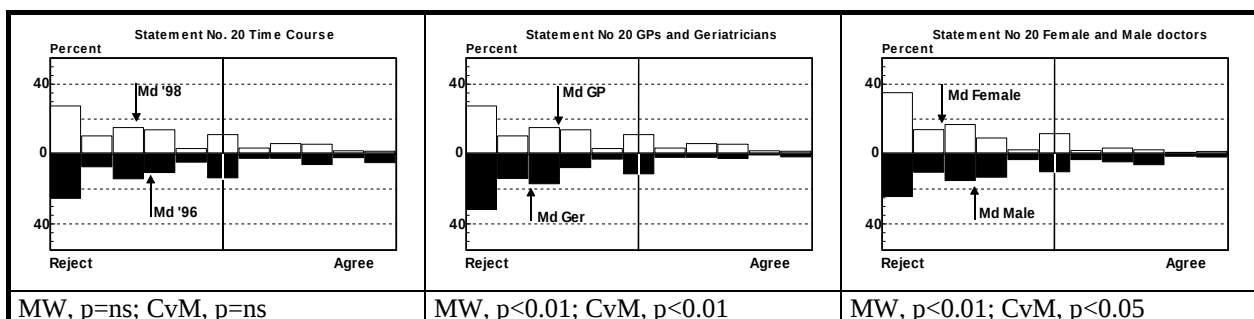


Figure A20. “There is no reason to substitute patients with atrophic gastritis with vitamin B12”

A 21 Statement 21

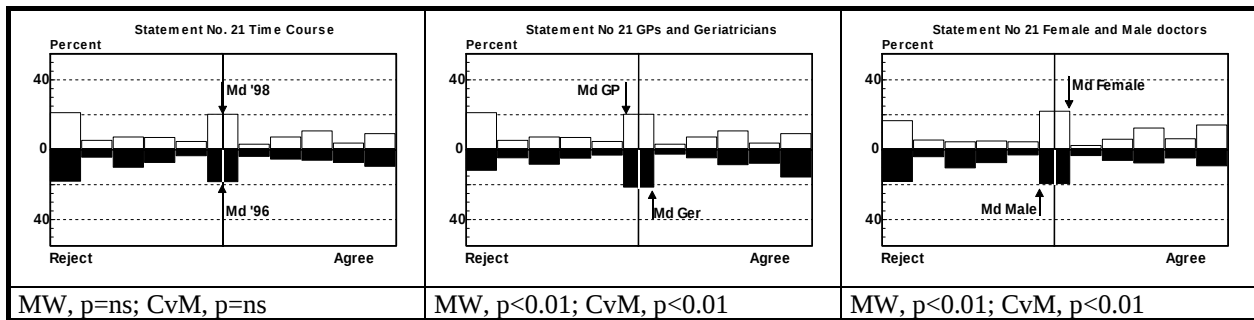


Figure A21. "As a precaution, I prescribe vitamin B12 to all my patients with atrophic gastritis"

A 22 Statement 22

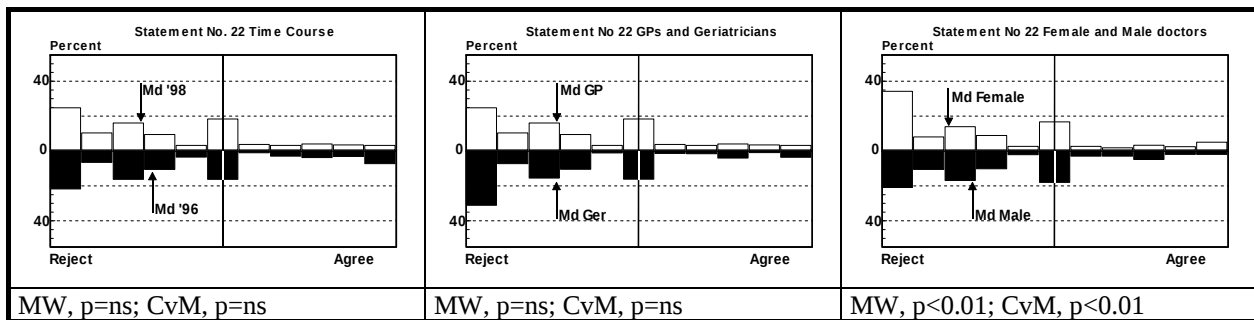


Figure A22. "There is no reason to substitute patients with vitamin B12 after gastric surgery"

A 23 Statement 23

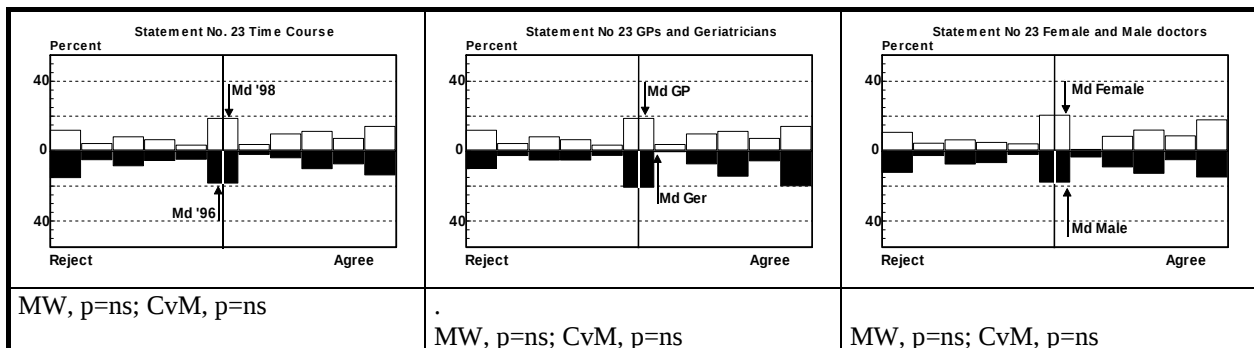


Figure A23. "As a precaution I prescribe vitamin B12 to all patients with gastric resections"

A 24 Statement 24

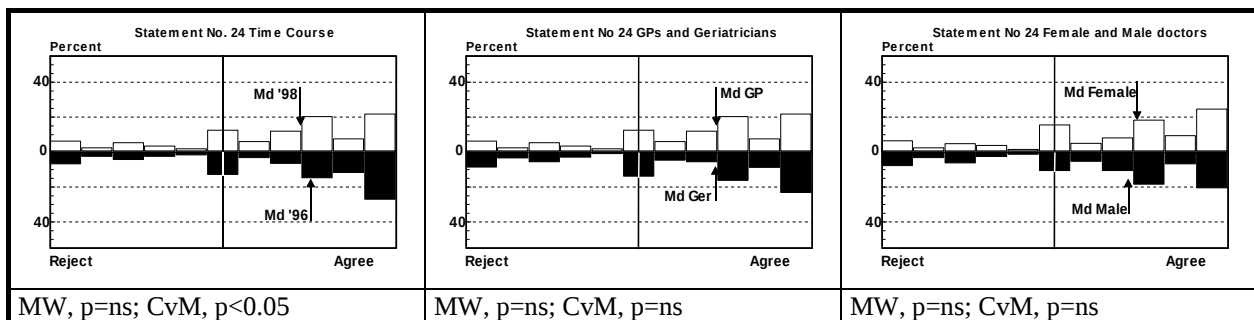


Figure A24. "It is still acceptable to treat a patient with obscure neuropathy with vitamin B12 during 6-36 months and evaluate treatment efficiency by clinical parameters (e.g. performance, walking distance, reappearance of vibration sense or reflexes, reduction of sensory loss, reduction of hair loss, reduction of muscular pain)"