The rise and fall of FMF research – Fifty years of publications

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterized by recurrent self limited episodes of fever, peritonitis, pleuritis, arthritis or erysipelas-like erythema (1). This recurrent polyserositis predominantly affects populations living in Armenia, Turkey and the Middle East. However, sporadic cases or small series have been reported in Spain, Italy, Germany, Poland, Japan and Australia. The disease was recognized as a specific entity only in 1945 and was first described by S. Siegal – a physician from Mount Sinai Hospital in New York (2).

At the beginning most studies focused on sporadic cases or small series which attempted to establish the common clinical manifestations of the disease, the nature of amyloidosis which may complicate it and various unsuccessful therapeutic trials (3-5). Later studies investigated the pathophysiology of the disease, looking for a possible role of the immune system (6-8). During the following years, the field of FMF research expanded and many studies on various issues have been published.

However, in the last year (2004) a trend reflecting an on-going decline in research on FMF has been noted. As co-editor of the FMF section in the current supplement I became particularly interested in this issue and realized in fact that the proportion of publications on FMF has become quite small. In order to identify a possible reason for this, we decided to analyze the patterns and contents of publications of all papers on FMF since 1955 (i.e., over the last 50 years). We have tried to understand the underlying causes or driving forces for the peaks and nadirs in their amount, quality and the subjects investigated during these years.

Method

We screened PUBMED for all publications using the search term: "Familial Mediterranean Fever" without any limitations and divided the results into 4 different categories, defined as follows:

1. Case reports and Letters to the Editor: Descriptions of 1-3 cases of FMF patients in the same article.
2. Reviews and Editorials: Either descriptions of special cases or a comment on an article published in the same issue of the Journal.
3. Epidemiological studies: Studies analysing various cohorts of FMF patients, or highlighting special clinical manifestations, treatment, associations with other diseases, etc.
4. Basic science investigations: Any study where "bench work" was needed or employed: for example, studies in which mutations were analyzed or serum cytokines were measured, as well as investigations of the molecular effect of pyrin within the cells.

We also classified the papers according to the years in which they were written, the countries in which the work was conducted, and the journals in which they were published.

Results

The first paper on FMF which appeared in the PubMed dated from 1955 (9). Up

Fig. 1. A graph showing the yearly publications on FMF between 1955-2004. Several peaks of publications are shown. Adeclining trend can be noted for the year 2004.

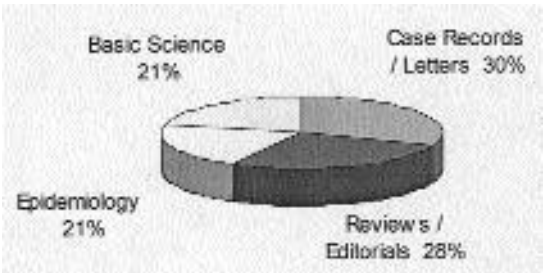


Fig. 2. Distribution of total publications according to the different categories since 1955.

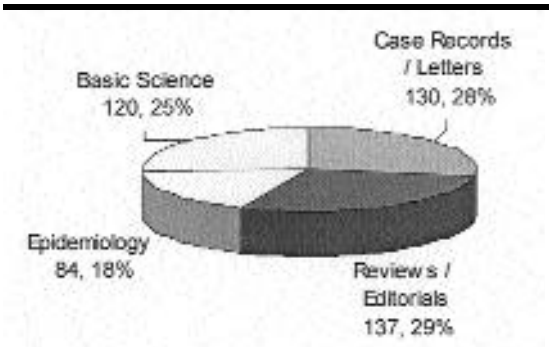


Fig. 3. Distribution of total publications according to the different categories between 1998 and 2004. The exact number of publications and the relative percentage of each category are also given.

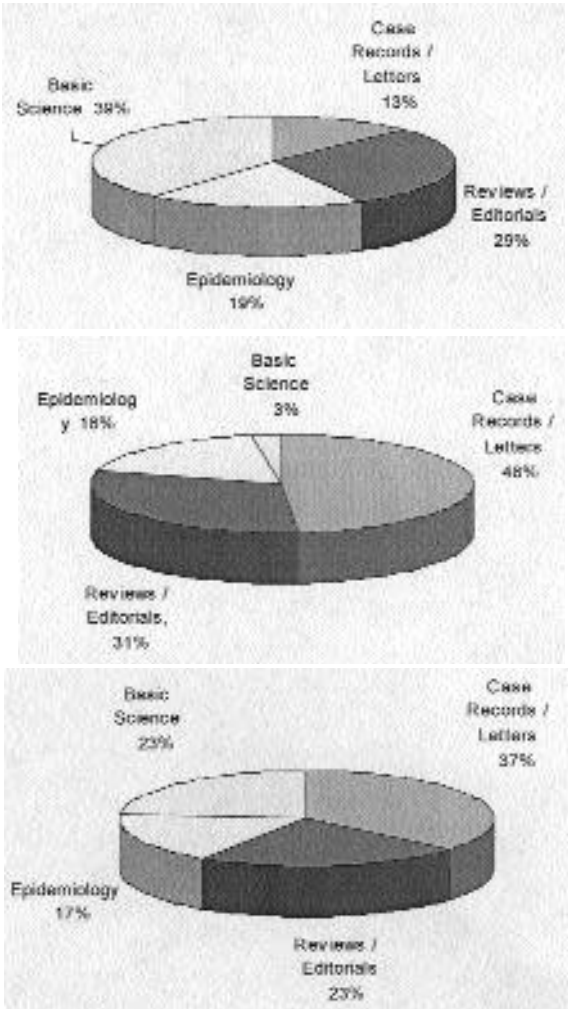


Fig. 4. Distribution of total publications according to the different categories during the years 1977 (**a**), 1989 (**b**), and 1992 (**c**).

to 31 December 2004, a total of 1,721 publications appeared under this heading. However, when we screened each paper separately, we realized that many came up mistakenly since they dealt with other "Periodic diseases" such as "periodic paralysis", "periodic migraine" etc. Therefore, we excluded these publications and analyzed 1,228 that dealt with FMF only. An additional 104 papers on other periodic autoinflammatory diseases, e.g. TNF receptor associated periodic syndrome (TRAPS), Hyper IgD syndrome (HIDS) and Muckle-Wells syndrome/Familial cold urticaria (MWS/FCU), were also screened.

Figure 1 presents a graph showing the total number of publications on FMF that have appeared each year since 1955. It can be seen that at the beginning there were relatively few, most of them case reports or reviews sparked by the recognition of a new clinical entity. However, in the years 1977, 1981-2, 1989, 1992 and from 1998 to 2004 there were some peaks, with the highest number of papers appearing in 2003 followed by a slight decline one year later.

Analysis of the papers by category showed that almost 60% of the papers were case reports, letters or reviews, whereas only 21% reported original basic research and a similar percentage consisted of epidemiological analyses of FMF cohorts (Fig. 2). However, analysis of the publications from recent years (1998 – 2004) disclosed a slight increase in the proportion of basic research being done, although the percentage of case reports and reviews remained the same (~60%) and epidemiological studies were slightly decreased (Fig. 3).

Analysis of the various categories of publications during the peaks demonstrated in Figure 1 is shown in Figure 4. In 1977 and from 1998 onwards, the increase in the number of publications was due to a relatively larger proportion of research in basic science whereas during the peaks of 1982 (not shown), 1989 and 1992 the "lion's share" consisted of case descriptions and reviews.

One question that came up during the current screening of publications on FMF and other periodic fever syndromes was whether research in the two fields might not have a mutual effect. Figure 5 shows that since 1994 there has been a gradual increase in the

Fig. 5. The emergence of publications of periodic diseases as compared with FMF publications since 1994.

research on FMF and periodic fevers with a possible trend in the opposite direction during the year 2004.

Regarding the countries from which the largest numbers of publications emerged, we discovered the following. During the first ten years (1955-1965) most of the papers came from the United States, France, Israel and Armenia (and Russia) (Fig. 6). Since the late 1960s, Turkey has become a major source of FMF research and publications, and during the past ten years most of the publications have come from Turkey, Israel, the USAand western Europe (France, Italy and Spain). In the USA, most of the patients studied in the 1960s and 1970s were of Armenian origin, whereas lately many patients are either North African Jews or Arabs. In Europe, most patients are of North African origin, although some studies describe small cohorts of ethnic Greeks and Italians (10, 11). Figures 6 and 7 demonstrate the total number of publications according to the different countries. A noticeable flurry of publications could be seen during the years 1998-2003 in all the countries involved in FMF research (Fig. 6). Nevertheless, Israel and Turkey have contributed the largest number of papers during the past 50 years (Fig. 7).

Discussion

The motivation to investigate the pattern of publication in the area of FMF during the last 50 years was the impression that in the last year (2004) there has been a sharp decline in the number of papers published. The question that must be asked is whether this represents an incidental change or if it re-

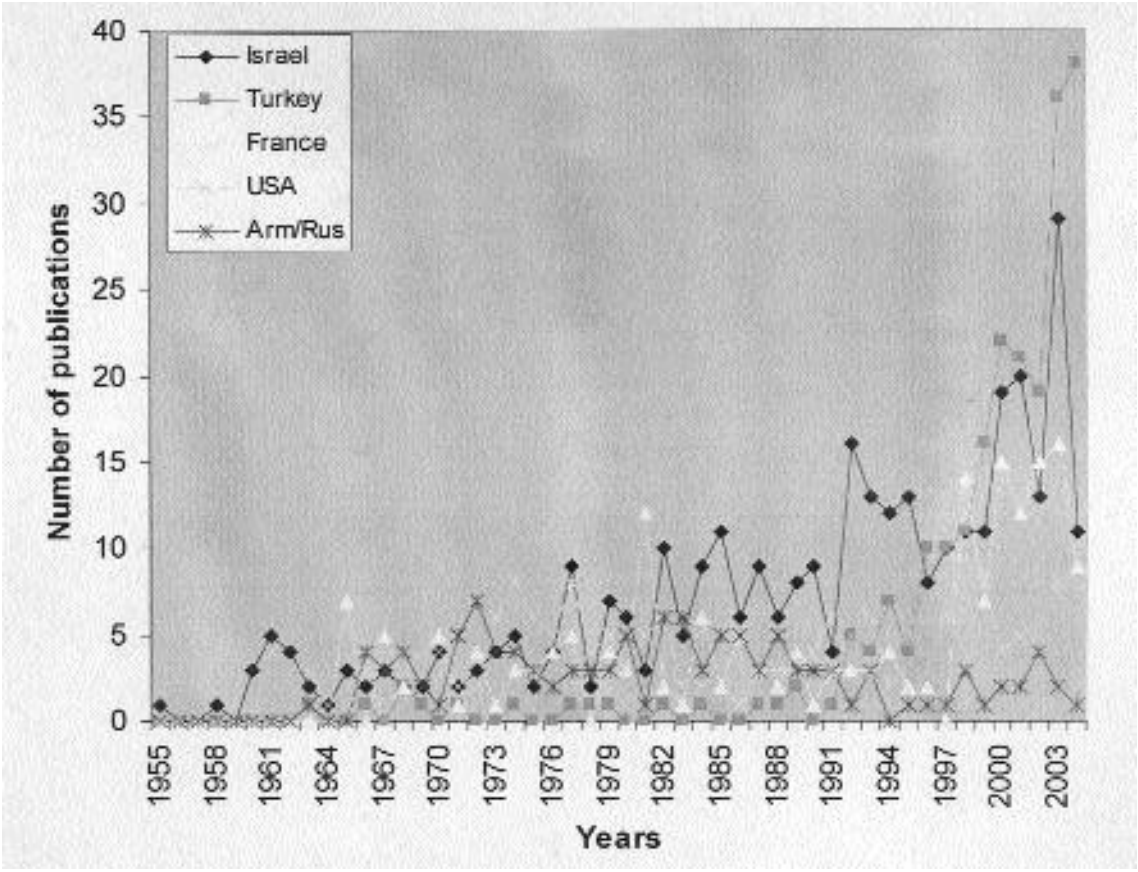
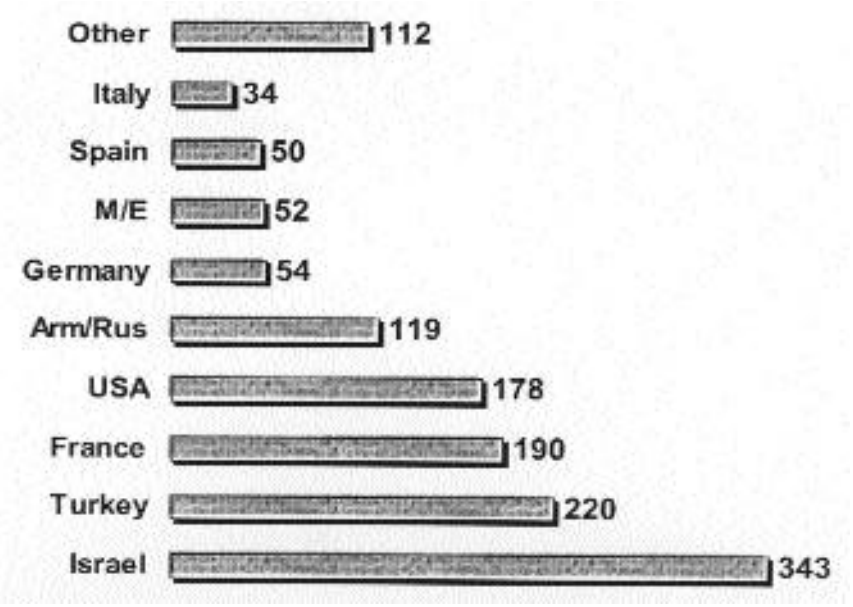


Fig. 6. A graph showing the number of publications in each of the five countries since 1955. A striking increase in the number can be seen from 1978. Turkey has become a major center of research since then.



ùThe total number of publications contributed by each of the countries since 1955. Arm/Russ: Armenia and Russia. M/E: Middle Eastern countries such as Kuwait, Egypt, and Jordan. Other countries include Japan, Australia and the UK.

flects the start of a trend presaging a somewhat bleak future for FMF research. Our analysis disclosed several points.

As expected, over the years increased awareness of the disease led to the participation of many authors even from countries where FMF is not prevalent. Many were attracted by this fascinating disease and started to describe sporadic cases which they encountered or to review the subject in order to disseminate the available knowledge on FMF among physicians in their countries. A smaller number of researchers sought to understand the pathophysiology of the disease by beginning to do basic research.

What immediately sprang to eye as a result of this survey was the dominant proportion of case reports and reviews over the years, including the last 7 years. Almost 60% of the publications fell into these categories, whereas epidemiological or bench work studies remained around 20% each. This distribution of publications may be considered acceptable during the years immediately following the description of a new clinical entity, since case reports can contribute data that will help clinicians recognize patients with the new disease. However, when our knowledge of a disease has become well established, the description of an additional case is not contributory unless it exemplifies a very special and unusual disease course or treatment.

Looking at the graph in Figure 1, several peaks were evident in the years 1977, 1981-2, 1989, 1992 and from 1998 to 2003. Why are there peaks and nadirs in the number of publications rather than a steady increase? In order to explain this finding we again examined the various papers for each of these years. The peak in 1977 was due to a relative rise in "basic science" papers exploring the possible role of the immune system in FMF, HLA correlations with the disease, and serum levels of complement in FMF (7, 12) (Fig. 4a). These studies were carried out by Armenian, Israeli and French groups in parallel. In 1981-1982 and in 1989, the increase in the number of papers was due to a significant rise in the number of case reports and reviews. The reason for this is not clear. However, the proportion of research papers in this year was markedly low (Fig. 4b) and 13 out of the 39 publications (33%) were written in languages other than English (Russian, German, Dutch and Hebrew). In the year 1992, there were 47 papers of which 28 (60%) were either case reports or reviews and 11 (23%) were bench work publications. In this year, the gene for FMF was located in the short arm of chromosome 16 and there was a meeting in Jerusalem on the topic "Pregnancy and Rheumatic Diseases" (13). Some of the studies presented here dealt with FMF and pregnancy and were published in a special issue of the *Journal of Reproductive Immunology*. It is possible that the meeting provided the stimulus for the increased number of publications in this year. The most impressive burst in FMF publications took place from 1998 to 2003. In these years the relative proportion of "basic science" studies also slightly increased. Several events related to FMF occurred during these years. The most significant was the isolation of the MEFV gene at the end of 1997 (14,15). Secondly, there were several international conferences on FMF – in Jerusalem (1997), Antalya (2000) and Montpellier (2003). In addition, a special annual supplement of the journal *Clinical and Experimental Rheumatology* dedicated to FMF and Behcet's disease has been appearing every year since 2001. It seems that all of these activities and events pushed many researchers to increase and enhance their research in order to present and/or publish their findings.

An additional indirect factor was the identification of genes involved in other periodic fever syndromes (16,17). Their similarities led to the search for underlying common denominators, thereby further contributing to the field of FMF. However, in 2004 the number of publications on periodic fever diseases was still increasing whereas the publications on FMF decreased (Fig. 5). If this trend continues, the positive effect of research into periodic fever syndromes on FMF studies will not last.

Since the genes associated with FMF and other periodic fever diseases play a major role in inflammation, it is expected that research interest will shift towards the molecular basis of the inflammatory process rather than of a particular disease. Moreover, since we already know how to diagnose and treat patients with FMF, the issues re-

maining to be elucidated are connected with the pathogenesis of the disease. These subjects are more complex and demanding and therefore fewer researchers are willing or capable of dealing with them. This may be an additional reason for a possible decline in the amount of FMF research and publications in the coming years.

Regarding the contribution of the various countries, Figures 6 and 7 show that the leading states are Israel, Turkey, France, the USA, and Armenia/ Russia. This is not surprising since FMF is most common in these countries. In France, most of the patients are of North African origin whereas in the USA the patients are either of Armenian descent or are immigrants from North Africa and the Middle East. It can also be seen that the great boost in publications occurred following 1997 (the year the MEFVgene was isolated). Still, most of the studies consisted of case reports, reviews or epidemiological analyses rather than bench work research. Overall, the number of publications declined in 2004 in most countries except for Turkey (Figs. 6, 7).

In summary, it seems that the stimulus for more research and publications in FMF can be traced back to major discoveries made in the fields of etiology or therapy (such as the introduction of colchicine or the isolation of the MEFV gene) (13-18). Other factors contributing to the writing of papers are the organization of international conferences or the editing of special issues of international journals dedicated to this disease. If these objectives are lacking, the danger of serious decline in FMF research is to be expected.

In the future, research on FMF should concentrate on reaching a basic understanding of the role of the MEFV gene in the inflammatory attacks, and on elucidating the mechanism by which colchicine or other potential medications exert their beneficial effect. Epidemiological studies should also be performed in order to resolve the practical problems of patients, such as the justification for amniocentesis in pregnant FMF patients taking colchicine or regarding the possible relationship between FMF attacks and peritoneal fibrosis. They should also try to investigate the inter-relationship between FMF and other inflammatory diseases.

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