said he; “they are well enough trained.” “Well,” I replied, “you have been teaching students at least for twenty-five years?” “Yes,” said he. Then I asked him: “Can you tell me the symptoms of which the majority of people complain when they fall sick?” After some consideration he said, “No.” I said, “The most common complaint is exhaustion. Can you tell me what is exhaustion?” He again, after a little consideration, said “No.” “So,” I said, “here is a symptom of the most common kind, a symptom which, when understood, throws a flood of light upon the patient’s state, and yet you, who reckon to be able to teach students how to examine patients, have never given it the slightest consideration.” I quote this incident to show what should be the first step in investigating disease, and the only individual whose opportunity permits him to take it. The necessity that the general practitioner should participate in other fields of research is obvious as soon as a real perception of medical research is obtained.

I know quite well that these views at present will fail to carry conviction. All I wish you to do is to pause from time to time and ask whether they are true.

Commentary: A thesis that still warrants defence and promotion

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Introduction

Sir James Mackenzie (1852 to 1925) is known as ‘the father of general practice-based research’. 1 His eponymous legacy includes the Chairs of General Practice at the Universities of Aberdeen and Edinburgh, and the building where the authors of this commentary pursue their research, as well as the principal annual lecture of the Royal College of General Practitioners. From humble agricultural origins in rural Perthshire, Mackenzie overcame early social and educational hurdles to study medicine in Edinburgh, then pursued a career in general practice in Burnley. During this full-time clinical post, he initiated the systematic observation of his patients that led to his stellar research career, including an established international reputation in cardiology, discovery of novel and important insights into heart rhythms and the use of digitalis, appointment as a Fellow of the Royal Society and a knighthood.

At St Andrews University, the Chair of Public Health and Social Medicine is also named after Mackenzie, and it is at St Andrews University that his heart remains (literally, in the anatomy department). 2 Although he had re-located his professional and academic base to London when his career took off, he left there at its height, at the age of 64 years, to establish the Institute for Clinical Research in St Andrews. This is where he was based at the time he presented the accompanying re-printed article. 3 Although the institute was ultimately short lived, surviving only briefly after Mackenzie’s death, it was innovative in bringing together all the General Practitioners (GPs) working in the town, for the purposes of collecting and using clinical data for research. These included the systematic recording of routine observations, which were used in longitudinal studies, and the development of record-keeping systems that eventually influenced national policy. By working with general practice colleagues in St Andrews, he made real his key insight: that systematic observation and recording of symptoms and signs in a whole population could provide essential
information on the epidemiology, prognosis and mechanisms of disease.

Through this pioneering approach, he demonstrated the importance of epidemiology in non-infectious disease, the role of high-quality routine records in this endeavour and the importance of the generalist in researching diseases that were (and still are) often considered to be in the domain of the specialist. He presented, discussed and exemplified these themes in the accompanying article, and, in doing so, highlighted some issues that were as important and controversial in 1921 as they are today.

**Lessons from Mackenzie that still resonate**

**Primary care research**

At the start of Mackenzie's career in 1879, general practice was seen as 'the lowest place in the [medical] profession', by himself and among others. A century later, the discipline of academic general practice was making substantial contributions to university teaching and research (as described in 'The Mackenzie Report'), and by 2010, one of the emeritus Mackenzie Professors of General Practice described the success of primary care research in comparison with other university disciplines. By the time in his career Mackenzie presented this article, he had demonstrated a broader view of his academic discipline, certainly more than that with which he had left Edinburgh, and probably more than most clinical academics currently hold. He considered that primary care generated many or most of the unanswered research questions about many or most of the commonest diseases, and that it was GPs who were best placed and best equipped to collect the relevant data with which to answer them. He regretted the compartmentalizing of medical research into specialties and its effect of narrowing the field of vision of the researchers. Similarly, he saw basic and laboratory science (particularly pathology) as subservient to clinical science, with its main purpose being to identify the biological mechanisms behind clinical observations, rather than to drive clinical practice.

'[The specialist’s] methods are no doubt of great value in detecting disease after it has advanced so far as to damage the tissues, but the aim of medicine being to prevent and cure disease, he does not help to find out the disease before it has produced damage. It is this extraordinary limitation of outlook which retards the progress of medicine.'

This principle drove him to seek the true prognostic nature of signs (such as heart murmurs), resulting in the reversal of the practice of consigning all individuals with a heart murmur to a career as an invalid, and his identification of auricular fibrillation, and management thereof, before it was understood physiologically or pathologically. Nonetheless, he did, at times, support collaboration between clinicians and basic scientists, as well as between specialists and generalists. It was perhaps a lack of this collaboration in his later years that led to more rejection than acceptance of his output by his contemporaries. After the success and fame of the main part of his career, his theories moved too far out of step with the thinking of the time, and he would not entertain their revision. Today, the lesson is the strengths of an open-minded generalist approach, but in collaboration with multiple subject-specific experts, allowing translation from ‘the laboratory to the bedside and back again’ (or actually beyond the bedside into the consulting room and further into the community).

**Prevention as the ‘highest aim’ of medical research**

Although research effort at the time focused on the management of established disease (or of ‘attributed disease’: signs presumed to be associated with pathology observed post-mortem), Mackenzie believed that the prevention of disease was the most important focus for research. Although this is now at the heart of epidemiology and public health, Mackenzie’s thesis was important in its establishment as a key principle. His starting point was ‘the prevention of diseases which are common among the people of the country’. He was hampered by two main factors: it was unknown which were the common diseases (because population-based research had not been done, and current knowledge was based on information from specialist centres), and the precursors of serious disease were also unknown. The answer to both of these questions could best come from general practice, where most diseases were presented and managed, and where undifferentiated symptoms and signs also presented. By documenting and following up early signs to establish their prognostic significance, it would eventually be clear which ones needed intervention, as indicators of future serious disease, and which ones could be ignored.

This focus on symptoms rather than established disease was derided in his day, but Mackenzie’s adherence to his belief has now proven its worth. This effort is still a major pursuit in today’s academic general practice community, e.g. in determining which clinical presentations indicate significant cancer risk, and therefore require urgent intervention. Mackenzie was concerned with his inability to give accurate prognoses to common presentations, and noted that this also hampered good medical care and disease prevention and knowing whether and when to intervene and even whom to recruit for military service. Although much work has been done in this field since 1921, these quandaries are still important, and there remain many unanswered
questions. Furthermore, without an understanding of which symptoms place the greatest burden on the health services, irrespective of serious disease, it is impossible to provide adequate resources to deal with them. As well as research on the epidemiology of signs and symptoms, current research focuses on the discovery of biomarkers, such as urine proteomics, to allow the early detection and management of disease and evaluation of responses to treatment. This is beyond Mackenzie’s imagination but within his principled approach, so long as biomarker discovery is pursued in collaboration with generalist clinical researchers to ensure population relevance.

Importance of observation in medical research
Mackenzie asserted that we need to base medical practice in research derived from observation, especially history taking. Again, his reliance on these basic techniques in preference to technological investigation drew derision, as he describes here. However, his views will come as no surprise to medical undergraduates and generalist clinical trainees, who are still taught to let history, then examination, serve as the basis for their clinical practice. In the modern era, where high volumes of clinical data and technologies, such as high-throughput genotyping or expensive imaging techniques, often predominate (at least as a proportion of overall funding), it is salutary to recall Mackenzie’s emphasis on observation. There is little point in working with high-quality genotype data if the quality of the phenotype derived from observation is weak. Similarly, in studies of gene–environment interaction, it is estimated that high-quality measurement of continuous traits, derived through meticulous observation, can reduce the required sample size by a factor of twenty.

Careful observation remains central to clinical, epidemiological and translational research, and increasingly extends beyond quantification to the use of parallel qualitative methods, both in the development of meaningful research instruments and to explain in depth the results that arise. In clinical practice, particularly primary care, most interventions may be considered ‘complex’, and there is now strong guidance that trials of complex interventions should not proceed without preparatory and parallel qualitative and observational components along with quantitative measurement. Mixed methods approaches are more commonplace, and are aimed at applying the results of studies to the individual in the consulting room, who often differs in important ways from those studied in clinical trials, and whose views of an intervention’s relevance and acceptability will be critical to real-world impact. Current clinical research places important emphasis on the involvement of (potential) users in the design of interventions and their evaluations, and there are examples where this has proven influential. Observation of patients is equally central to the important step of translating research beyond the clinical trial to implementation in practice, and the evaluation of this implementation. The introduction of service users (i.e. patients) to professional research teams is novel in clinical research, but a natural development of the patient-centred observational approach promoted by Mackenzie, who trusted his patients’ word more than his colleagues’ opinions.

As with his views on multi-disciplinary collaboration, however, it is also instructive to note Mackenzie’s latter tendency to eschew technology completely, and the negative effect of this. He saw the chief role for machines, such as the electrocardiograph, which he mistrusted, as being to allow the physician’s diagnostic skills to be honed sufficiently to allow him to discard it. Clearly, modern medicine has rightly embraced technology in diagnosis, but there is a balance to be struck between technology and personal observation.

Importance of medical records in research
Of course, there is little point in undertaking detailed high-quality observation if the observer does not record his/her findings. For both clinical practice and research, these records need to be systematic and consistent, to allow subsequent review and analysis. Although in modern clinical practice, the chief purposes of keeping records might be medico-legal and the recording and facilitation of patient care, Mackenzie saw it as being ‘to lay the basis of prognosis’ and to identify, in groups of patients with assembled records, patterns of signs, symptoms and other factors associated with eventual outcomes. Research based on routinely collected medical records is now increasingly commonplace and influential, on a scale far beyond that which could have been imagined in 1921. Considerable current effort is expended on combining large and very large data sets to allow the generation of sample sizes of sufficient power to detect important but rare outcomes, or important but small risks or extreme phenotype analyses. As well as presenting complex bioinformatics and diplomatic and logistic challenges, this work needs to be accompanied by detailed consideration of the ethical and legal aspects, including data sharing and access, and respect for the views and rights of the individual patients who have contributed the data. Although research studies must collect and record precise data according to rigorous protocols, this is not true of the more pragmatic and practical clinical data, which contribute to these data sets. We therefore return to Mackenzie’s belief in the value of high-quality record keeping and storage, which was one of the four aims of the St Andrews Institute for Clinical Research, and regarded as one of its most important legacies. The Institute’s main funding was from the Medical Research Council, who are one of the funders currently seeking to
support bioinformatics initiatives, along with European consortia, and this is important work. It needs, though, to be matched by medical education and training in the collection and recording of clinical data and resources to allow this to be done within the constraints of daily clinical practice or greater integration of patient-reported outcome measures into clinical records.

Role of basing research paradigms on current trends

Finally, we can learn from Mackenzie’s scepticism about restricting one’s view of health and illness to that dictated by current scientific trends or paradigms. Historically, we are aware of the persistence and penetrance of the Hippocratic approach to medicine, in which aetiology and treatment were determined according to perceived imbalances in the four humours. After >2000 years, it was only a systematic approach to medical science that discredited this view, in the century of Mackenzie’s birth. In his day, he rejected, with some success, theories of disease that were based only on histopathological (‘dead-house’) appearances of organs after death, arguing that it was the dynamic pre-morbid and diseased function, along with their associated symptoms and signs, that were vital in determining disease and identifying treatment needs (and outcomes). Subsequently, although recognizing the value of microbiology in the aetiology of illness, he was wary of exaggerated claims of its significance, or at least of its capacity to minimize the importance of other important factors. Current medical research is focused on a molecular understanding of physiology and disease, centring around genomics, proteomics and other ‘omics’. Early in this new age, we were promised as its most important outcome ‘a new taxonomy of disease’, based on a biological rather than a phenotypic framework. Although this may in the end occur, with some exceptions it has yet to materialize, and the additional value of biological disease definitions over existing definitions based on clinical observation needs to be established on a case-by-case basis rather than being assumed. It is possible that the view is based as much on current availability of technologies and expertise as on clinical need, though there is undoubtedly much to be gained from an understanding of humans and our diseases at a molecular level. A reductionist molecular approach to ‘dia-prognosis’ may be fruitful in identifying and targeting drug treatments, but we need to balance this with an integrational perspective, recognizing that combinations of conditions have complex effects in individuals. As in other matters, Mackenzie is likely to have rejected a molecular approach to medicine in his later life, at the cost of being able to integrate his own meticulous research into a bigger picture. The lesson for us, as researchers or practising physicians, is to be informed by all available scientific evidence, treating each source with appropriate critical review, and to ask what it means for our patients.

Conclusions

In this article, and throughout his career, Mackenzie promoted the importance of general practice-based research, founded on rigorous observation and record keeping and a critical approach to the prevailing research and educational consensus. These principles, coupled with hard work, dedication and vision, allowed great advances in practice, research and policy. Current medical research continues to be informed by many of his ideals, but the generalist approach, so crucial in integrating and implementing findings from diverse scientific sources, remains in danger of being swamped by specialist single-field studies. Even today, medical research funding bodies focus their resources on the development of specific interventions, rather than on disease prevention or on understanding how to apply effective interventions in real-world populations with high levels of comorbidity.

The academic primary care community continues to debate the nature of the ‘basic research’ that is required to underpin and develop our discipline, and the putative conclusions of this debate follow naturally from Mackenzie’s article. We have much to learn from Mackenzie’s vision and persistence, and just as much to learn from his latter more negative attitudes. Perhaps, most importantly, we should begin our research, as Mackenzie did, by asking what clinical questions need to be answered, rather than what use we can find for the available technology.

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