Introduction

In April 2002, the Swedish Government appointed a Special Investigator to propose measures aimed at boosting knowledge of health problems relating to amalgam and other dental materials. The Investigator's duties also included reviewing current regulations concerning individuals' scope for having their dental fillings removed at a subsidised price, and proposing measures to improve care and consideration for patients who associate their symptoms with dental materials.

The Investigator submitted a final report (in Swedish) to the Minister for Health and Social Affairs, Lars Engqvist, on 3 June 2003. Enclosed with the report were annexes that made up part of the documentation compiled by the Commission. One of the annexes is an account of the past five years' scientific publications concerning amalgam, mercury and health, including a risk analysis in terms of environmental medicine. The author of this report is Maths Berlin, a Professor Emeritus of Environmental Medicine.

An English translation of this internationally acclaimed annex is published here, with a summary of the final report.

Summary

The use of amalgam as a dental-filling material has been discussed in the *Riksdag* (Swedish Parliament) since the early 1980s. The reason is that many patients who have associated their pathological symptoms with amalgam have felt they have not been taken seriously in the healthcare sector. Accordingly, their perception is that they have not received the treatment to which they considered themselves entitled.

Amalgam is controversial as a filling material because of the risk of side-effects. The debate shows that researchers in the field have disagreed concerning the health risks of amalgam. This disagreement has related, for example, to the quantity of mercury that leaks from amalgam fillings and the mercury levels deemed capable of affecting individual amalgam bearers' health.

Over the past few decades, the National Swedish Board of Health and Welfare has been repeatedly commissioned by the Swedish Government to compile research findings in the field and propose healthcare programmes. Back in the early 1980s, the Board drew up recommendations on healthcare programmes etc for this group of patients. Since then, its general recommendations have been issued and revised several times.

The Riksdag and the Government decided in 1994 that amalgam should be phased out. In 1999 the decision was taken that subsidies would be granted for amalgam fillings by means of reduced charges for dental care.

There has been a marked decrease in the use of amalgam in Sweden. However, this dental-filling material has still not been entirely phased out. At the same time, side-effects caused by other dental materials have been noted.

Great efforts have thus been made to improve the care and consideration these patients receive. Nonetheless, those who relate their symptoms to amalgam or other dental materials still feel that

they are meeting a nonchalant response in the care services, and not receiving the treatment they believe that they need.

These patients, who often have a long history of illness, have undergone many courses of treatment with only a limited effect on their symptoms. Many have, in due course, had their fillings removed. In some cases, they have reported mitigation of their symptoms as a result.

This is the background to the Government's appointment of a Special Investigator to propose measures aimed at boosting knowledge of health problems relating to amalgam and other dental materials, and to improve care and consideration for patients who associate their symptoms with such materials.

The Commission's assignment

The Commission's directives are headed *Consideration for, and investigation and care of, people who associate their symptoms with dental materials etc* (Dir. 2002:60). Under these directives, the Commission is assigned to propose measures 'aimed at boosting knowledge of health problems relating to amalgam and other materials'. The assignment includes reviewing current regulations concerning individuals' scope for having their dental fillings removed at a subsidised price.

The Commission's task also includes investigating how information about the care provided, the consideration these patients receive and side-effects caused by dental materials is disseminated to healthcare staff. If necessary, the Commission is to propose measures to improve knowledge.

Major research over the past five years is to be reported and, where possible, the scale of the health problems ascribed to dental materials assessed.

The Commission is to propose allocation of the SEK 35 million granted by the Government to improve knowledge of amalgam and other dental materials.

In September 2002, the Commission issued an interim report proposing a grant of SEK 15m to boost knowledge of amalgam and other dental materials. In December 2002, pursuant to the Commission's proposals in this interim report, *Ill-Health Due to Dental-Filling Materials* (SOU 2002:76), the Government resolved to

grant these funds to the Centre for Metal Biology, a foundation in Uppsala,[1] for its activities.

The Commission's discussions and proposals

The Commission has striven to compile wide-ranging documentation of existing knowledge about the issues to which its assignment relates. An account of this material is given in the report and a number of annexes, and forms the basis of the Commission's discussions and proposals.

Background

The material collected by the Commission shows that many patients still feel that they are not taken seriously by the healthcare services when they attribute their problems to dental materials. Many testify that they are diagnosed as suffering from mental disorders and treated nonchalantly; many have difficulties in obtaining the care they believe they need. Many of them are, moreover, severely ill and have been so for a long time. Having the material in their dental fillings replaced is seen as a last possible means of regaining their health.

It is also evident from the Commission's documentation that there is a need for improved knowledge about risks of side-effects from dental materials. This also applies to diagnosis and treatment of such side-effects. In addition, clinical research and development are needed to devise more effective diagnostic and treatment methods.

In terms of dental-filling materials in the population, amalgam still predominates. The Commission's documentation shows that 74 per cent of the adult inhabitants of Sweden still have amalgam in their mouths, often in combination with other materials.

As for the materials used today, the picture is different. Composites are the group of materials used most, but gold alloys, ceramics, glass ionomer cements and amalgam are also used.

[1] Translator's note. These funds were granted for further evaluation of data concerning patients and for development of diagnostic methods and treatment plans to enhance knowledge of health problems related to amalgam and other dental materials, according to the plan drawn up by the Centre for Metal Biology in Uppsala (Government Decision, 19 December 2002).

The use of amalgam has decreased sharply, according to data reported by the National Board of Health and Welfare and the Federation of Swedish County Councils. However, one-fifth of adults still report that they have been given amalgam fillings in the past two years, according to a survey ordered by the Commission.

The Commission has also ordered a report on the past five years' published research results concerning amalgam, mercury and health, including a risk analysis in environmental medical terms This task was entrusted to Maths Berlin, a Professor Emeritus of Environmental Medicine.

Professor Berlin reports that researchers have been able to show effects of mercury at lower concentrations than before. The conclusion he draws is that 'the safety margin that it was thought existed with respect to mercury exposure from amalgam has been erased.'

State of knowledge

Based on its risk analysis in terms of environmental medicine and its account of the current state of research, the Commission considers that there are compelling reasons to suspect that, in sensitive individuals, amalgam can cause or contribute to pathological symptoms.

With reference to the precautionary principle, the Commission therefore deems it advisable for the Government and Riksdag to consider further measures to speed up the implementation of its objectives for the phase-out of amalgam in dental care. Environmental considerations, too, point in this direction.

Proposed allocation of research funds

The Commission finds that clinical research is necessary to afford knowledge of how side-effects of dental materials can be efficiently diagnosed, and to determine the relevance of various treatment methods. Accordingly, ascertaining the prevalence of these ailments in the population should be feasible.

The Commission considers that wide-ranging collaboration between researchers and the Swedish county councils' healthcare services is required to bring about efficient clinical research. The

Commission also points to the need for follow-up studies of the health of people who have their fillings replaced under Sections 6 and 7 of the Dental Care Ordinance.

The Commission proposes that the Swedish Research Council or a similar institution be assigned to devise a detailed, coherent research programme on the theme of *dental materials and health — diagnostics and treatment*, and that research funds of up to SEK 18m thereafter be announced and distributed. The Commission considers that the patients' organisation should be represented in the task force that distributes these funds.

The Commission also proposes that the organisation that has distributed the research funds should hold seminars and conferences to disseminate the findings of this research to healthcare staff involved in clinical work.

Care and consideration

The Commission's directives state that 'patients who associate their ailments with amalgam fillings often feel that they receive inadequate consideration in the healthcare services'. This is confirmed by, for example, the roughly 50 letters received by the Commission, the questionnaire survey among members of the Swedish Association of Dental Mercury Patients and other material that the Commission has studied.

The Commission believes that it would be advantageous to collect in regional resource centres, for investigation and treatment, all patients with a wide range of symptoms and pathological symptoms that are difficult to diagnose. This would afford greater scope than is currently available for the healthcare staff involved to specialise in treating these patients. It would also provide a sufficiently large patient base to permit evaluation of various treatment methods.

The Commission considers that, in every region, there should be at least one unit with advanced and varied skills in the investigation and treatment of these patients. A unit of this kind should serve as a healthcare resource, with the function of developing diagnostic and treatment methods and responsibility for in-service training of staff in healthcare and dental services in the region concerned.

The Commission proposes no organisational arrangements. Instead, it considers this a matter on which the individual county

councils should decide. There are already several models for such units in Sweden, and these are mentioned in the report.

Irrespective of which model is chosen, concentrating investigation and treatment of this patient group in units of the type proposed should be worthwhile in macroeconomic terms. These patients, after all, cost a great deal in the form of recurrent care inputs, sickness benefit, etc.

The Commission also notes that there is a need for dental surgeries where highly sensitive patients can be treated.

The Commission takes note of the national programme concerning the healthcare services' response to people with disabilities. This programme is to form the basis of in-service training for healthcare staff at county councils and municipalities. The purpose of this training is to improve consideration for people with disabilities throughout the public sector.

The Commission assumes that, in their staff in-service training, the county councils will also raise the specific issues relating to encounters with patients who suffer from long-term, complex illnesses that are not readily diagnosed.

The Commission also mentions the role of the municipal patients' advisory committees in providing support and help for this controversial group of patients in their contacts with the healthcare and dental-care services.

Proposed addition to the Higher Education Ordinance

The Commission proposes that the account in the Higher Education Ordinance of objectives for the University Degree in Dental Surgery be supplemented by requirements concerning knowledge of dental materials and how they affect the oral cavity and the environment.

The Commission believes that doctors, dentists and other healthcare professionals should, in their training, be given more knowledge than they are today concerning side-effects of dental materials and consideration for patients who associate their symptoms with dental materials.

Current rules concerning subsidised filling replacement

The Commission's tasks include investigating the reasons why the county councils have applied the provisions in Sections 6 and 7 of the Dental Care Ordinance differently, and why relatively few people have had their fillings replaced under these regulations to date. This task also includes considering whether the regulatory system should be amended to prevent the regulations from unnecessarily impeding filling replacement among patients in this group.

Section 6 of the Dental Care Ordinance regulates scope for subsidising replacement of dental fillings occasioned by allergy and/or changes in the mucous membrane adjacent to fillings. Section 7 relates to the replacement of fillings as part of a programme of medical rehabilitation in the event of chronic pathological symptoms. There is no need to demonstrate any connection between these pathological symptoms and dental-filling materials in order for patients to receive subsidised replacement under Section 7. However, for this subsidy to be approved, there must be a plan of investigation and treatment, drawn up jointly by the physician and dentist who are to provide the treatment.

In its report, the Commission has given an account of assessments and views of how the regulatory system is currently being applied. These have been put forward by the National Board of Health and Welfare, the Federation of Swedish County Councils, the patients' organisation and individual patients. The Commission has also analysed how far the present system is compatible with the rule of law.

The Commission holds the view that the lack of a detailed governmental set of regulations with clearly worded provisions may be a key part of the explanation for the problems that have been noted in various evaluations of subsidised dental care in Sweden.

Proposed amendments to the Dental Care Act and Dental Care Ordinance

The Commission presents proposals for amendments to clarify and simplify both the Dental Care Act and the Dental Care Ordinance.

One key proposal is that the National Board of Health and Welfare should be authorised to issue further regulations on such

matters as the replacement of dental fillings. The amendments proposed by the Commission presuppose that such regulations are issued.

The Commission has carefully considered the question of whether, for reasons relating to the rule of law, people should be enabled to appeal to an administrative court against a county council's decision. The Commission finds that this option is worth considering. However, such discussions should take place in a concerted fashion for all groups affected by the Dental Care Ordinance. The matter should therefore be discussed in conjunction with a major overview of the Ordinance.

The Commission's proposals for clarifying the governmental regulations should mean that they are applied in a more uniform and predictable way in the future. This concerns such matters as applications for replacement of dental fillings.

At present, the provisions concerning replacement of dental fillings in Sections 6 and 7 of the Ordinance have no formal backing in the Dental Care Act. Insertion of a new Section 8b into the Act is therefore proposed. This should clarify the county councils' responsibility for providing dental care for those who need particular support for replacement of dental materials owing to their 'deviant reactions to such materials or as part of care and treatment for lasting pathological symptoms'. Section 15b proposes an addition to the effect that such dental care should be covered by provisions concerning charges for care in the open healthcare services.

This amendment would make it possible for 'Replacement of dental fillings' to become a special category in the Dental Care Ordinance.

The Commission proposes that Sections 6 and 7 be combined and made terminologically consistent. The term 'medical rehabilitation' should be replaced by the phrase 'care and treatment' throughout.

The Commission also proposes that not only replacement of dental fillings, but also replacement of other dental materials, should be eligible for subsidies. This would involve a return to the situation before the reform of dental care, when compensation was paid by the Social Insurance Office on the basis of dental-care charges. In the Commission's view, the National Board of Health and Welfare should define, in its regulations, what is meant by 'other dental materials'.

The Commission proposes that the Dental Care Ordinance should clearly state the scope for obtaining subsidised dental care, without any connection between symptoms and dental materials being ascertained, when dental care is provided as part of the care and treatment given for long-term pathological symptoms.

It is proposed that the requirement of an investigation and treatment plan in the present Section 7 be abolished. This is the provision that has caused most problems in the application of this statute, and been most difficult to comply with.

The Commission proposes that this provision be replaced by a requirement of a preliminary assessment of the dentist's treatment proposal under Section 10, and by a requirement that a registered doctor should issue a medical certificate.

The requirement in Section 10 that the dentist's treatment proposal be subjected to a preliminary assessment is currently laid down in Section 6, but not in Section 7. The Commission considers that the proposed amendment would make the Ordinance more consistent.

The Commission also points out that it is important for an application for preliminary assessment to make it clear that it is the individual patient who is the applicant, or who has instigated the application, since the issue is one of a financial benefit for an individual recipient.

Under the proposal, the medical certificate should make it clear that the patient is being investigated for his or her long-term pathological symptoms, and that there are no medical reasons why dental materials should not be replaced as part of the patient's care and treatment. The Commission proposes that special forms for such certificates be designed, for nationwide use.

The Commission also finds that there are, at present, no established methods of determining whether a patient's health will improve as a result of filling replacement. The doctor issuing the certificate can therefore, in general, not be expected to possess any specialist knowledge that would prompt a recommendation that the fillings be replaced. In general, the initiative is therefore taken by the patient. For this reason, the Commission proposes that the medical certificate should state:

- who took the initiative for the certificate
- that the patient has ailments that require regular contact with a doctor, and that there are no medical obstacles to replacement

of the patient's fillings (such as some other severe illness that may become worse as a result of the replacement)
- that there is an agreement on follow-up after the replacement.

The Commission considers that physicians' professional responsibility includes issuing certificates in accordance with the provisions of the Dental Care Ordinance. The same applies to dentists who make applications for preliminary assessments and thereafter carry out replacement of fillings.

The Commission refers to the provisions concerning certificates that are contained in various laws and regulations, and that apply to all healthcare professionals. These are described in detail in Chapter 4.

The Commission has considered the option of entirely abolishing the requirement of preliminary assessment of dentists' treatment proposals when it comes to measures according to the present Sections 6 and 7. The requirement of preliminary assessment applies to several other groups that are covered by the Dental Care Ordinance, and the Commission therefore considers that this issue, too, should be discussed in conjunction with a comprehensive overview of the entire Ordinance. The matter should be brought to the fore again in a future evaluation of the Swedish county councils' subsidies for dental care.

The cost of all subsidies of dental care provided in 2001 as part of treatment for illness was SEK 179 million. Of this sum, SEK 17.6m was used for subsidising filling replacement under Sections 6 and 7 of the Dental Care Ordinance. The cost of subsidising Section 7 alone was SEK 4.5m.

The Commission considers that the proposed amendments may entail subsidy increases in the range of SEK 1–2 million. In particular, it is subsidised replacement of dental fillings under the present Section 7 that will be affected by the proposals.

Discussions are currently in progress between the central government and the county councils concerning future compensation for dental-care subsidies. The Commission's view is that the parties concerned should be able to note the need for a higher compensation rate for subsidisation of 'replacement of dental fillings and other dental materials' as a result of the Commission's proposals.

Improved supervision of dental materials

There is an extensive system of regulations covering medical devices and products that include dental materials. The system entails certification requirements for certain products, a requirement concerning information from the manufacturer and a requirement that the user should report deviations to the manufacturer and the Swedish Medical Products Agency. The Swedish Environmental Code also imposes certain requirements on dental materials and their handling at dental clinics. A detailed account of this matter is given in the report.

The Swedish Medical Products Agency and the National Board of Health and Welfare exercise supervision under the Medical Devices Act and the regulations connected with this Act. The municipalities and the National Chemicals Inspectorate exercise supervision under the Environmental Code.

The Commission considers that supervision under this extensive regulatory system, where dental materials are concerned, should be made more efficient. The Commission does not rule out the necessity of a comprehensive overview of the same, in order to improve control and supervision of dental materials and other matters.

The Commission's discussions have included the pros and cons of joint quality requirements in the purchase of dental products, aimed at accelerating the trend towards improved information about side-effects, more detailed declarations of contents and more products that have undergone clinical trials.

Another option noted by the Commission is that of voluntary commitments concerning inspection of how dental materials are marketed and information is given to patients about various materials and the risks, if any, of side-effects.

Proposed group with the function of monitoring developments

Finally, the Commission proposes that the Government should appoint a group comprising representatives of the parties concerned, with the function of monitoring, over the next few years, developments in the areas dealt with by the Commission. The group should include spokesmen for the patients concerned, the principals of healthcare and dental care, professional practitioners, the research community and the education sector, and also for the

government agencies involved. The group's tasks should include serving as a preparatory body in matters dealt with by the Commission. Another task should be to arrange seminars and hearings with representatives of healthcare, research, education and patients concerning the application of the Dental Care Ordinance, the healthcare sector's response to patients, developments in education and research, etc. The Commission proposes that up to SEK 2 million be made available for this group's activities.

It is the Commission's hope that the issues of amalgam and other dental materials that have now been considered within the framework of its assignment will not need to be investigated further. The aforesaid special group, comprising representatives of the parties concerned and engaged in following trends and developments in this field, should be a step in the right direction.

Contents

The Dental Material Commission — Care and Consideration

'The Dental Material Commission — Care and Consideration' assigned Maths Berlin, in autumn 2002, to report on the past five years' research literature on amalgam and the health hazards, if any, of mercury.

Maths Berlin is a Professor Emeritus with long experience of the effects of mercury on animals and humans. He chaired the WHO Task Group on Environmental Health Criteria for Inorganic Mercury (WHO Environmental Health Criteria 118, 1991) and a similar group with the function of drawing up health criteria for methylmercury.

Professor Berlin compiled the environmental medicine risk analysis of mercury and amalgam issued by the Swedish Council for Planning and Coordination of Research (FRN) in 1998 (FRN, Report 1998:22). This risk analysis was based on literature published between 1993 and November 1997. The present risk analysis builds further on this material, and analyses literature published between November 1997 and November 2002.

1. Background

In April 2002 the Swedish Government appointed a Special Investigator to propose measures to boost knowledge of health problems relating to amalgam and other dental materials, and to improve care of patients who associate their symptoms with such materials. The directives for the Commission emphasise that the Special Investigator should assess the knowledge situation with respect to such health problems and pinpoint areas on which further studies should focus. The Investigator was also assigned to report on key research in recent years, focusing on the past five-year period.

The author was assigned by the Investigator to summarise and evaluate research findings, regarding the environmental medical aspects of exposure to mercury from amalgam, that were published during the period from November 1997 to November 2002. The summary is to continue and supplement the risk analysis that was carried out for the Swedish Council for Planning and Coordination of Research in 1997.

1.1 Data collection

The task of collecting relevant publications was conducted according to the same principles as in 1997. A Medline search for 'mercury' yielded 3,600 references. From these, 936 references of conceivable relevance were selected. After abstracts and summaries had been studied, just over 700 references remained to be read and assessed, and this activity generated an additional number of secondary references of importance to the assessment.

Jointly with the Swedish Research Council, the Commission held a seminar to which Swedish mercury researchers were invited.[1] These were briefed on the key features of the past five years' research findings and my assessment of the same. The results were discussed, and an opportunity for commenting on the presentation and proposing additions was provided. A preliminary report was

[1] The seminar, at Lastberget near Stockholm on 6 February 2003, was attended by Maths Berlin (rapporteur), Gunnar Bergenholtz (moderator), Göran Möller, Per Hultman, Marie Vahter, Lars Friberg, Karin Warfvinge, Jan Marcusson, Staffan Scherfving, Gunnar Nordberg, Mats Hanson, Ulf Lindh, Jan Ekstrand, Sven Langworth and Per Dalén. Certain members of the Dental Material Commission were also present: Helena Starup (chairman), Mariana Blixt, Bo Jordin, Christer Malmström, Lars Sjödin, Bengt Järvholm (expert), and Ann-Marie Lidmark and Ann-Kristin Myrman (secretaries).

then drawn up and dispatched, along with a request for written comments. Based on the opinions received, this report was completed and submitted to the Special Investigator.

The present report starts by summarising the results from the 1997 risk analysis (FRN Report 98:22). An account of the new research findings follows. Finally, these are summarised, along with an evaluation of the risks and hazards entailed by amalgam mercury and proposals on how to manage the same.

2. Summary of the 1997 risk analysis

In 1997, the Swedish Council for Planning and Coordination of Research was commissioned by the Swedish Government to review and extend knowledge of the health hazards, if any, of mercury from amalgam. I was then assigned to carry out a review of literature, in the form of published research findings, on the subject. This report was written as a continuation of the 1997 report.

In the 1997 risk analysis, it was found that:

- The WHO estimate of amalgam bearers' daily mercury uptake was 3–7 μg, which was the best estimate available at the time. This uptake gives rise to urinary mercury secretion of around 5 μg/g creatinine. However, WHO found wide variation between individuals.
- In subsequent studies of amalgam bearers, uptake of up to 100 μg daily has been observed in extreme cases. The individuals concerned had urinary secretion of around 50 μg/g creatinine. This secretion rate is as high as, or higher than, the lowest exposure shown to provoke clinically demonstrable symptoms in mercury-exposed workers.
- There are no scientific grounds for assuming that the prevalence of clinically demonstrable effects of mercury exposure from dental amalgam exceeds 10 per cent.
- No known epidemiological population study has demonstrated any adverse health effects in amalgam bearers.
- Mercury is a potent toxin that affects the basic functions of the cell by bonding strongly with sulfhydryl and selenohydryl groups on albumen molecules in cell membranes, receptors and intracellular signal links, and by modifying the tertiary structure.

- The structure of albumen molecules is genetically determined, and this leaves ample scope for genetic polymorphism to manifest itself in varying sensitivity and types of reaction to mercury exposure.
- It is probable that, besides local hypersensitivity reactions, mercury in amalgam fillings exerts side-effects just like most potent pharmaceuticals. Some support for this conclusion is to be found in clinical observations reported to date. At a rate that is probably below 10 per cent, however, these side-effects cannot be demonstrated by means of population-based epidemiological studies.

Mercury is thus a multipotent cytotoxin that intervenes in the primary processes of the cell. This creates scope for a broad spectrum of possible side-effects. The analysis performed in 1997 identified the following health risks from mercury in dental fillings:

- Risk of impairment in the functions of the central nervous system.
- Risk of impairment in kidney function.
- Risk of impairment in the immune system.
- Risk of impairment in foetal development, especially development of the nervous system.

The presentation below is an account of the past five years' research publications, in so far as these may prompt us to supplement or modify the assessments and conclusions contained in the 1997 risk analysis.

3. New research findings

3.1 Studies in molecular biology

In the past five years, several studies of the effects of mercury at cell level have been conducted and published. These studies were performed on cell lines in cultures or suspensions of various origins. Intracellular measurement of mercury concentration has not, however, been feasible. The dose has therefore been represented by the estimated concentration in the medium concerned. Media usually contain proteins and other molecules that can bind mercury. It is therefore impossible to gauge any cellular concentration.

Nevertheless, the estimated concentration in the medium is, in many studies, very high. These concentrations are both non-physiological and, in the amalgam context, unrealistic. Publications referring to medium concentrations of mercury exceeding 1 μM have therefore, as a rule, been regarded as irrelevant and excluded from this summary.

Modified redox potential

One hypothesis often propounded in the literature is that mercury is toxic because it induces production of free oxygen radicals and modifies the redox potential of the cell. Several mechanisms for this effect have been proposed (Ercal et al. 2001) and are reviewed in brief below.

Olivieri et al. (2000) reported that mercuric chloride ($HgCl_2$) in a concentration of 50 μg/l reduces the cellular content of glutathione by 30 per cent in neuroblastoma cells, thereby decreasing their reductive capacity. Another observation was an increased release of ß-amyloid (Aß) peptide and elevated phosphorylation of tau protein.

Mahboob et al. (2001) found that mice exposed to $HgCl_2$ (0.8 μg in two peroral doses per week, for two weeks), which showed no influence on weight increase or food intake, had increased lipidoxidation in the kidneys, testicles and epididymides, and an elevated concentration of glutathione (GSH) and superoxide dismutase in the testicles. Administering a dose 10 times as large resulted in a significant reduction in weight increase, in GSH concentration in the epididymides, and also in the activity of glutathione disulphide reductase (GR) and glutathione reductase (GPx) in the kidneys and epididymides.

Goering et al. (2002) exposed rats to 1.2 and 4 mg/m^3 of mercury vapour for two hours daily during 11 days. The rats showed no clinical or histopathological signs of toxic influence. A dose-related increase in the mercury concentration in the brain and kidneys and a 30 % increase in free oxygen radicals in the frontal cortex at a dose of 1 mg/m^3 were observed. A statistically significant decrease in GSH concentration and GPx activity was seen in the kidneys at a dose of 2 mg/m^3. No such change in the brain was detectable at any dose. The authors' conclusion is that neither oxidative stress nor changes in GSH concentration and activity of an-

tioxidant enzymes play any significant part in the toxic effect of mercury vapour on the brain and kidneys.

Wolfreys and Oliviera (1997) found that the increase in sensitivity to IgE stimulation in the peritoneal mast cells of mercury-sensitive rats is due to intracellular increase of free oxygen radicals produced by mercury. Mice exposed to mercury vapour, at 0.5 mg/m^3 for two hours, showed an elevated mercury concentration in motor neurons in the spine and signs of oxidative damage to DNA (Pamphlett et al. 1998).

The difference in results may be explained by the fact that Goering et al. determined the degree of oxidative stress in whole tissues, while the other authors determined oxidation in individual cell types.

In determining mercury concentrations in amalgam bearers' saliva, Pizzichini et al. (2001, 2002) found a significant correlation between mercury in saliva and the number of amalgam fillings in both men and women. Determination of total antioxidant activity (TAA) in saliva and plasma showed a significant inverse correlation between mercury concentration in plasma and TAA in both genders. In addition, antioxidant activity showed a significant negative correlation with mercury concentrations in women's saliva. In men, no such correlation was found.

The question of the importance of oxidative stress in causing an early toxic effect of mercury exposure is still uncertain. Nevertheless, it is difficult to believe that this effect alone could explain the differences in toxicity for various organs and species to which the mercury gives rise.

Phosphorylation and intercellular signalling

It has been suggested that mercury in low concentrations may affect phosphorylation and thereby intercellular signalling. Huang and Narahashi (1997) used voltage-clamp technology to study the effect of 0.5 μM $HgCl_2$ on GABA-induced currents from dorsal root ganglia in rat neurons. They found that mercury increases GABA-induced currents, and attributed this effect to an inhibition of protein kinase A (PKA).

Rosenspire et al. (1998) found that 0.13 μM $HgCl_2$ boosted phosphorylation of tyrosine in proteins from B-cell lymphoma cells from mouse. The same research group (Mattingly et al. 2001)

reported that 0.6 μM $HgCl_2$ inhibits T cell-receptor-mediated activation of RAS in Jurkat cells, which are a human T cell line. Königsberg et al. (2001) studied the effect of 0.5 μM on mitochondrion function in a foetal liver-cell line. They found ultrastructural modification of the mitochondria. The respiratory functions of the cell remained intact, but they found that the modification had involved uncoupling from signal links in the cell.

Cytoskeleton of the nerve cells

Mercury inhibits the development of, and breaks down, cytoskeleton structures in nerve cells. This was shown by Pendergrass et al. (1997) when they made rats inhale mercury vapour for 14 days. At approximately 0.35 μg/g mercury in brain tissue, bonding of GTP to tubulin was inhibited. This process is necessary for polymerisation of tubulin, which in turn is a key component of the cytoskeleton.

The same group of researchers, Leong et al. (2001), added $HgCl_2$ to cultures of neurons from a snail with growing nerve germs. They were able to show that concentrations of $HgCl_2$ below and close to 0.1 μM inhibit the growth of nerve germs and also cause retrograde degradation of the cytoskeleton in nerve cells.

Apoptosis in nerve tissue

Monnet-Tschudi (1998) studied the incidence of apoptosis (programmed natural cell death) in cultures of foetal rat brain. She found that a concentration of 1 nM of $HgCl_2$ speeds up spontaneous apoptosis in immature cultures. A concentration of methyl mercury a thousand times higher was required for the same effect. In more differentiated cultures without spontaneous apoptosis, no effect was observed. A high proportion of the apoptotic cells were astrocytes.

Retinal pigment epithelial cells

Toimela and Tähti (2001) studied the effect of $HgCl_2$ on cultured retinal pigment epithelial cells from pig and from a human cell line. They observed that 0.1 μM mercury reduced glutamate uptake by

some 25 per cent. They interpreted this effect as due to inhibition of protein kinase C (PKC).

3.2 The nervous system

Knowledge of the mechanisms of neurotoxic effects exerted by mercury vapour is highly deficient. Perhaps as a result, we lack specific indices of nervous-system impairment caused by mercury vapour.

Data from animal experiments

Exposure to mercury vapour in rat (Warfvinge et al. 1992), mouse (Warfvinge 1995) and monkey (Warfvinge et al. 1994; Warfvinge 2000) causes accumulation of mercury in the brain and spinal cord. Mercury was often concentrated in neurons, especially motor neurons and astroglia cells. With toxic exposure, loss of Purkinje cells and granulocytes in the cerebellar cortex arises in rat (Sörensen et al. 2000). Whether similar changes arise in other parts of the brain has not yet been investigated by means of modern methods. Myelin sheaths of dorsal nerve roots also manifest changes (Schionning et al. 1998).

Accumulation in the retina

The retina of the eye accumulates mercury when there is exposure to mercury vapour. Mercury remains in the retina for a very long time — often for years. Accumulation of mercury is seen, in monkeys, in the inner portion of the retina, in pigment epithelial cells and capillary walls (Warfvinge and Bruun 2000).

Brain development and toxicokinetics in the foetus and mother

During the past five-year period, there have been few publications elucidating the effect of mercury vapour on foetal development. Studies clarifying its effect on the growing brain and foetal development in general are entirely lacking. According to information

received, however, several major epidemiological studies are under way in the USA.

A German prospective study of 3,946 pregnant women was carried out. The women were interviewed regarding mercury exposure at the workplace. The mothers-to-be exposed to mercury or mercury compounds showed a significantly elevated risk of giving birth to babies who were small for their gestational age (Seidler et al. 1999). Nevertheless, the exposure criteria were dubious: they mean that other exposure to chemical substances also took place. Nor can chance significance be excluded.

Studies of the toxicokinetics of mercury in humans, including pregnant and lactating women, have been conducted by Swedish researchers. These studies confirm the picture previously obtained from animal experiments, and have provided quantitative information. The mother's amalgam fillings are reflected in the quantities of inorganic mercury in the placenta (Ask et al. 2002), in umbilical-cord blood, in breast milk (Vahter et al. 2000) and in amniotic fluid (Luglie et al. 2000).

The conclusion from the information available is that the mercury contained in breast milk is not a substantial source of infants' mercury exposure (Oskarsson et al. 1996; Drexler & Schaller 1998).

Amalgam removal involves a rise of some 30 per cent in plasma levels of inorganic mercury. After a phase of rapid decline, the plasma level decreases with a half-life of around 46 days (Sandborgh-Englund G 1998).

Neuropsychological tests

In occupationally exposed workers, it has been clinically feasible to demonstrate changes in brain potentials induced by visual stimulation and changes in conduction velocity in peripheral sensory nerve fibres. This result suggests that both the central nervous system (CNS) and the peripheral nervous system (PNS) are affected. These effects arise at relatively high exposure levels (Urban et al. 1999). At lower exposure levels, impairment of cognitive, sensory and motor functions occurs. Mood may also be modified. These changes have been quantified using batteries of neuropsychological tests.

At a level of mercury exposure caused by one of their duties, 13 men (mean age: 45 years) were exposed to mercury vapour for two to four weeks. After the exposure ceased, the men's blood mercury concentration averaged 48 μg/l of blood (corresponding to approx. 150 μg/g creatinine), with a range of 21–84 μg/l. One year after exposure had ceased, all the men were subjected to a battery of neuropsychological tests, and compared with a control group of 13 non-exposed workers.

Compared with the control group, the exposed group displayed cognitive deficits in terms of motor coordination, rapid reception of information with and without motor elements, verbal capacity, verbal memory, visual problem-solving and comprehension. The men exposed also had more emotional problems, such as an increased focus on bodily functions, depression, anxiety and being more socially withdrawn (Haut et al. 1999).

With batteries of neuropsychological tests, several studies of populations that are occupationally exposed to mercury vapour have been conducted. These studies have had two main purposes: to identify the lowest exposure level that gives rise to demonstrable health effects, and to investigate how far the health effects that have arisen are reversible if exposure ceases.

Early 2002 saw the publication of a meta-analysis of 44 epidemiological studies of populations that are occupationally exposed to mercury vapour. Twelve of these studies were included in the analysis, which comprised 686 exposed persons and 579 controls. In nine neuropsychological performance parameters, statistically significant differences between exposed persons and controls were found, with a dose-response association for exposure corresponding to 18–34 μg Hg per litre of urine (Meyer-Baron et al. 2002).

In an Italian multicentre study of 122 workers exposed to mercury vapour and 196 controls, a statistically significant decline in motor performance and a significant decrease in blood prolactin concentrations were found, with a dose-response association. Mean secretion of mercury in urine was 10.4 $\pm$ 6.9 μg/l for the exposed subjects and 1.9 $\pm$ 2.8 μg/l for the controls (Lucchini et al. 2002).

Persistent effects of mercury exposure

In one American survey, the reversibility of symptoms induced by exposure to mercury vapour was studied. The survey covered 205

workers whose mean age was 71 years. Of these workers, 104 had been heavily exposed more than 19 years previously, with mercury secretion in excess of 600 μg/l urine. The other 101 workers had not been exposed. Conduction velocity in peripheral nerves was significantly correlated with cumulative mercury exposure, which suggests residual peripheral neuropathy. Motor co-ordination was also reduced to a statistically significant degree, with a dose-response association (Letz et al. 2000).

In a Norwegian survey of 75 chloralkali workers compared with 52 controls, a dose-related effect on attention capacity and visual-motor capacity was found 12 years after termination of exposure. This group's exposure to mercury was considerably lower than that of the above-mentioned American cohort. For the Norwegian workers, mean mercury secretion was roughly 100 μg/l urine during their work period (Mathiesen et al. 1999).

Alzheimer's disease

The question of whether mercury exposure from amalgam can cause Alzheimer's disease (AD) has been raised. This is because some in vitro studies have found effects of inorganic mercury on nerve tissue that resemble those seen in Alzheimer's.

In a study of 68 Alzheimer's patients and 33 controls, no significant difference was detected between the patients and controls in terms of mercury concentrations in the various parts of the brain. Nor was there any difference with respect to the presence of amalgam fillings (Saxe et al. 1999).

Another study involved a comparison of mercury concentrations in blood between 33 Alzheimer's patients on the one hand and, first, a group of 45 patients suffering from depression and, secondly, a group of 65 patients with a variety of non-psychiatric illnesses, on the other. The mercury concentrations were more than twice as high in the Alzheimer's patients as in both the control groups. Nevertheless, no association was found between elevated mercury concentrations and the presence of amalgam fillings (Hock et al. 1998).

3.3 The immune system and blood cells

Data from animal experiments

Substantial research inputs have been made over the past five-year period to survey the mechanisms underlying autoimmune reactions provoked by mercury in sensitive rat and mouse strains. These studies have essentially increased our knowledge; nonetheless, they have not succeeded in elucidating this complex phenomenon.

The effects of mercury on the immune system are governed by genotype, mercury dose and the status of the immune system concerned. Reactions to mercury vary between different bred strains and between species. Reaction intensity increases with the mercury dose, while there appears to be a dose threshold below which no reaction can be produced (Nielsen and Hultman 1999). In mercury-sensitive strains, too, the reactions decrease after a certain period of exposure (Roether et al. 2002).

If mercury-sensitive newborn rats are injected with $HgCl_2$, resistance to mercury arises. This suggests that the system can offset the stimulation of mercury (Field et al. 2000).

Amalgam fillings in the teeth of mercury-sensitive rats give sufficiently high mercury exposure to provoke an autoimmune syndrome with a rise of immunoglobulins in plasma and immunocomplex deposition in the kidneys (Hultman et al. 1998).

In animal experiments, mercury can modify the functioning of the immune system in various pathological states. Mice treated with injections of subtoxic doses of $HgCl_2$ are, for example, more susceptible to leishmaniasis infestation than untreated animals (Bagenstose et al. 2001).

Both mercury-sensitive and mercury-resistant mice show reduced immunity against malaria protozoa after injection of subtoxic doses of $HgCl_2$ (Silbergeld et al. 2000). In mice with a genetically conditioned tendency to develop the autoimmune syndrome systemic lupus erythematosus (SLE), development of the disease is accelerated if mercury is injected in subtoxic doses (Pollard et al, 2001). In mice with a genetic predisposition for diabetes (non-obese diabetic [NOD] mice), the development of diabetes is inhibited if subtoxic doses of $HgCl_2$ are injected (Brenden et al. 2001).

Lichen

One side-effect of amalgam fillings that is not particularly unusual is oral lichen. Larsson (1998) describes accumulation of mercury in the tissue affected, and accumulation of dendritic cells. Little et al. (2001) showed that a culture of human oral keratocytes, on exposure to subtoxic concentrations of $HgCl_2$ (10 μM), expresses ICAM-1, which in turn induces T cell binding, release of TNF- α and interleukin-8 and down-regulation of interleukin-1α. This induces activation of the immune system, which is not seen in experiments with cutaneous keratocytes.

Occupational exposure

Effects on the immune system of occupational exposure to mercury vapour have been studied in several surveys of worker populations. The workers were exposed to mercury levels below and at around the threshold value for permitted exposure, which corresponds to a urinary secretion rate of mercury of some 50 μg/g creatinine. These results were summarised by Moszczynski (1999). The studies reported statistically significant deviations in the number of cell elements, cytokine concentrations and immunoglobulin concentrations in the exposed workers. Nevertheless, these findings are contradictory: both stimulating and inhibitory effects were found to exist.

In a later study, 20 workers exposed to mercury vapour had mean urinary secretion of mercury of 45 μg/l. The study reported that the number of CD4+ and CD45RA+ and the total number of CD4+ T-lymphocytes were significantly lower than in the controls. The numbers of CD57+ and CD16+ NK (Natural Killer) cells were also found to be negatively correlated with the mercury concentration in urine (Park et al. 2000).

Another group of 19 workers exposed to mercury vapour had a mean urinary secretion of mercury of 9.7 $\pm$ 5.5 μg/l. In this group, Vimercati et al. (2001) found an inverse correlation between mercury in urine and the numbers of CD13+ and CD15+ leucocytes and NK cells. A reduced capacity for chemotaxis in polymorphonuclear leucocytes was also found. Loftenius et al. (1998) studied the effect of amalgam removal on mononuclear lymphocytes from 10 patients. They found no statistically significant

change in the number of cell types. However, they found a rise in IL-6 in plasma after 48 hours. The mercury concentration in plasma rose by some 10 per cent.

In 47 chloralkali workers with mercury exposure corresponding to 5.9 nmol/mmol creatinine, an increase in autoantibodies against myeloperoxidase and proteinase 3 was observed. This increase was correlated with the mercury concentration in urine (Ellingsen et al. 2000a).

Reduced enzyme activity in erythrocytes

Zabinski et al. (2000) reported that enzyme activity for several enzymes in erythrocytes — G-6PD, AchE, GR and SOD — was significantly reduced in a group comprising 46 chloralkali workers, with a urinary mercury concentration of 77 μg/l. Bulat et al. (1998) observed reduced activity for GPx and SOD in erythrocytes for a group of 42 chloralkali workers, with a urinary secretion rate of 23.2 $\pm$ 11.3 nmol/mmol creatinine.

In a group of 16 workers exposed to mercury vapour, reduced levels of glutathione and elevated catalase activity in red blood cells were observed. Mean urinary secretion of mercury in this group was 18.5 $\pm$ 8.8 μg/l (Queiroz et al. 1998).

Autoimmune diseases

The tendency of mercury to induce autoimmunity gives rise to suspicion that mercury may boost the risk of autoimmune diseases, such as multiple sclerosis (MS). In a Canadian case-reference study, this hypothesis was tested (Bangsi et al. 1998). The findings of this survey, which covered 143 MS patients and 128 controls, provided no support for the hypothesis. True, persons with more than 15 fillings showed an excess risk of 2.57 times the risk of getting MS among persons without fillings, but this difference was not statistically significant.

Similar results were obtained in an Italian survey comprising 132 MS patients and 423 controls (Casetta et al. 2001). A British survey of 39 female MS patients and 62 matched controls showed a significant correlation between the prevalence of caries and the risk of MS. However, no significant difference was found between the MS

patients and the controls in terms of how many amalgam fillings they had (McGrother et al. 1999).

Mercury-resistant and antibiotic-resistant bacteria

Results from experimental studies have aroused suspicions that release of mercury in the oral cavity could produce mercury-resistant bacterial flora and, by the same token, antibiotic resistance. In several surveys of humans, this suspicion has not found support. In a British survey of 83 children, half of whom had amalgam fillings and the other half of whom lacked them, no differences were found in the prevalence of mercury-resistant or antibiotic-resistant bacteria (Pike et al. 2002).

3.4 Kidneys

Understanding of the mechanisms whereby the kidneys absorb and secrete mercury has improved considerably, largely thanks to new methods in molecular biology. The current state of knowledge has been summarised in an article in *Pharmacological Reviews* (Zalups 2000).

In a cross-section study in Scotland, 180 dentists were compared with 180 academics at Scottish universities. Kidney disease was found to be ten times more common among the dentists (6.5 %) than in the controls. The dentists' mean urinary secretion was 2.58 nmol/mmol creatinine (Ritchie et al. 2002).

Among 47 chloralkali workers with a mean urinary mercury concentration of 5.9 nmol/mmol creatinine, secretion of N-acetyl-ß-D-glucosaminidase (NAG) was measured. The results showed that in those with mercury secretion that exceeded the mean for the group, NAG secretion was also elevated (Ellingsen et al. 2000a).

3.5 Thyroid and muscular atrophy

Ellingsen et al. (2000b) reported finding impaired thyroid function in a group of 47 chloralkali workers, whom they compared with 47 controls. The exposed workers showed a statistically significant rise in reverse T3 (rT_3) — a rise that was dose-related. The mean

urinary concentration of mercury was 5.9 nmol/mmol creatinine, with a range of 1.1–16.8.

Atrophy and capillary damage in thigh muscle were observed in five out of six workers in dental care who had a urinary mercury-secretion rate of 13–67 μg/l at the time of the biopsy. These changes may, according to the authors, have been induced by the effect of the mercury on the nervous system or on capillaries. There might also be a direct effect on muscle fibres (Nadorfy-Lopez et al. 2000).

3.6 Testicles

Exposure to mercury vapour causes mercury to accumulate in the testicles, where it is eliminated very slowly. Daily administration of $HgCl_2$ to mice in a dose that did not affect body weight caused a reduced sperm count, modified sperm morphology and lower fertility. It proved possible to offset this effect by administering vitamin E (Rao and Sharma 2001).

Monsees et al. (2000) studied the *in vitro* effect of $HgCl_2$ on Sertoli cells from rat. They observed that concentrations below 1 μM of $HgCl_2$ sharply reduced inhibin production. Clinical observations have prompted suspicions of associations between acrodynia (Pink Disease) and epididymis obstruction (de Kretser et al. 1998).

3.7 Polymorphism

During the five-year period under review, several case descriptions involving acute mercury exposure, with concentrations usually well above what may be expected from amalgam, have been published. These case descriptions have been published because the symptoms are unexpected. Mercury concentrations are documented with urine and blood figures, and the symptoms have subsided when the exposure ceased. Accordingly, there is no doubt that the high mercury concentrations genuinely caused the symptoms.

Besides oral lichen — which is sometimes combined with facial exanthema — the symptoms present have been a range of dermal syndromes, such as systemic contact dermatitis (baboon syndrome) (Alegre et al. 2000; Bartolome et al. 2000). Three cases of

nummular dermatitis, which were cured by amalgam removal, are described by Adachi et al. (2000) and Pigatto et al. (2002). In a review article, Britschgi and Pichler (2000) assert that mercury can induce acute generalised exanthematous pustulosis. In another review article, Boyd et al. (2000) summarise experience of skin diseases caused by mercury.

One article describes a five-year-old boy who, after massive mercury exposure, developed tics, extensive blinking, head-twisting and shoulder-jerking as his sole symptoms (Li et al. 2000).

There have also been descriptions of several cases where, in children with hypertension and elevated catecholamine secretion induced by mercury exposure, the symptomatology has resembled phaeochromocytoma (Laurans et al. 2001; Torres et al. 2000; Wössmann et al. 1999; Kosan et al. 2001). A 48-year-old man developed aspects of severe, acute polyarthritis (Karatas et al. 2002) as a result of massive mercury exposure. Dalén (2000) describes a historical case with symptoms suggesting gastroenteral influence.

The cases referred to above evince pronounced polymorphism in ways of reacting to mercury exposure. The conclusion is that the clinical picture of exposure to mercury vapour may vary greatly.

3.8 Gender differences

Knowledge of the dose-response association for exposure to mercury vapour and inorganic mercury compounds is derived mainly from epidemiological studies of occupationally exposed populations. The great majority of subjects studied have been men.

To permit conclusions to be generalised to the whole population, one must assume that sensitivity to mercury is equally distributed. There is well-founded reason to question support for such an assumption. Data from animal experiments do not show a consistent picture; but neither do they provide support for the thesis that men and women are equally sensitive to mercury.

In one study, 30 Sprague-Dawley rats received a daily dose of $HgCl_2$ by gastric tube, in doses from 0 to 10 mg/kg. The rats were killed after 14 days, and distribution and uptake of mercury were studied. No significant gender difference emerged with respect to signs of toxicity or concentration of mercury in various organs.

Previous studies of rats and mice have shown gender differences in the kidneys' uptake of mercury, but in divergent directions (Khan et al. 2001). In mice that had received intraperitoneal injections of $HgCl_2$ corresponding to 0.5mg/kg or been exposed to mercury vapour in low doses, gender differences were demonstrated. With autometallography, uptake of mercury in motor neurons was shown to occur to a larger extent among females than among males. Males were also found to accumulate more mercury in the kidneys than females (Pamphlett et al. 1997; Pamphlett and Coote 1998).

Hultman and Nielsen (2001) studied the importance of dose, gender and genetic composition in two mouse strains. They found that the same dose produced quantitative differences in mercury uptake both between the two strains and between the genders. This suggests differences in toxicokinetics between the genders and different strains. They also found that the concentration of mercury in tissue that is required for an autoimmune reaction to be induced varies between strains and the genders. This suggests variation in sensitivity to mercury between strains and between genders.

Data from humans are notably scant. One study was carried out in which diurnal variation in the kidneys' mercury secretion was investigated. No demonstrable diurnal variation in men, but significant diurnal variation in women, was found (Woods et al. 1998).

Barregård et al. (1999) determined mercury concentration in test biopsies from 36 kidneys donated for transplantation — half from men and half from women. Mercury concentration in the kidneys was statistically significantly higher in women than in men. As discussed above (3.1), TAA in saliva was found to be significantly inversely correlated with mercury concentration in saliva in women, but not in men (Pizzichini et al. 2001, 2002).

3.9 Side-effects and their incidence

'Side-effect' is a clinical pharmacological term relating to unintended repercussions over and above the therapeutic effect. In toxicology, reference is made to especially sensitive populations, who have a dose-response association and/or a way of reacting that significantly deviates from the majority of the population. These

deviant populations may be conditioned by genetic differences, age and gender differences or pathological states.

The fact that a person feels ill as a result of amalgam fillings may be due to various factors. It may be because the person perceives a connection between the symptoms and the oral cavity, or that the symptoms are connected with a dentist's manipulations. Alternatively, amalgam may be perceived as an explanation for malaise of a different origin, if a credible explanation is sought. Research has been carried out to find methods of distinguishing between these alternative explanations.

Clinical surveys

In a summary of just over 400 patients referred to Huddinge Hospital with suspicion of amalgam-related conditions, the authors consider that some 30 per cent of cases were attributable to diagnoses other than amalgam influence. These diagnoses included, for example, heart disease, chronic collagenosis, neurological disease and cancer; in the authors' opinion, these could explain the patients' condition. In other cases, there was speculation about the causes and it was found that the summary did not support the hypothesis that amalgam had contributed to the patients' pathological condition. The argument for this was that no connection between their symptoms and elevated mercury concentrations in their blood or urine were demonstrable (Langworth et al. 2002).

This survey supports the hypothesis that, among those who believe themselves to be suffering as a result of amalgam, the true cause is not always amalgam. However, it does not rule out the possibility that amalgam influence can be found in some of these persons. The diagnoses mentioned in this study include impaired thyroid function, oral lichen, kidney disease, fatigue, vertigo, somatisation tendency, depression and anxiety — all of which are symptoms that may be associated with mercury exposure.

A Swiss dentist followed up 75 of the 90 patients he had treated with amalgam removal according to the patients' own wishes. All the patients had psychoneurological symptoms or muscular and joint pains of various kinds. Sixty-eight per cent of the patients felt that they were much better at the time of their annual check-ups following the removal. Another 12 per cent felt better, 9 per cent

were slightly better, 7 per cent were unchanged and one of the patients felt worse after the removal (Engel 1998).

In a similar Swedish questionnaire survey comprising 445 patients of one dentist, the patients' amalgam fillings were removed because of prolonged, unexplained ailments. Here, the health of 80 per cent of the patients whose fillings had been removed was found to be good or better, while that of 11 per cent was unchanged and 9 per cent felt that it had deteriorated or were doubtful. More than half the patients stated that they had experienced symptoms in connection with having their fillings removed. These symptoms often began after a few days and commonly lasted about a week (Strömberg and Langworth 1998).

Provocation tests

One study was carried out in the form of provocation tests. Initially, an advertisement was placed in the daily press inviting people suffering from amalgam-related disease to apply. Of those who registered their interest, 39 were tested by being given gas to inhale through a mouthpiece for five or 10 minutes. The gas was blindly switched from each occasion to the next between pure air and air containing mercury. The mercury concentrations varied between 25 and 200 $\mu g/m^3$. Exposure occurred at intervals of two to three weeks. Each patient's symptoms were registered after every exposure occasion. In two persons, the results showed unequivocal mercury sensitivity, while suspected sensitivity was found in another two, although not with statistically significant results (Strömberg et al. 1999). The survey appears to be highly illuminating. The provocation dose corresponded, at its highest level, to the daily exposure dose for an amalgam bearer, or roughly one-hundredth of the permitted daily dose for an industrial worker. It is possible that optimal discrimination would have been increased a slightly higher exposure dose.

Allergy diagnostics with epicutaneous tests (patch testing) can sometimes, besides skin reactions, provoke systemic effects with such symptoms as headache, vertigo, fatigue and general malaise (Kunkeler et al. 2000; Inerot and Möller 2000). A group of 65 patients who had all reacted with intensified subjective symptoms in conjunction with amalgam removal, were subjected to provocation experiments by means of patch testing.

The tests were carried out blind, with a concentration of roughly 10 mg of metallic mercury, 4 mg phenylmercuric acetate and mercury-free substances. For a week after the skin application, the patients had to keep a log according to a questionnaire on their symptoms. Some reacted with increased symptoms of substances containing mercury, and were described as 'mercury-intolerant'. The patients who did not react were described as 'mercury-tolerant' (Marcusson 1996).

Neutrophils from 14 intolerant and 14 tolerant patients and 14 controls were tested. The cells were exposed to $HgCl_2$ and compared in terms of the release of superoxide. A statistically significant difference between tolerant and intolerant patients was observed. There was a correlation between the activity of superoxide dismutase (SOD) in lymphocytes and the symptom score, and also between superoxide formation and the symptom score for the mercury-exposed patients (Marcusson et al. 2000).

4. Risk analysis — definition of three new hazards

Not infrequently, progress in research raises more questions than it answers. Since 1997, three new health risks have emerged that, with reasonable suspicion, may conceivably be attributed to mercury from amalgam. These hazards involve influence on the retina of the eye, testicle function and thyroid function.

Suspicion of effects on the retina is founded mainly on the fact that mercury accumulates in the retina, with lasting retention especially in the pigment epithelium. Whether this mercury accumulation can contribute to the incidence of degenerative changes, such as retinal detachment or macular degeneration, cannot be assessed without further research.

In the testicles, too, accumulation of mercury takes place with lasting retention as a result of exposure to inorganic mercury. Clinical observations and experimental studies confirm that functional impairment may arise from exposure to mercury. Information on dose-response association is, however, lacking and amalgam risk therefore cannot be assessed at present.

Mercury accumulates in the thyroid as a result of exposure to mercury vapour. This may be associated with observed impairment of T4 deiodisation. In this case, too, the information available is

insufficient to permit assessment of whether there is a risk of amalgam causing thyroid disease.

Scientific support for influence at low concentrations

The 1997 risk analysis assumed that the minimum exposure level that gives rise to demonstrable impairment of the nervous system is represented by urinary secretion of mercury at roughly 50 μg/l. Subsequent research findings have shown that influence arises at considerably lower exposure levels. There is scientific evidence for influence from mercury concentrations in urine of some 25 μg/l, and from even lower levels.

In a cross-section study of 49 dentists and dental nurses, mercury secretion in their urine was measured before and six hours after administration of sodium-2,3-dimercaptopropane-1-sulfonate (DMPS), a mercury-chelating substance (Echeverria et al. 1998). Before chelation, the mercury concentration in urine averaged 0.95 μg/l; after six hours it was 9 μg/l. The statistical analysis showed, throughout the dose range, a significant correlation between dose in terms of secretion after chelating and aggregate subjective symptoms. Conversely, there was a correlation between secretion after chelation and the results of tests of motor function.

The dose-response curve for this group of dental-care personnel covers roughly the same dose range as that incurred by amalgam bearers. Nevertheless, it is unclear how far the mercury concentration in urine before chelation is representative of exposure further back in time. It cannot be excluded that the dental-care staff's exposure may have been higher further back in time.

In the Scottish study referred to above (Ritchie et al, 2002), 180 dentists were compared with an equal number of controls of university employees. Mean urinary mercury secretion was four times as large among the dentists as among the controls and five times as large as that in the dental-care personnel above before chelation. Statistically significantly more often than the controls, the dentists showed memory impairment and deterioration in psychomotor function. These changes were not, however, correlated with the mercury secretion in their urine.

A Swedish prospective cross-section study of 1,462 women aged 38–60 was conducted, with a follow-up after five years. In this study, no correlation was found between symptoms and exposure

to mercury from amalgam (Ahlqwist et al. 1999). The yardstick of exposure used was the mercury content of serum, and effects were gauged by responses to a questionnaire concerning symptoms.

The statistical sensitivity of this Swedish study is much greater, but the effect measure is relatively insensitive and the dose measure less specific than in the chelation study. Nevertheless, it should be emphasised that the effects referred to here are subclinical effects, i.e. observed functional impairment, and that the symptoms fall within the normal variation in the population. Accordingly, these effects can be demonstrated only at group level.

At present it may be considered unproven, but not excluded, that subclinical psychomotor functional impairment caused by mercury is demonstrable in groups at the mean exposure level for amalgam bearers.

Influence on foetal development

The risk of influence on foetal development was pointed out in the 1997 risk analysis. This is not contradicted by more recent results that may suggest an elevated risk, among women exposed to mercury in the course of their work, of giving birth to babies who are small for their gestational age. In addition, there are experiments on animals indicating that one expected effect of exposure to low doses of mercury vapour is inhibition of brain development. In these experiments, this inhibition resulted in reduced cognitive and motor capacity. Such inhibition of brain development falls within the normal range in the population.

These effects in animal experiments resemble those observed after exposure to methyl mercury. However, the dose of mercury that yields the effect has been only about one-tenth of the dose of mercury that exerts an effect following exposure to methyl mercury. Only through epidemiological studies using batteries of neuropsychological tests and possibly neurophysiological survey methods can these effects be demonstrated.

The risk of inhibition of brain development during the foetal stage and early childhood is obvious. This hazard is a contraindication for amalgam fillings in children and women of fertile age, until a quantification of the risk prompts a different assessment.

Influence on the immune system

The clinical studies of how mercury vapour influences the immune system show clearly that effects can be demonstrated down to dose levels corresponding to exposure to amalgam. The clinical significance of these effects, on the other hand, is unclear. The observations based on animal experiments provide evidence that genetic make-up and gender have a bearing on the nature and intensity of reactions.

Published surveys of the association between amalgam and multiple sclerosis are of limited sensitivity, but appear to rule out amalgam as a major aetiological factor in the development of MS. Available clinical information provides no guidance as to whether mercury from amalgam can affect the course of the disease of MS.

Experimental data prompt the question of whether removing amalgam in the event of autoimmune diseases is justified. No general reply to this question can be given; instead, in the current situation the circumstances must be weighed up in each individual case. Nevertheless, it would seem imperative for clinicians to bear this option in mind. The same applies to parasitic diseases, such as malaria.

Risk of kidney disease

Over the past five-year period, another survey has emerged that shows an elevated risk of developing kidney disease among those who are occupationally exposed to mercury. This observation was made on a group of dentists whose exposure was fairly low. The survey confirms the findings of earlier surveys.

The question is whether this is an effect induced solely by mercury exposure or whether it is the result of a combination of factors. It would appear vital for nephrologists to devote attention to this issue.

Varying sensitivity between individuals

There are strong indications of a gender difference in terms of mercury metabolism in data from animal experiments and in clinical observations. Information on what this may entail regarding differences in sensitivity to mercury exposure is entirely lacking.

This is a fundamental shortcoming that invalidates every risk analysis.

The cases of acute or subacute mercury intoxication referred to above illustrate a pronounced polymorphism in the range of symptoms. This suggests that the toxic effect of mercury has several targets, and this probably contributes to the variation in sensitivity between individuals. This is not surprising, in view of the omnipotence of the mercury atom in the biochemical dynamics of the cell. For genetic reasons, particularly sensitive groups in the population may be expected to show equally marked polymorphism in their mode of reaction to amalgam.

In purely theoretical terms, it is highly probable — verging on certainty — that individuals with genetically conditioned deviant sensitivity to mercury exist. The clinical observations referred to above support this conclusion. Diagnosis is a problem that requires further research. At present, the golden diagnostic standard appears to be blind provocation with realistic concentrations of mercury vapour. However, this method is too laborious, time-consuming and costly to be incorporated into clinical routine.

The most probable side-effect of amalgam seems to be a reaction mediated by the immune system. This does not exclude the possibility of genetically conditioned high sensitivity to mercury in the nervous system. Mercury is not the only environmental factor that provokes an immune-system-mediated reaction. Other metals and organic molecules can also induce such reactions in sensitive individuals.

There are no facts indicating that all those who believe that they are affected by amalgam are in fact so affected. It is therefore more probable that, for many people, the symptoms have other causes. But it is also likely that many people with side-effects from amalgam fillings are unaware of a causal connection.

There is no evidence that the frequency of pathological side-effects of amalgam due to genetically conditioned high sensitivity exceeds 1 %. It is therefore impossible to demonstrate these states by means of epidemiological studies of representative population samples. It is unclear whether subclinical influence on mood and motor function can be caused by the mercury concentrations to which amalgam bearers are exposed. These effects have been observed in occupationally exposed persons within the same dose range.

5. Summary and conclusions

The past five years' research has yielded further evidence that amalgam can give rise to side-effects in a sensitive portion of the population. Thus:

- Research in molecular biology has elucidated mechanisms that may underlie the toxic effects of mercury.
- Studies of the effects of mercury on the immune system in rodents have enhanced knowledge of the mechanisms whereby mercury affects the immune system. Clinical studies of occupationally exposed employees have objectively confirmed subclinical influence of mercury on the immune system at low levels of mercury exposure.
- The thyroid has been identified as the target organ for the toxic effect of mercury in occupational exposure to mercury vapour in low doses.
- Experimental studies of primates and rodents have revealed that mercury is accumulated and persists for years in the retina as a result of exposure to mercury vapour. The consequences of this accumulation are, however, unclear.
- Clinical studies of the effects of mercury on occupationally exposed workers, using modern diagnostic methods, have elucidated the connection between dose and effect. They have also identified and quantified neuropsychological symptoms at low exposure levels.
- The lowest exposure, in terms of urinary mercury secretion, that has been found to give rise to a demonstrable toxic effect has fallen from 30–50 mg/l till 10–25 mg/l. Accordingly, the safety margin that it was thought existed with respect to mercury exposure from amalgam has been erased.
- Studies of workers previously exposed to mercury have shown that prolonged exposure to mercury vapour, with mercury concentrations in urine of some 100 mg/l, may result in symptoms emanating from the nervous system that persist decades after exposure has ceased. This suggests that exposure causes lasting damage to the central nervous system, which complicates the interpretation of results of low-dose studies of occupationally exposed populations.
- Clinical reports of acute or subacute cases of mercury intoxication where modern diagnostic methods have been applied

have revealed a remarkably high degree of polymorphism in human reactions to toxic mercury exposure.
- Both animal experiments and clinical observations have demonstrated gender differences in the toxicokinetics of mercury.
- Additional facts have come to light that may indicate that mercury vapour can affect human foetal development.
- Clinical provocation studies, with exposure to small quantities of mercury through skin exposure or inhalation, have confirmed that individuals with deviant high sensitivity exist.

With reference to the fact that mercury is a multipotent toxin with effects on several levels of the biochemical dynamics of the cell, amalgam must be considered to be an unsuitable material for dental restoration. This is especially true since fully adequate and less toxic alternatives are available.

With reference to the risk of inhibiting influence on the growing brain, it is not compatible with science and well-tried experience to use amalgam fillings in children and fertile women. Every doctor and dentist should, where patients are suffering from unclear pathological states and autoimmune diseases, consider whether side-effects from mercury released from amalgam may be one contributory cause of the symptoms.

Removal of existing amalgam fillings should not be undertaken unless there are medical reasons for doing so. The reason is that the risk of complications from the removal may exceed the risk of side-effects from the amalgam. The risk of removal is due mainly to the fact that dental substance is drilled away, which may itself result in problems with existing teeth.

6. Environmental medical views of risk management

For medical reasons, amalgam should be eliminated in dental care as soon as possible. This will confer gains in three respects. The prevalence of side-effects from patients' mercury exposure will decline; occupational exposure to mercury can cease in dental care; and one of our largest sources of mercury in the environment can be eliminated.

Dental materials left in patients' mouths should be treated as drugs for administrative purposes. Accordingly, toxicological and

clinical testing should be required. Reporting of side-effects should also take place according to the same norms that apply to drugs.

It is imperative for doctors and dentists to be made aware of the fact that all dental restoration materials can give rise to side-effects, and that this eventuality should always be considered when the patient's pathological state is unclear. Side-effects may conceivably both cause, and be contributory factors in, various pathological states.

7. Clinical management

Special clinical units should be created with the function of investigating unclear pathological states when there is any suspicion of an environmentally related cause. These units should have access to all medical specialities and the research skills that are required for assessment and treatment of this category of patients. Mercury exposure from amalgam is only one of many conceivable agents that may conceivably induce syndromes that are difficult to diagnose. Units of this kind may possibly be linked to environmental-medicine units at regional hospitals.

It is imperative for cost-effective routines to be created for diagnosis of the side-effects of amalgam. At present, the golden standard for specific diagnosis should be blind provocation with mercury vapour. However, this method is not suitable for routine clinical use.

It is essential to develop alternative clinical tests that are simple and cost-effective to use. This requires suspected cases to be assembled in a few locations and systematically studied with all available and relevant methods in a scientific manner.

8. Need for research

In most studies of the effects of mercury, the subjects have been men. It is imperative to elucidate the differences, if any, between men and women in metabolism and the toxicokinetics of mercury after exposure to mercury vapour.

Epidemiological surveys of the *in utero* effects of mercury exposure on foetal brain development should be carried out to further clarify the hazards, if any.

Epidemiological studies designed to investigate associations, if any, between amalgam load and degenerative retinal diseases are urgently required.

Likewise, epidemiological studies designed to find any associations that may exist between thyroid disease and amalgam fillings are advisable.

Co-ordinated clinical studies of people who undergo amalgam removal on suspicion of side-effects from mercury should be carried out. Thorough investigations before, during and after removal, using all clinically available methods and focusing on the immune system, thyroid and nervous system, should be carried out. Muscle biopsy should be performed in cases where there is pronounced muscle pain.

Initiation of clinical and experimental basic research to clarify the mechanisms whereby mercury vapour affects the central nervous system is highly essential. Today, knowledge of these mechanisms is poor.

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Abbreviations

Aß	ß-amyloid
AchE	acetylcholinesterase
AD	Alzheimer's disease
CNS	central nervous system
DMPS	sodium 2,3-dimercaptopropane-1-sulfonate
GABA	ϒ-aminobutyric acid (gamma-amino butyric acid)
GPx	glutathione reductase
GR	glutathione disulphide reductase
G-6PD	glucose-6-phosphate dehydrogenase
GSH	reduced glutathione
GTP	guanosine triphosphate
Hg	mercury
ICAM-1	intercellular adhesion molecule 1
MS	multiple sclerosis
NAG	N-acetyl-ß-D-glucosaminidase
PKA	protein kinase A
PKC	protein kinase C
PNS	peripheral nervous system
rT_3	reverse T3
SOD	superoxide dismutase
TAA	total antioxidant activity
U-Hg	urinary mercury

1 nmol Hg/mmol creatinine = 1.79mg Hg/g creatinine
1 mg Hg/g creatinine = 0.56 nmol Hg/mmol creatinine