The Independent Medical Expert Group (IMEG)

Report and recommendations on medical and scientific aspects of the Armed Forces Compensation Scheme

March 2015

Topic 6 – Recognised Diseases

Ahead of the papers on diabetes mellitus, testicular cancer and leukaemias we have reproduced the introduction to Recognised Diseases included in the May 2013 IMEG Report.

1. Lord Boyce in his review of the AFCS raised the issue that while under the War Pensions scheme the majority of medical discharge cases suffering from physical disorders receive entitlement to war pension; this is not the case under the AFCS. This is a reflection of the different standards of proof required in the two schemes. The standard of proof in AFCS is 'on the balance of probabilities' (or 'more likely than not'), which is the standard of proof in both civil compensation and the statutory compensation scheme for civilian occupational injury and disease, the Industrial Injuries Scheme.

2. At its inception in 1917, the standard of proof used in the War Pensions Scheme was "on the balance of probabilities". This was changed in 1943, at the height of the Second World War, when for injuries and disorders arising in service, the burden of proof, transferred to MoD to demonstrate that a service cause was "beyond reasonable doubt" not the cause of the disease. The change was introduced at this time because inadequate record keeping was leading to large numbers of claimants unfairly not receiving compensation.

3. In his report, Lord Boyce proposed that the IMEG should develop a list of Recognised Diseases for the AFCS. By this he meant that IMEG should review the medical literature and receive evidence from experts to provide guidance about the circumstances when "on the balance of probabilities", a disease having onset in or around service was more likely than not to be attributable to service in the Armed Forces.

4. The normal burden of proof in civil compensation and other statutory compensation schemes such as the Industrial Injuries Disablement Benefit (IIDB) Scheme is "on the balance of probabilities". For claims under AFCS this implies demonstrating that military service is more likely than not (more than 50:50) the predominant cause of the injury or disease in the individual case. In the Industrial Injuries Disablement Benefit Scheme, for those conditions where there is sufficient evidence that this level of proof is satisfied, the disease is 'prescribed', i.e. attributable in the individual case to the particular cause in relation to clearly specified circumstances of exposure.

5. In the individual case, attribution is usually based on sufficient evidence to answer the questions:

- Does the particular agent or exposure cause the disease, at least in some circumstances?

- If so, were the circumstances of the individual case such that the agent or exposure is more likely than not to have been the cause of the disease?

6. Recognition of a particular agent as the cause of a disease, and attribution in the individual case, is most clear when the cause is specific to the disease, or nearly so, and the probability of causation is high. Such conditions are now relatively uncommon but a relevant example is occupational asthma, asthma whose primary cause is an agent inhaled at work. The majority of cases of occupational asthma are due to the development of an allergic reaction to the specific cause encountered in the workplace (e.g. flour in a baker). Asthma develops after an initial

symptom-free period of exposure and recurs on re-exposure to the specific cause, in concentrations which do not cause respiratory symptoms in others similarly exposed or previously in the affected individual. Inhalation testing with the specific agent will provoke an asthmatic reaction in the sensitised individual (but not in others not sensitised). Also, for many agents evidence of a specific immunological reaction (i.e. specific IgE antibody) will be found. In principle, the specific cause of asthma can be demonstrated in the individual case.

7. The majority of diseases however are not specific to a particular cause. A particular cause may increase the frequency of occurrence of a disease, which can have other recognised causes. As an example, lung cancer is well known to be caused by smoking cigarettes. More than 90% of cases in the general population occur in cigarette smokers. A smoker of 20 cigarettes a day during adult life will increase his or her chances of developing lung cancer by some twenty-fold. In the case of lung cancer in a smoker of 20 cigarettes a day for 40 years we can say with confidence that it is likely that the lung cancer is attributable to the smoking of cigarettes.

8. However, there are also other causes of lung cancer, such as asbestos and ionising radiation. When are we entitled to attribute lung cancer in an individual to asbestos exposure? The lung cancer caused by asbestos is indistinguishable from a lung cancer of other cause, such as smoking, so it has no specific distinguishing features. We have to ask the question: in what circumstances would it be more likely than not that the lung cancer was caused by exposure to asbestos. As the individual case has no distinguishing (or specific) features, we have to look at populations of people exposed in their work to asbestos. Among these, are there any circumstances where the frequency of the disease has increased sufficiently to make it more likely than not in the individual case that the lung cancer would be unlikely to have occurred in the absence of occupational exposure to asbestos? The answer is that, among other circumstances, the frequency (or incidence) of lung cancer was more than doubled in asbestos textile workers, both smokers and non smokers, who worked for 20 years or more in an asbestos textile factory. In these circumstances we can conclude it is more likely than not the lung cancer is attributable to asbestos.

9. Why is a greater than doubling in the frequency of the disease so critical in determining attribution to a particular cause? We can consider a hypothetical 100 men working in a particular occupation (fig 1). Among these 100 men, as in the general population, the number of new cases of a particular disease is 10 each year, i.e. no different.

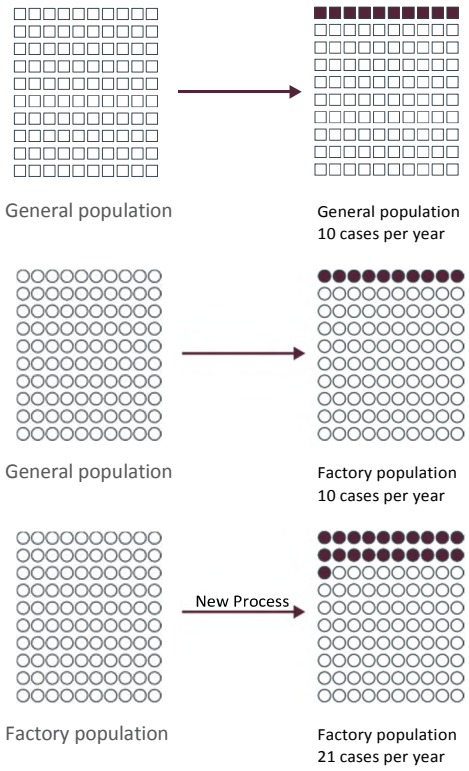

Fig 1. Increased incidence of disease from ten per year to 21 per year in factory population following the introduction of a new process

Sometime later, after the introduction of a new process, the number of cases of the disease in these 100 men increases to 21 each year, i.e. more than 2 times the previous frequency. We cannot distinguish the additional 11 cases from the 10 in whom the disease would otherwise have occurred. What we can say is that in any particular individual among the 21 cases, there is a more than 50:50 chance, or a greater than doubling of risk, that the disease would not have occurred without exposure to the particular cause. On the balance of probabilities it is therefore more likely than not that the disease is attributable to the particular cause in the individual case. We can say that 'but for' his working in this factory it is unlikely the man would have developed the disease. The balance of probabilities has shifted to 'more likely than not' and in this circumstance the disease can be attributed to the particular cause.

10. In the case of Recognised Diseases in the AFCS, we are therefore looking for evidence that service in the Armed Forces is consistently associated with an increase in the frequency of a particular disease or illness and whether there are circumstances where the frequency is more than doubled, making it more likely than not in the individual case that the disease was attributable to a cause in service.

11. It is also important to distinguish "all or none" diseases from "more or less" diseases. A well-recognised "all or none" physiological condition is pregnancy: one cannot be a bit pregnant. In contrast, many important conditions including high blood pressure, hearing loss and mental health disorders are 'more or less' conditions. These have a continuum of frequency of symptoms without a clear distinction between those with and without the condition. The definition of disease is therefore less clear and subject to expert opinion.

12. The epidemiological evidence informing these determinations should be of high quality, drawn from several independent studies and sufficiently consistent and robust that further research at a later date would be unlikely to overturn it.

A. Diabetes mellitus

1. The term diabetes mellitus (DM) applies to syndromes of abnormal carbohydrate metabolism characterised by raised blood glucose levels (hyperglycaemia) sustained sufficiently long to cause damage to kidneys, eyes, nerves and arteries. DM is associated with a relative or absolute impairment in insulin secretion and varying degrees of resistance to the action of insulin. DM is usually considered as primary or secondary.

2. Primary diabetes is divided into Type 1 (T1DM) and Type 2 (T2DM). Type 1, previously known as insulin dependent or juvenile onset diabetes, is responsible for 5-15% of cases while Type 2 (T2DM) accounts for some 90% of cases. Type 2 was previously called non-insulin dependent or maturity onset diabetes. These terms are however inaccurate. Treatment for both types of primary diabetes depends on severity and both types may require insulin. Equally T2DM, usually presenting in middle age or older, is now increasingly being diagnosed in overweight children and young adults.

3. T1DM typically, but not always, has its clinical onset in childhood or young adulthood. In recent years more cases have been diagnosed under the age 5 years. Up to 50% of cases are diagnosed after age 18 years while about 5% of newly diagnosed Caucasian diabetics over the age of 65 years have type 1. Before puberty T1DM is equally common in males and females. After puberty, there is a preponderance of males although less than a twofold increase in risk.

4. T1DM is considered to involve an autoimmune mediated progressive destruction of the ß (beta) cells of the pancreas, which secrete insulin, leading to an absolute deficiency of insulin. Auto-antibodies to pancreatic tissue can be detected in the blood. This process typically develops over many years, with the pre-diabetic phase being asymptomatic. T1DM probably occurs when environmental factors, whose precise aetiology is unknown, act in a genetically susceptible person. Genetic factors account for about 40% of the risk with multiple genes involved, so a clear familial pattern is not always observed. In terms of environmental factors involved, the evidence is conflicting and the mechanism as yet unknown. Viruses are believed to be the most likely environmental triggers; these include Coxsackie B, mumps, cytomegalovirus and rubella. Serological studies confirm that Coxsackie B infection is relatively common in patients newly diagnosed with T1DM. 20% children who survive intra-uterine rubella develop T1DM with autoimmune markers. It may be that the virus is part of the final common pathway to clinical T1DM enhancing the established autoimmune activity and onset of clinical symptoms. Other possible trigger factors include bovine serum albumin from cows' milk and toxins, e.g. found in food, may also be involved (1) (2).

5. High susceptibility to T1DM is found in European populations throughout the world, while African and East Asian populations are relatively spared. The incidence is higher in Northern European countries and declines progressively towards the equator. Diagnosis in children is more frequent in the winter months and in many countries there have been marked increases in incidence over 10 - 20 year periods (3) (4).

6. T2DM is a more heterogeneous disorder characterised by raised blood glucose in the absence of the features of T1DM, with a relative insulin deficiency caused by resistance to the action of insulin. The tendency to T2DM is again considered to be a function of genetic and environmental factors. It occurs typically in middle aged and older adults with rates rising with age. It now affects 3-4% of the white population in most countries with rates rising to 8-11% in Eastern Europe and North America. It is very common in some immigrant populations living in affluent countries including in the UK. In UK the prevalence in the white adult population is 4% and 10-15% in adult Asian or Afro-Caribbeans. As childhood obesity rates rise, the diagnosis is becoming more common in younger people.

7. The geographical spread of T2DM is different from that of T1DM and prevalence is rising especially rapidly in developing countries. This is related to Westernization and the obesity epidemic. The thrifty gene hypothesis proposes that excess energy is stored as fat in anticipation of lean times; however in an age of fast food, motor cars, decreased physical labour and recreational exercise the deposited fat is not consumed as energy but accumulates, causing obesity.

8. T2DM is also a progressive disorder; over time the ability to produce insulin reduces, in some cases with beta cell failure and, ultimately, requirement for insulin replacement as with T1DM.

9. T2DM appears to be polygenic with several gene loci now identified as having an influence on insulin secretion or resistance and obesity. T2DM is not inherited by simple Mendelian rules and the recent explosion in numbers of cases strongly suggests that environmental factors are key both in explaining the increasing incidence and in offering potential factors for modification. Obesity and pregnancy increase insulin resistance while chronic hyperglycaemia can impair insulin sensitivity and inhibit insulin release.

Specific risk factors for T2DM

10. **Obesity** especially its level, distribution and the age at which fat is laid down. Once BMI reaches 28 kg / m2 the risks increase steeply and at 35 kg / m2 the risk may be 40 times greater than for a person with a BMI of 22 kg / m2. Truncal and visceral fat is especially hazardous as is weight gain in the early twenties.

11. **Physical inactivity** appears to be an independent risk factor. This is due to insulin resistance with sedentary people three times as likely as those taking regular physical exercise to be affected.

12. **The Barker hypothesis** suggests that poor foetal growth can lead to abnormal metabolic effects “the metabolic syndrome” with hyperglycaemia, hypertension and dyslipidaemia. This is particularly the case in those who are underweight at birth and subsequently become obese. Animal studies suggest that malnutrition in utero may lead to reduced pancreatic cell mass and so impair insulin secretory reserve.

13. Other causes of hyperglycaemia which can present during military service include **diabetes as a complication of pregnancy**, both pre and post gestation. Several predisposing factors may be involved.

14. Lastly there is a rare condition now called **Maturity Onset Diabetes of the Young**. Cases of this have a family history of diabetes diagnosed young; with no family history of obesity and importantly no pancreatic beta cell autoantibodies as found in T1DM. This disorder has several variants and is caused by mutations in the glucokinase genes. It responds well to treatment with sulphonylureas.

15. Secondary diabetes arises from a variety of congenital and acquired causes. For the purposes of AFCS, congenital syndromes are unlikely to be an issue. The relevant chromosomal disorders e.g. Down's syndrome: Turner's syndrome: and Klinefelter's syndrome, typically result in significant disability from birth or childhood and are incompatible with military enlistment. Acquired causes relevant to military service include pancreatic disease, pancreatitis, or cancer. Pancreatic tissue can also be reduced or destroyed by trauma including surgery.

16. Secondary diabetes may also follow endocrine disorders where there is excess production of hormones that oppose the action of insulin e.g. thyrotoxicosis: acromegaly and Cushing's syndrome. Again these will be rare in the military population and unlikely to be causally related to service.

17. A third major cause of secondary diabetes is therapeutic drugs, in particular glucocorticoid steroids. Circumstances where corticosteroids are used orally and long term are unlikely to be consistent with military service even in a downgraded capacity e.g. chronic lung disease: inflammatory bowel disease and joint disease. Another major group of therapeutic drugs are those used to lower blood pressure including diuretics and beta blockers. Finally drugs used to treat HIV infection.

Recognised disease status

18. There is no published study of incidence of primary diabetes mellitus of either T1DM or T2DM in any occupational or other identifiable group including military personnel and veterans. While both for service entry and retention in service following diagnosis of diabetes, cases are considered on their merits, it is unlikely that T1DM is compatible with full-time fully deployable regular service in any branch of the military. The position with T2DM, especially if well controlled by diet or diet with oral hypoglycaemics may be less rigid but again fully deployable regular service in a forward role is unlikely. As discussed above primary T1DM remains a disorder of unknown aetiology and so cannot, on balance of probabilities, be attributable to service. In relation to T2DM the major non genetic and modifiable factors are matters of lifestyle and personal choice. Military diet and restrictions e.g. on operational deployment rations are advised by professional dieticians and are not diabetogenic.

19. In terms of secondary DM, two main mechanisms are involved. First loss or damage to pancreatic tissue and the beta cells which secrete insulin. This might arise through combat related abdominal injury or other service-related trauma. Destruction of pancreatic tissue could be due to infection when Article 12 of the 2011 AFCS Order refers. It could also occur due to a tumour itself or arising from its treatment. There are few circumstances where the cause of pancreatic cancer in an individual is known e.g. it is accepted as a radiogenic disorder, but if the cancer is due to service, and diabetes mellitus is a consequence, it too will be accepted as due to service. Surgery for a condition which is not attributable to service, even where it takes place during service, is not itself, nor are any expectable

consequences, due to service. A frequent cause of pancreatitis, especially chronic pancreatitis is alcohol which is expressly excluded under the Scheme.

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B. Testicular cancer

1. Although the incidence of testicular cancer in the UK has increased in recent years, it remains relatively rare with about 2000 cases diagnosed a year. It represents about 1% of all male cancers and mortality rate has been declining since the mid 1970s and introduction of platinum based chemotherapy. The disorder, as other testicular problems such as low sperm count, poor, quality sperm and maldescent of testis, has been increasing in incidence over the last forty years in almost all parts of the world. There is marked geographical and racial variation and the tumour is most common in Northern Europe and in higher socioeconomic groups with much lower rates in Asian, African and African Americans. This pattern suggests a causal role for both genetic and environmental factors (1).

2. Testis cancers are predominantly germ cell tumours (GCT) and a single tumour often includes a variety of cell types. This pathological complexity leads to different classification systems, which are difficult to align. In clinical terms testis tumours are usefully sub-divided into three groups, all derived from germ cells at different stages of development. The age specific incidence of testis tumours is unusual. There is a small peak in infancy and tumours are then uncommon until puberty when the incidence begins to rise and testis tumours are the most common solid tumour of young men in the 15 - 35 years age group. There is a sharp decline in incidence in older men. This pattern suggests that causative factors may operate in utero or early life while the increased incidence after puberty suggests that hormonal influences also play a part in tumour development (2).

3. Testis cancer is diagnosed clinically and where there is a painless solid lump within the testis, the diagnosis is made, until proven otherwise. In today's more open and better educated society, which includes men's health as well as high profile cases involving sporting celebrities, awareness and early diagnosis of the disorder amongst young men has helped improve prognosis. A small number of patients continue to present with metastatic spread e.g. with respiratory symptoms; bone pain; neurological symptoms or venous thrombosis. Investigation in suspected cases includes scrotal ultrasound, radiology of chest, abdomen and pelvis. Three serum tumour markers are also measured. Serum markers do not make the diagnosis but very high values are rare in the absence of cancer. Treatment advances in radiotherapy and chemotherapy mean that mortality is improving and many patients can be

expected to achieve a normal life span. Relatively high dose chemotherapy and radiotherapy may be required and with improved prognosis, long term toxicity from these is a risk. The most frequent sequelae of treatment are cardiovascular effects: second cancers and reduced fertility. The latter is usually temporary, with sperm count recovering with time from treatment.

4. High oestrogen exposure in utero has been suggested as a casual influence. However evidence on incidence of testis cancer in the sons of women receiving diethyl stilboestrol has been inconsistent and there is no direct link between maternal oestrogen levels during pregnancy and testis cancer in humans (3). In 1994 it was suggested that the emerging testis cancer epidemic might correlate with increased maternal smoking during pregnancy. Several studies have investigated this hypothesis with conflicting results (4).

5. Testis tumours run in families with relative risk increased 6 - 10 fold in brothers or sons of affected men. Chromosomal abnormalities are common in GCT and a specific mutation has been associated with familial testis cancer, especially bilateral disease (5).

6. Undescended or maldescended testes (cryptorch(id)ism) are a strong risk factor for testicular cancer (6). If only one testis is maldescended the increased risk of cancer applies to both testes. Undescended or maldescended testes are also associated with long term consequences on testis function including spermatogenesis. The rate of cryptorch(id)ism in pre-pubertal boys from prospective studies is between 2 and 8 %. Low birth weights, prematurity, being small for gestational age, are risk factors and low maternal oestrogen levels and placental insufficiency may be relevant (6). Other postulated influences include maternal diabetes including gestational diabetes. A recent Californian study suggested that maternal prenatal DDT exposure might have a role (7). It is not known whether these associations of cryptorch(id)ism share common aetiological factors with testis cancer or might be themselves direct causes of testis cancer.

7. Several studies in different populations suggest that taller adult height but not increasing body weight is correlated with risk of testicular cancer (8). Other studies of varying power and rigour have looked at occupational exposure to wood dust, degreasing agents, chromate and azo-based dyes, and dimethyl formamide with inconclusive results (2). Few studies have considered ionising or non-ionising radiation as causal factors for testis cancer. Those which have done so include few cases and their results are inconsistent. BEIR, UNSCEAR and UK Health Protection Agency Advisory Group on Ionising Radiation (AGIR) have considered the evidence too weak to come to firm conclusions on radiogenicity (9). In AFCS terms this means that at this date, on the balance of probabilities, no dose of ionising radiation can be considered to cause testicular cancer).

8. Of relevance to the Armed Forces population, is evidence on exercise / sport, and testicular trauma. Most of the work exploring a role for trauma has been case-control in design with the risk of recall bias in terms of identifying trauma in the period leading to diagnosis. Similarly, studies which attempt to correlate cancer development with previous sporting activity have produced inconsistent results (10) (11).

9. Several studies report raised relative risks associated with post pubertal mumps but case numbers were small and the 1994 UK Testicular Cancer Study Group found no relation between mumps and testis cancer (6). In AFCS terms, mumps arising in service is unlikely to be accepted as attributable to service (see Article 12 AFCS Order 2011).

10. Testicular cancer has not been thought of or widely studied as an occupational disorder and where associations with employment have been reported e.g. farmers, painters and tanners, their results have been inconsistent, case numbers small and causative agents / mechanism unknown. Military studies have included a large study of US naval personnel comparing the incidence of testicular cancer with the US national cancer surveillance statistic. Age adjusted incidence of testis cancer for the navy overall was not significantly different from the general US population. However naval aviation support equipment technicians and enginemen, with tasks similar to civilian motor mechanics, had raised incidence rates both relative to the US navy overall and the civilian population (12). Studies of Vietnam veterans have produced conflicting results. A case control study which dichotomised, simply on the basis of service in Vietnam, showed a significant increased risk of testis cancer (13) in army, navy, and air force veterans but not in marines. It was proposed that exposure to Agent Orange was the potential cause (14). A later study used a series of surrogates to reflect exposure to Agent Orange e.g. combat troop: ground troop and geographical location. In this study only naval personnel had increased risk of testis cancer, the group least likely to have Agent Orange exposure (15).

11. A case control study was published in 1997 on testis cancer in Royal Navy personnel (16). Cases between 1976 and 1994 were identified and controls, four to each case, were matched on date of birth and length of service. In total 110 cases of testis cancer were identified. Five cases had maldescended testes, all surgically corrected, and two had atrophic testis. A radiation history was obtained for each case and service branch noted i.e. general: submarine: Fleet Air Arm: Royal Marine and finally, rank was noted. The results suggested an increased risk in Fleet Air Arm relative to other branches of the service and specifically the risk was in air engineers but not aircrew. There was no increased risk in submariners or when length of service or time served on nuclear vessels was considered. The overall numbers of cases, especially in the subgroups were small and the study statistical power very low. The findings are of interest but a further larger study is required.

12. In conclusion while a number of associations are established, none is related to occupation and at this date, testis cancer remains a disorder of unknown aetiology. There is no reliable evidence of increased risk associated with UK military service in general, nor service in navy, army or air force. Equally no link is identified with any specific service occupation or exposure. No circumstances can presently be identified where testis cancer could be accepted as a recognised disorder for AFCS purposes.

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C. The leukaemias

1. The leukaemias are cancers of the white blood cells. They are described as acute or chronic and dependent on cell lineage, there are two major groups, myeloid and lymphoid. They arise when stem and progenitor cells in the bone marrow are genetically altered giving rise to malignant transformation. The abnormal cells do not mature into normal cells but continue to proliferate and expand in the marrow at the expense of healthy cells and, over time, lead to low red cell and platelet counts. The abnormal cells enter the blood stream giving a high white cell count and may also be found in lymph nodes, spleen and liver (1).

2. As yet the cause and pathogenesis of the leukaemias remains incompletely understood. Established potentially occupation-related causal factors include ionising radiation and exposure to chemicals (particularly benzene), but in the individual case, cause is rarely

established. The leukaemias are classified into sub-groups, now based on molecular genetics. This approach means classifications are not settled but are amended over time to reflect emerging understanding and emphases (2). The focus of this note is occupational causes of the most common types, Acute lymphatic leukaemia (ALL): Chronic lymphatic leukaemia (CLL): Acute myeloid leukaemia (AML) and Chronic myeloid leukaemia (CML).

Sub-Types of leukaemia

3. **Acute lymphoblastic leukaemia (ALL)**. 85% of cases of ALL occur in children and present with pallor, bleeding, bruising, anaemia, infection and fever. Recent years have seen significant advances in therapy for childhood ALL, particularly for those aged between 1 and 10 years. There is a much poorer prognosis in adults with this diagnosis and current evidence suggests that the disorders in children and adults are different biologically and genetically. It is now recognised that in most childhood cases the first genetic events in key stem cells arise in utero (3) with further environmental exposures / events required to trigger this pre-leukaemic state into a clinical disorder. The evidence suggests that infection may be an important trigger in the development of childhood clinical ALL. It is not known if infection plays any part in the development of adult ALL (4).

4. **Acute myeloid leukaemia (AML)**. By contrast 80% of patients with AML are adults and only 20% children. In adults while it may be seen at any age, the median age of clinical onset is 68 years. In older patients it may be associated with, and evolve as, an end stage from the myelodysplastic syndrome. Clinically and biologically, AML in children and adults seems to be the same disorder. It most typically presents with anaemia and bleeding due to bone marrow failure. In most cases there is no obvious cause but exposure to chemicals, notably benzene, cytotoxic drugs and ionising radiation can be relevant. As survival rates for solid tumours continue to improve, an increasing source of cases is adults who have survived radiotherapy / chemotherapy for other cancers (5).

5. **Chronic lymphatic leukaemia (CLL)**. This is the most common lymphoid neoplasm in Europe and North America and its cause remains unknown. The parent cell is the mature B lymphocyte. The diagnosis is usually made fortuitously on discovery of a raised blood lymphocyte count. There is no standard therapeutic regime and present best practice is to defer active treatment until patients are symptomatic or there are signs of bone marrow failure. The disease can occur in families with about 10% of cases having a family history in first degree relatives. Some studies have suggested an association with industrial and agricultural chemicals but results are inconsistent and study size, design and exposure ascertainment of varying quality. It has generally been accepted that, in contrast to other types of leukaemia, there was no causal relation to ionising radiation (6). However some post Chernobyl case reports and larger studies have suggested that radiation exposure might increase the risk. More evidence is awaited. In these new studies it should be noted the disease is occurring in younger adults, appears clinically more aggressive and the morphology of the cells is different. At present no causal link between ionising radiation and CLL is established (7) (8).

6. **Chronic myeloid leukaemia (CML)**. This accounts for 15% of adult cases of leukaemia but less than 5% of childhood leukaemia. It occurs when the tip of chromosome 9 translocates on to chromosome 22 (Philadelphia chromosome) producing the fusion gene bcr-abl which drives the disease. It is a heterogeneous disorder with an initial chronic indolent phase followed on average at 3 - 6 years with transformation to blast cells and acute leukaemia,

often in previous years heralding only a few months' survival. Patients may be asymptomatic at diagnosis or may present with fatigue, sweats fever, pruritus (itch) or abdominal heaviness due to an enlarged spleen. There is no evidence of familial predisposition nor association with particular HLA or other genotypes (9). In terms of a causal role for ionising radiation, studies of British radiologists and technicians in the first half of last century showed increased rates of CML (10) (11) and similarly the 2005 15 countries' nuclear workers' study showed a small excess of CML (12). New treatments particularly the advent of tyrosine kinase inhibitors e.g. imatinib, which act on the protein product of bcr-abl, a tyrosine kinase, have transformed the outlook. First line management with imatinib achieves complete remission in over 90% of patients, a much better result than with previous cytotoxics. Imatinib has side effects in some patients and there is risk of teratogenicity so the drug should be avoided in pregnancy. In patients under 50, if the response to imatinib is poor or there are contra-indications and the patient remains in chronic phase, allogeneic stem cell transplantation is usually offered. For advanced disease the options are combination chemotherapy or a trial of a new generation tyrosine inhibitor.

Occupational and service related exposures known or suspected of a causal link to the leukaemias

7. This section considers occupational exposures known or suspected of being causally related to the leukaemias).

Ionising radiation

8. Exposure to ionising radiation in all its forms is part of being alive. Ionising radiation is taken to mean radiation of high enough energy to displace electrons from atoms and includes cosmic rays, gamma rays, X-rays, alpha and beta radiation. Tissues vary in their sensitivity to ionising radiation and different types of ionising radiation have different capacity to cause tissue damage and hence adverse health effects. Bone marrow is very sensitive to ionising radiation.

9. Evidence that ionising radiation can cause human cancer including leukaemia has come from several sources. These include follow-up of patients therapeutically irradiated for malignant conditions, such as cancer of the cervix, and non-malignant conditions like ankylosing spondylitis (13), nuclear industry worker follow-up studies (12) and most notably from the Japanese atomic bomb survivor studies (14) (15).

10. Cancers induced by ionising radiation are indistinguishable from those due to other more common risk factors such as diet, tobacco, alcohol etc. In addition to the dose of radiation delivered, the type of radiation, its duration of exposure i.e. an acute high dose or a chronic low or fractionated dose, the particular tissue irradiated and the age of the individual at the time of the radiation as well as at time of clinical onset of the malignancy are all known to be important. Taking the overall evidence on these matters into account and in the absence of a positive threshold dose of ionising radiation, the convention is to accept that no dose of ionising radiation is completely free from risk of cancer and that the risk increases linearly with dose. The Japanese atomic bomb survivor data demonstrates evidence of an increase in cancer incidence in individuals exposed to levels of ionising radiation of 50 mSv and above. These studies show that leukaemia appears first after whole body irradiation with a

latent period of two years and a peak at six to seven years post exposure. Risk is highest in children and young adults.

11. The Japanese survivor data are generally used for risk estimates but in 2002 they were revised downward (by about 8%) to take into account the small contribution of neutron exposure (16). There is a standard international approach to estimation of the probability that a particular cancer in a particular patient is causally linked to ionising radiation (17). This also takes into account the factors above and acknowledges that the atomic bomb exposure was high dose, short duration while most occupational exposure is low dose over a long period of time. There are some animal studies that suggest that for the same overall dose, high acute exposure is more harmful than delivery over a prolonged period of time.

12. While Health and Safety statute law does not apply to the Armed Forces, Defence workplace practice aims to meet or exceed mandatory and best practice protective and surveillance measures. Radiation occupational exposure limits apply and classified radiation workers are routinely monitored by the Defence Radiological Protection Service. Statutory limits for classified radiation workers are whole body 20 mSv per annum and 6 mSv for unclassified workers. This compares with 2.6 mSv per annum for average UK background exposure for all man made exposure. Potential military enclosed sources of ionising radiation include smoke alarms, compasses and helicopter emergency lighting. There are few military personnel who are classified radiation workers. This designation applies where annual exposure of 6 mSv per annum or more can be anticipated and includes medical, dental and industrial radiologists and technicians. The ship's company on nuclear submarines are not classified radiation workers.

13. In the late 1990s following public and media concern over adverse health and environmental effects of depleted uranium munitions, the Royal Society set up an expert working group to investigate the issues. Depleted uranium is both toxic and weakly radiogenic. The Working Group reviewed the literature, consulted widely and estimated intakes of depleted uranium over a wide range of typical battlefield exposures. They went on to calculate potential health risks. Their 2002 Report (18), found that munitions containing penetrator rods of depleted uranium do not pose any increased detectable risk of developing fatal cancers over the general risk of dying from cancer over a normal life-time.

14. As discussed in the Recognised Diseases Introductory Section, to accept a disorder as a recognised disease under the AFCS we need to identify service circumstances where, in the individual case, its frequency has increased sufficiently to make it, more likely than not, that it would not have developed without the service exposure. For leukaemia that means establishing a minimum dose level of ionising radiation that increases the risk of the leukaemia by a factor of two or more. If an exposure doubles risk, for every 50 cases occurring naturally in the population there will be another 50 cases due to the exposure. So for an individual case out of the resultant 100 it is impossible to say whether or not it is due to radiation unless the risk is more than doubled. Only then can we consider the individual case facts i.e. actual dose, age at exposure, and attained age.

15. What then is the minimum dose to double a person's risk? This is the dose that gives an Excess Relative Risk (ERR) of 1. Because risk varies with age at exposure, sex and time between exposure and clinical onset of disease, the value is not constant over time. If we assume male sex, exposure at age 18 and latency for leukaemia of two years, using the US National Academy of Sciences risk model derived from the atomic bomb survivor cohort and accepting that US and UK background risk is similar, the minimum doubling dose is 50 mSv

(19). If we set age at exposure at 30, 40 or 50 years the minimum doubling dose rises to 230 mSv but is constant over these ages. No dose approaching these levels, single acute or cumulative, has been recorded by Defence Radiological Protection Services from 6 April 2005.

Non-ionising radiation

16. **Extremely low frequency electric and magnetic fields (EMF)** – Occupational. EMF exposures are ubiquitous being found around all electric conductors. Occupational studies have tended to focus on occupations most likely to be at risk with little information on other "electrical" jobs where tasks may expose personnel to electric and magnetic fields at least occasionally. Present understanding is that electricians, electrical engineers and especially power cable workers and welders are at highest risk. The risks of leukaemia from these occupational studies and meta-analyses is generally low although results have been inconsistent and no dose response relationship is demonstrable (20) (21). A 2008 updated meta analysis considering occupational studies published between 1993 and 2007 found an overall increase in risk of 17%. The analysis considered excess risks for the specific leukaemias but it is notable that the early studies found CLL to be most common while the later work identified ALL as the most likely type (22). We conclude that present overall evidence does not support a causal link between exposure to electromagnetic fields and the leukaemias.

17. **Radiofrequency waves**. These are a form of non-ionizing radiation with frequencies ranging from a few kHz to several hundred Ghz. General community exposure is associated with radio and television broadcast antennae, satellite navigation systems, mobile phones and masts while occupational exposures include radar system operation, dielectric heaters, use or maintenance of broadcasting and telecommunications equipment. There are also medical uses including magnetic resonance imaging (MRI), diathermy and electrocautery. It is widely recognised that radiofrequency field exposure causes heating in body tissues, skin erythema and burns. Acute intense heat might damage the lens although cataract formation is not observed in humans following low dose chronic exposure. Heat effects are used to establish Radiofrequency Exposure guidelines. The present evidence on other adverse health effects including carcinogenicity in humans is limited. There is yet no evidence of carcinogenesis or leukaemogenesis in humans (23). There are a number of military occupational studies looking at radiofrequency exposure and cancer including leukaemia. In one Polish study based on service records there appeared to be increased risk in of several types of cancer (24). A later paper criticised the study attributing the results to inadequate methodology and not a real effect (25). Two US navy studies evaluated radar exposed naval personnel and veterans for cancer mortality and found no risk increases for cancer in general, leukaemia or brain cancer. In one of the US studies an increased risk of non lymphatic leukaemia was noted but this was not replicated in the other study and was observed in only one of three highly exposed sub groups (26) (27).

Chemicals

18. The nature of service life and principle service occupations are unlikely to precisely replicate civilian industrial worker experience in terms of potential or, actual exposure to chemical agents causally linked to the leukaemias. Formaldehyde is a colourless gas used mainly in the manufacture of resins for wood, paper and textiles and in the synthesis of a range of organic chemicals. Formaldehyde is most familiar as an aqueous solution of formalin, clear colourless and with a strong odour. Aqueous solutions of formalin are used as germicides and formaldehyde is contained in disinfectants and preservatives as well as engine exhaust fumes. It is considered that formaldehyde can cause nasopharyngeal cancer in humans,

although the evidence is conflicting. Findings in studies on leukaemia both in domestically and occupationally exposed populations have been inconsistent. The overall evidence was examined in the 2006 International Agency for Research on Cancer (IARC) monograph (28) when it was concluded that there was not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. This was revisited in a 2012 Monograph (29) when the Working Group was not in full agreement. A small majority found the evidence of a causal association "sufficient" but a minority considered it "limited" and concluded that more evidence was required. In particular, replication of a then pre-publication study that reported changes in the blood of exposed workers characteristic of myeloid leukaemia and myelodysplastic syndrome (29). A recent study of 14,000 chemical workers from six factories exposed to formaldehyde, many to high levels of exposure, found no increased risk of myeloid leukaemia (30).

19. Benzene was traditionally used in a variety of manufacturing processes involving leather, and rubber manufacture, paint spraying and removing, dry cleaning and printing. It has now been overtaken as a solvent by non aromatic chemicals but is still present in coal derivatives and petrol distillates. It was the first chemical shown to cause leukaemia, specifically AML (30). Later reports suggest that other types of leukaemia may also be due to benzene exposure and a dose response effect is now established between benzene exposure and the occurrence of AML. Studies have explored the mechanism of benzene haematotoxicity as well as the dose levels and exposure duration required for development of leukaemia. It is now clear that effects vary widely between individuals and that early benzene toxicity is reversible if exposure ceases. Adverse effects may also have a latent period of years before onset of symptoms or clinical disease (31). The evidence is that chronic exposure is more likely than acute dose to be associated with the development of acute myeloid leukaemia. One study (32) established that exposure to benzene at more than 20 ppm for more than six years was required for the development of AML. High level (more than 100 ppm) but short term exposures may cause transient blood changes with no long term effects. Long term low dose exposure (above 20 ppm) can cause reduced blood cell counts (33). Removal from benzene results in the peripheral blood picture returning to normal over a few months but longer term risk of leukaemia in this circumstance is unknown.

20. In conclusion, circumstances in which on balance of probabilities and post 6 April 2005, the leukaemias may be considered as recognised diseases, due to service occupational exposure are limited. This is because of the nature of principle service occupations and the working patterns, high standards of Health and Safety practice and prevention. Most individual cases are of unknown aetiology and cannot by their very nature be due to service. A possible occupational causal link including a formal Probability of causation calculation would be explored on the case facts where a minimum occupational dose of 50 mSv ionising radiation or more is registered. A chemical causal link to the leukaemias is most unlikely in the military context. Where, exceptionally, an award under AFCS is appropriate, the descriptor and award in the 2011 Order will be Table 4 Item 1 or 2. This will provide an award at Level 6 i.e. £140,000 and, from service termination for life, a GIP band B, based on 75% service salary.

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