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SPECIAL ARTICLE

GA^{2}LEN – The Global Allergy and Asthma European Network

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The European Community's Network on Allergies and Asthma was launched officially on 12 February 2004 in the presence of the European Commissioner Phillipe Bousquin. The current round of European Union funding for research includes two major new types of funding vehicle: integrated projects and networks of excellence. GA^{2}LEN represents one of the first networks of excellence to be put into play by the European Commission, and Commissioner Bousquin was careful to point out that as well as addressing a major public health problem in Europe, the new network should serve as a standard bearer for this new form of European funding and research co-operation. So, what lies beyond the political rhetoric? Why do we need a European Network at this time and what does it hope to achieve during the 5 years of its life?

Everyone agrees that allergic diseases such as asthma, allergic rhinitis (AR) and eczema have all increased over the last 30–40 years [1]. The European country with the highest prevalence of allergic disease is the UK where up to 32% of 13–14-year-olds report symptoms of asthma. While the prevalence rates vary between different European countries, the general upward trend is universal, making this a concern for all Europeans. Despite recent evidence that there has been a levelling off of the rate of asthma and related conditions in the UK [2], there remain worries that the prevalence rates could start to rise again in the UK and of course other countries have no wish to emulate the rates of asthma and allergic disease that are seen in the UK. Asthma is a major factor in children losing days from school, with potential consequences for their level of educational achievement while in adults asthma is an important cause of absence from the workplace. Besides the personal inconvenience, this represents a significant loss of productivity, and some estimates are as high as 9 billion working days lost because of asthma each year in the European Union. Asthma has direct medical costs in the form of medication and hospital care, with about 5% of the European medication budget currently being spent on caring for asthma. AR and eczema may not cause so many admissions to hospital as asthma but they also consume considerable amounts of healthcare resources in the form of medication.

Europe's potential contribution

Europe has contributed a great deal to our understanding of the causes behind this recent upsurge in asthma and allergic disease. There is now a general consensus that environmental factors associated with post-war prosperity have been responsible for the increasing number of people with allergic diseases [3]. However, there is no single clear explanation for this rise and many rival theories have been put forward. It is clear that some people are more at risk than others, because of their genetic inheritance. Equally, people with similar genetic inheritance have differing risks of developing allergic sensitization and allergic diseases depending on the level of prosperity in their respective countries. One of the principal goals of the new network is to bring together the groups working on the different theories behind the rise in allergies, in order to reach a more consistent and coherent view of what is truly important and how the various environmental factors may interact with each other and with genetically susceptible individuals to cause sensitization and disease.

Europe has contributed many original observations to the field but while some groups do work closely together and conduct collaborative research, there remains a high degree of fragmentation in the field. One of the main objectives of the Framework 6 programme is to bring together research groups that work in similar areas but are not currently linked up. The intention is to generate a European scientific research area, which will allow research groups to capitalize on each other's expertise but will also create a 'European laboratory' in which scientific questions can be tested in a variety of environments. Europe presents a very wide range of social, economic and climatic environments. This has been the wellspring for many of the important epidemiological observations made in the last 15 years [4]. It also represents a tremendous opportunity to test out the effectiveness of intervention strategies at different stages of the prosperity curve, to look at populations with different diets and different genetic backgrounds and perhaps to arrive at some wider understanding of which measures work across Europe and which are valid in a more restricted setting.

At the core of the GA^{2}LEN network are 25 research institutes, university departments and hospitals, spread across 16 European countries. Further research institutes will be involved either by liaison with a founder member in their country or by joining the network as it evolves and progresses over the next 5 years. The network has two additional partners: the European Academy of Allergology and Clinical Immunology, a scientific society comprising over 2500 scientists and clinicians working in the field of allergy and immunology, and the European Federation of Allergy and Asthma Associations, a patients' organization that will bring a vital perspective to the research and treatment agendas of the new network.

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Why the name?

Although the network will be European, the problem of allergies and asthma is a global issue, and we expect that ideas and information generated in the European theatre will inform science and policy throughout the world. Moreover, students of the history of medicine may recall that Galenus was the first physician to recognize the link between the nose and the lung.

What will the network do?

The activities supported by the network fall into three principal areas. These are an internal communication programme, a set of joint research projects on relevant issues and an external communication programme that will address education, scientific exchange, promulgation of best practice to the profession and to the public and the development of partnerships with industry and policy makers.

The internal communication programme is designed to bring together the existing body of knowledge and information that is held by the different partners and, where appropriate, to make this available to the entire network. A core element of this will be to generate databases of birth cohorts, population-based studies, gene banks and clinical networks that may accelerate the process of analysing risk factors and implementing strategies to prevent and reduce asthma and allergic diseases. In addition, the internal communications programme will support exchanges of researchers and other personnel between the principal centres, both to facilitate the research projects and to build up durable links between the research groups. A series of summer schools for young researchers is also planned. The first of these took place in Madeira and Dubrovnik during the summer of 2004.

The network's work packages

At the heart of the network is a set of nine research programmes addressing key steps in the development and progression of allergic diseases and asthma. The first four of these programmes will address areas in the initiation of allergic sensitization. These include the role of diet and nutritional factors in the onset of allergic disease, the role of infections in protecting children from the development of allergic sensitization, and the role of indoor air pollution and occupational exposure, especially in offices, as a factor in the development of asthma and allergies. Figure 1 shows the participants of the GA²LEN Workpackage Leaders meeting, held in Paris, 2004.

Nutrition and allergic disease

The possible role of nutrition and dietary factors in causation of allergy has been suspected for some time. Diet varies quite considerably across Europe and has changed in many different ways in the past 40 years. We now have access all year round to a range of foods that were previously unknown on the European continent. Vegetables and fruits that were once seasonal luxuries are now commonplace in our supermarkets. Even foodstuffs that have been present throughout this period may have changed in their content of essential minerals and nutrients. For example, selenium intake has been shown to be lower in people with asthma. Compared with North American soil, European soils are relatively poor in selenium. Changes in the sourcing of wheat during the last 30 years has led to a drift from Canadian and North American wheat to the consumption of European wheat. This has inevitably resulted in a reduced intake of selenium and it is legitimate to ask whether this might have contributed to the recent rise in asthma in Europe [5]. There are of course many other small but potentially important changes in European diet that need to be considered. Part of the role of the network will be to assess both the range of changes that have taken place and also their potential importance in the larger scale of things.

Infections and allergic disease

A lively debate concerns the possible role of childhood infections in protecting people from developing allergies and asthma. This forms part of the so-called hygiene hypothesis, which proposes that our immune systems have historically had to deal with a wide range of respiratory and water-borne

Fig. 1. Meeting of GA²LEN Workpackage Leaders at Paris CDG Airport in April 2004. (Left–right) Jean Bousquet (F), Norbert Fraeyman (B), Joanna Phillips (UK), Erika von Mutius (D), Francine Kaufmann (F), Peter Burney (UK), Benedicte Leynaert (F), Paul van Cauwenberge (B), Bert Brunekreef (NL), Kjell Larsson (SE), Aude Sirven (Management Office), Tony Frew (UK).

infections. While these infections were damaging, they may have damped down the immune system and prevented it from developing an allergic profile. Now that these infective insults are no longer operative, our immune systems may be reverting to their default setting, which is to produce an allergy-favouring phenotype (the T-helper type 2 cytokine pattern). This hypothesis has been strongly supported by evidence from the Baltic, from Germany and Italy. Some of the most persuasive evidence comes from studies of children brought up in farming communities where exposure to cow byres in the first year of life seems to have a strong protective effect against the development of allergic disease [6]. We need to understand how this piece of information can be extrapolated to the general population. It seems unlikely that we will be able to build cow byres and stables into all our houses but perhaps we could reproduce the beneficial effects of this lifestyle by a vaccination policy or the appropriate use of pro-biotics. The Baltic data suggest that the microbiology of our guts has changed dramatically in the more prosperous parts of Europe over the last 30 years [7]. Within the European network, it should be possible to establish and maintain comparative studies using the diversity of diet and environment in Europe and applying any therapeutic interventions in a variety of settings to establish the efficacy of microbiological intervention.

Air pollution and allergic disease

There is widespread public concern about the possible health effects of air pollution. Most of this is focused on the impact of outdoor air pollutants, which are principally the result of motor vehicle traffic and fossil fuel burning for the production of electric power. However, most Europeans spend much of their lives indoors and attention is now turning to the role of the indoor environment, including tobacco smoke, house dust mites, animal danders, moulds and fungi, as well as volatile organic compounds released from building materials and paintwork. It seems likely that these different factors may all be important, to varying degrees, in different areas, but the irrelative importance may vary according to the geography and climate. Factors that may be important in the north of Europe may be completely irrelevant in the south and there may be similar east–west gradients [8]. Recommendations for healthy housing may therefore need to be tailored to the local environment. The network expects to achieve a better understanding of the relative importance of these factors and the extent to which they are robust between centres, or variable according to other geographic and climatic variations.

Occupational factors in allergic disease

There is widespread awareness of the role of occupational chemical exposure in the causation of asthma but the traditional focus has been on paint spraying, the plastics industry and occupations that involve the handling of organic dusts (e.g. baking). The European Community Respiratory Health Survey identified office workers as a group who are particularly susceptible to asthma [9]. It remains unclear as to whether this is because of people with allergies and asthma selecting office work as a safer alternative to manual occupations or whether the office environment presents as yet unidentified hazards. One of the work packages in GA^{2}LEN will address the patterns of asthma among office workers with a view to identifying subgroups of workers who have work-related asthma together with any confounding variables. A separate study will look at the role of cleaning agents used in commercial and domestic settings as a potential cause of asthma.

Onset and progression of asthma

The second group of work packages will look at factors that affect the onset and progression of disease. It is well known that many people become sensitized but do not progress to clinical symptoms. Little is known about the factors that determine whether any given atopic individual will go on and develop symptoms. This means that care is needed in the interpretation of laboratory tests such as skin prick tests and specific IgE measurements. Ideally, these tests should give the clinician an indication of whether the patient's symptoms are caused by allergy but, for the time being, a considerable degree of diagnostic judgement is required. We know that there are considerable gender differences in the symptomatology of allergic disease. For example, boys are more likely to have asthma than girls but by adulthood, asthma is more common in women than men. There is epidemiological evidence to suggest that women's respiratory health is more likely to be affected by air pollution and smoking but the reasons for this remain uncertain. Gender differences also exist in relation to peoples' willingness to obtain medical care and in the way that health professionals treat their patients. One of the GA^{2}LEN work packages will address the biological and cultural issues associated with gender and allergic disease and will feed its findings into the strategies for patient education and health promotion.

Long-term outcomes of allergic disease

The third group of work packages will address long-term outcomes for allergic disease. We know that some patients with asthma will develop chronic respiratory disability while others remain relatively easy to control. Some of this variability relates to the 'remodelling' of the airways that occurs in asthma. Some of the classical remodelling changes are present from a very early age and indeed may antedate the onset of symptoms [10]. It is therefore unclear as to whether these early signs of remodelling are actually responsible for the functional disability that occurs in long-established asthma. Several of the groups involved in GA^{2}LEN have an interest in this area, with individual research programmes addressing the factors that determine chronicity and severity of asthma. GA^{2}LEN should bring these groups together to share tissue samples and ideas that may lead to new joint research programmes, as well as informing the existing research programmes addressing this important area of asthma biology.

Clinical care for patients with allergic disease

In parallel, the network will address the clinical care and quality of life of people with allergic diseases and asthma. We are all aware of wide variations in allergy practice in different

parts of Europe and indeed within individual European countries. To some extent, these variations reflect historic provision of services but they also reflect differing national priorities for the healthcare budget. Nobody is suggesting that all European countries should have a harmonized system for allergy care but there is clearly scope for us to learn from each other in the optimization of clinical care and the appropriate targeting of conditions where we can make a difference. Where appropriate, we expect that GA²LEN will enable specialist centres to share best practice and to advise national and regional policy makers on where to spend (and where not to spend) their healthcare budgets to optimize the care of patients with allergic diseases.

Genetics and post-genomics

Finally, the ninth work package will focus on the genetic aspects of asthma and allergies. As outlined above, the general consensus is that the recent rise in allergies and asthma must be driven by changes in the environment [3]. Nevertheless, we know that allergies have a strong genetic component and most researchers are convinced that the environmental factors must be working on a susceptible genotype or at the very least, that there may be genetically controlled pathways that we might be able to influence [11]. The genetics work package will therefore interface with all the other work packages, looking at the genetics, genomics and post-genomic aspects of the different interactions identified in the other research programmes. Several of the groups involved in GA²LEN have gene banks and other resources that might usefully be combined to provide greater insight into the genetic aspects of asthma and allergic disease.

Through these various activities, the participants in GA²LEN believe that we will achieve a better understanding of the causes, or perhaps more accurately the combinations of causes, of asthma and allergic disease. This in turn will allow us to give more robust and, to be candid, more honest advice to policy makers both in Europe and throughout the world. European science has made major contributions to our understanding of allergic disease and asthma. We have a tremendous resource in the diversity of our countries and environments as well as in the scientific culture of the continent. Some research groups have already established good collaborative relationships through previous European funding schemes or indeed through personal contacts but there is plenty of scope to increase interaction and collaboration, from which everyone will benefit. We earnestly hope that the funding provided by the EU through the Sixth Framework Programme will bring together the experts in the various centres and indeed throughout Europe to improve our understanding of allergic conditions, to develop novel diagnostic tests and treatment strategies, and most important of all to improve the lot of patients with allergic disease and the lot of future generations of children who may otherwise be caught up in the rising tide of allergy.

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