

TOPIC FOR DISCUSSION

The future endocrine patient. Reflections on the future of clinical endocrinology

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Abstract

In recent years the future position of clinical endocrinology has been extensively discussed by Western European endocrine societies. Clinical endocrinology seems to suffer from being too intellectual, generating too little income, and lacking too few spectacular interventions. In this manuscript we describe 'the endocrine patient' of the past, the present, and the future. Complete therapeutic breakthroughs resulting in 'cure' are compared with 'halfway technologies' which help in creating the (life-long) chronic endocrine patient. The potential use of molecular diagnostics in optimizing hormone replacement therapy is discussed. Clinical endocrinology is at risk of developing into a subspecialty where life-style drugs created for new diseases or conditions are offered, but also actively pursued by otherwise healthy individuals (e.g. in normal short stature, regulation of appetite, body composition, sexuality, reproduction and aging). The potential opportunities and risks for clinical endocrinology in creating 'the endocrine patient' of the future are discussed.

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Introduction

There is a continuous evolution within and between the disciplines, both scientifically and in terms of clinical practice. These developments also affect clinical endocrinology, a subspecialty in internal medicine and pediatrics which became established in the 1950s.

In a recent series of articles in which the current position of clinical endocrinology in a number of European countries was discussed, several potential threats concerning the future were raised (1–7). Endocrinology is perceived by some to have an 'identity' problem, with regard to its importance as a subspecialty in internal medicine. More and more general practitioners, cardiologists, nephrologists, urologists, and gynecologists actively participate in the care of endocrine patients. As endocrinologists in general do not carry out sophisticated and expensive (i.e. 'money-generating') procedures, their financial contribution to departments of medicine is smaller than that of most other subspecialties. In countries where the health care budget is mainly calculated on the basis of in-patient hospital care, the position of clinical endocrinology which has become more and more an out-patient specialty has weakened considerably. Nonetheless, a recent survey in The Netherlands showed that about

30% of all patients seen by internists have diseases which are part of clinical endocrinology.

In the present article we analyze the position of clinical endocrinology, describing 'the endocrine patient' of the past, the present, and especially of the future. In addition, the necessary infrastructure of an endocrine division, as well as some aspects of education are discussed.

The case of diabetes mellitus

Up until 1921, the year that insulin was discovered, most diabetic patients rapidly died from hyperglycemic coma despite rigorous dietary regulation (8, 9). The discovery and clinical introduction of insulin enormously improved this life-threatening condition, and it was infections, especially tuberculosis, which became the leading causes of death in patients with diabetes mellitus in the subsequent 20 years (Fig. 1). The discovery of antibiotic and tuberculostatic drugs diminished infection-related deaths in the subsequent 20 years. During this period secondary complications in the kidney were recognized in the now much longer surviving patients and by 1950–1960 renal insufficiency became the major cause of death. Renal dialysis and later kidney transplantation virtually eliminated renal failure as a

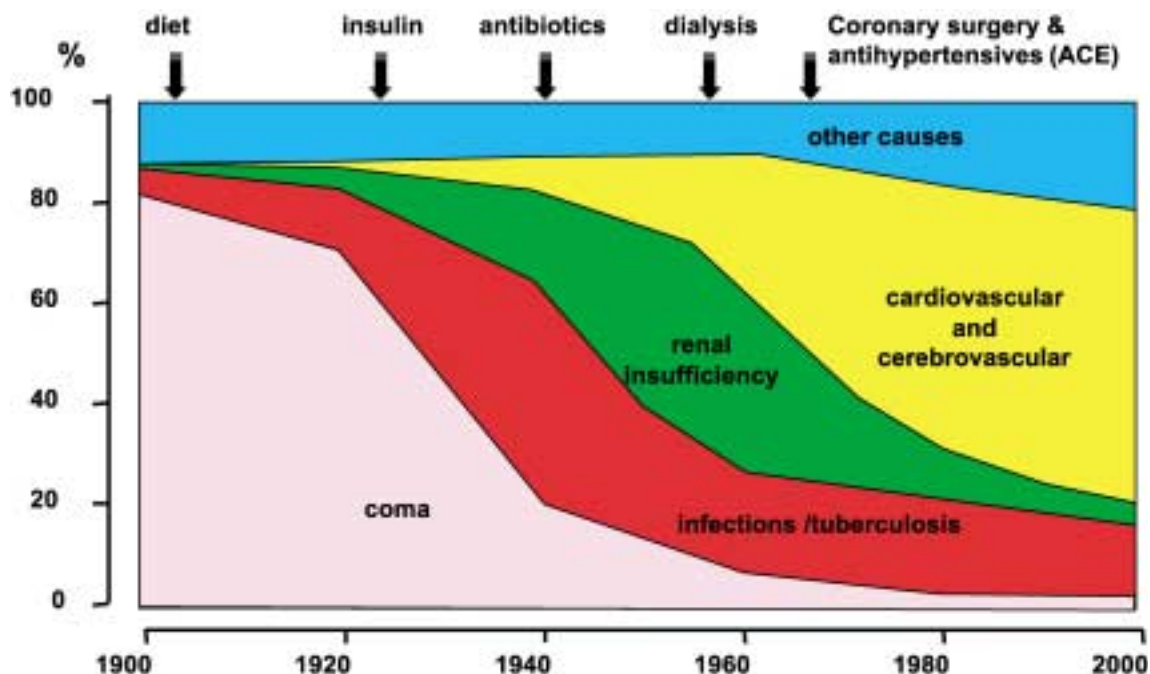


Figure 1 Causes of death of patients with diabetes mellitus in the 20th century. The left part of the figure (up to 1950) has been drawn on the basis of data in type 1 diabetic patients in the USA. These data were collected by E P Joslin (8, 9). The data in the right part of the figure (after 1950) represent the causes of death in patients with type 1 and type 2 diabetes mellitus in The Netherlands (supplied by the Dutch Diabetes Federation).

primary cause of death in diabetic patients in the subsequent years. Thereafter, cardio- and cerebro-vascular death became the most prominent cause of death at the turn of the century. Coronary heart surgery, coronary artery angioplasty, and new medical treatments lowering blood pressure, lipids and glucose levels have now been implemented in the daily treatment regimens of all diabetic patients.

The disease diabetes mellitus has been 'transmuted' several times during the 20th century both with regard to its course, as well as its cause (10). Until 1950 it was mainly type 1 diabetic patients suffering from auto-immune destruction of pancreatic β -cells that lived longer and longer as a consequence of the application of a number of major breakthroughs in endocrine and medical research, the biggest being the discovery of insulin. The number of patients that it was necessary to treat in order to prevent death by insulin was close to one. After 1950 an enormous switch in life style occurred in Western societies. A rapidly increasing number of patients presented themselves with type 2 diabetes mellitus, a disease which is, in the vast majority of cases, related to obesity. Diabetes mellitus now affects between 5 (Western Europe) and 7.8% (USA) of the population, and patients with type 1 diabetes now account for only 5–10% of all diabetes cases.

In a prediction model developed for the Dutch population it was calculated that diabetes mellitus would not

occur in 68% of female and 54% of male patients if the complete population would lose body weight to such an extent that obesity and overweight were eliminated. If the prevalence of physical inactivity could be eliminated, 22% (both females and males) of type 2 diabetes cases would be prevented. A combination of eliminating overweight, obesity and physical inactivity would prevent 75% (females) and 64% (males) of all cases of type 2 diabetes (11).

This epidemic of type 2 diabetes patients, together with new pathophysiological insights into the long-term effects of elevated glucose levels, elevated blood pressure and elevated lipid levels on the premature development of secondary complications and accelerated atherosclerosis has resulted in a massive medicalization of these patients. Many patients take 4–8 different types of medication over the 24-h period. In a recent meta-analysis of randomized controlled trials it was summarized that with regard to preventing cardiovascular mortality in type 2 diabetic patients the person-years that it is necessary to treat in order to prevent one death was over 400 for intensive glucose-lowering treatment, 265 for cholesterol-lowering medication, and about 125 for blood pressure lowering medication (including ACE-inhibitors) (12).

Over a period of 80 years diabetes mellitus has turned from a rare endocrine disease (deficiency of a hormone) which was treated by clinical endocrinologists into an epidemic (mostly caused by resistance to

a hormone) which is treated by general practitioners, nephrologists, cardiologists and internists primarily interested in vascular disease without or with an often marginal education in endocrinology.

Complete therapeutic breakthroughs versus 'half-way technologies': the creation of the chronic endocrine patient

Clinical endocrinology is one of the most quantitative and precise clinical disciplines as well as being one of the most successful (13). The availability of specific and sensitive hormone assays, dynamic tests of endocrine function, and advanced imaging techniques allows a highly efficient (early) diagnosis of an increasing number of endocrine diseases. However, a complete cure of these diseases is, in most instances, only offered by the (experienced) surgeon (e.g. primary hyperparathyroidism, removal of a 'cold' nodule in localized thyroid cancer, laparoscopic removal of steroid-producing adrenal adenomas and pheochromocytomas, transsphenoidal selective adenomectomy of pituitary microadenomas). In many endocrine diseases, however, the effects of medical, surgical and/or radiation therapy are often just too much or too little (e.g. management of Graves' disease, therapy of pituitary macroadenomas, assisted reproduction, treatment of type 1 and 2 diabetes, obesity). Many of the treatments in endocrinology are imperfect and are not directly targeted at the underlying pathophysiologies. These 'half-way technologies' (14) create 'the chronic endocrine patient' and many of these patients will remain under endocrine care for prolonged periods of time.

Pharmaceutical techniques have enabled endocrine replacement with pure, synthesized hormones and even designer molecules, like the new insulins. However, even the seemingly straightforward replacement therapy with hormones, like thyroxine (T_4), hydrocortisone, sex steroids, growth hormone and vitamin D is not perfect. Although related mortality has virtually been eliminated, the quality of life of many patients on (combined) replacement therapy with these hormones often remains not optimal. Many patients complain of tiredness and other vague problems, which suggest intrinsic imperfections of the hormone replacement strategies used to mimic normal hormone secretion (15–24). Most patients are offered standard doses of hormone replacement, while the measurement of plasma concentrations of thyrotropin (TSH), adrenocorticotropin, luteinizing hormone, follicle-stimulating hormone, free T_4 , cortisol, estradiol, testosterone, insulin-like growth factor-I (IGF-I) and calcium do not necessarily reflect the tissue effects in non-endocrine target tissues.

At present, the interest in research in the field of hormone (replacement) therapy seems, at least in part, to be commercially driven (25). Financial support by

drug companies not only by stimulating clinical research, but also by sponsoring and influencing meetings and symposia contributes to an increasing number of publications in the field of growth hormone treatment, whereas the number of publications on hydrocortisone and thyroxine treatment demonstrate a downwards trend, which by extrapolation might fully disappear around the year 2009 (Fig. 2). Interestingly, the daily costs of hormone replacement therapy in The Netherlands with hydrocortisone, thyroxine, vitamin D, testosterone, estradiol and growth hormone (GH) respectively turns out to be inversely related to the number of yearly publications concerning their use in treatment ($P < 0.01$).

What can be done in the coming years to improve this rather disappointing scene of a too aggressive treatment of hyperthyroidism (resulting frequently in hypothyroidism), of assisted reproduction (resulting frequently in multiple pregnancies) and of pituitary macroadenomas (resulting frequently in hypopituitarism)? New insights in the prevention and treatment of (auto-)immune diseases, individualized gradual ovulation induction, as well as the development of more potent and subtype-specific dopamine and somatostatin receptor analogs should eventually diminish the creation of so many 'chronic endocrine patients'. Hormone replacement therapy will be improved by determining the actual dose needed in individual patients by characterizing the set-points of their pituitary–thyroid, pituitary–adrenal, as well as GH–IGF-I axes, by studying frequently occurring polymorphisms in the thyroid hormone receptor and deiodinases, the glucocorticoid receptor and the IGF-I genes (26–29).

Molecular endocrinology

The characterization of a number of single-gene endocrine disorders has contributed to our understanding of the pathophysiology of these disorders (13). The availability of genetic tools has expanded our knowledge about the pathogenesis of such diverse conditions as precocious puberty, McCune Albright syndrome, Carney's syndrome, about 30% of acromegalic pituitary tumors, toxic thyroid adenomas, and (bilateral) hyperplastic and/or adenomatous adrenal tumors causing Cushing's syndrome. However, the practical use of DNA diagnostics in day-to-day clinical endocrinology remains mainly limited to those few families with multiple endocrine neoplasia (type 1 and 2) and Von Hippel-Lindau's disease. In these hereditary tumor syndromes DNA examination of (newborn) family members is helpful in the early diagnosis, as well as in carrying out preventive surgical intervention (e.g. medullary thyroid cancer). However, in neonatal population screening for 21-hydroxylase deficiency, congenital hypothyroidism and phenylketonuria, the measurements of serum 17-hydroxyprogesterone, T_4

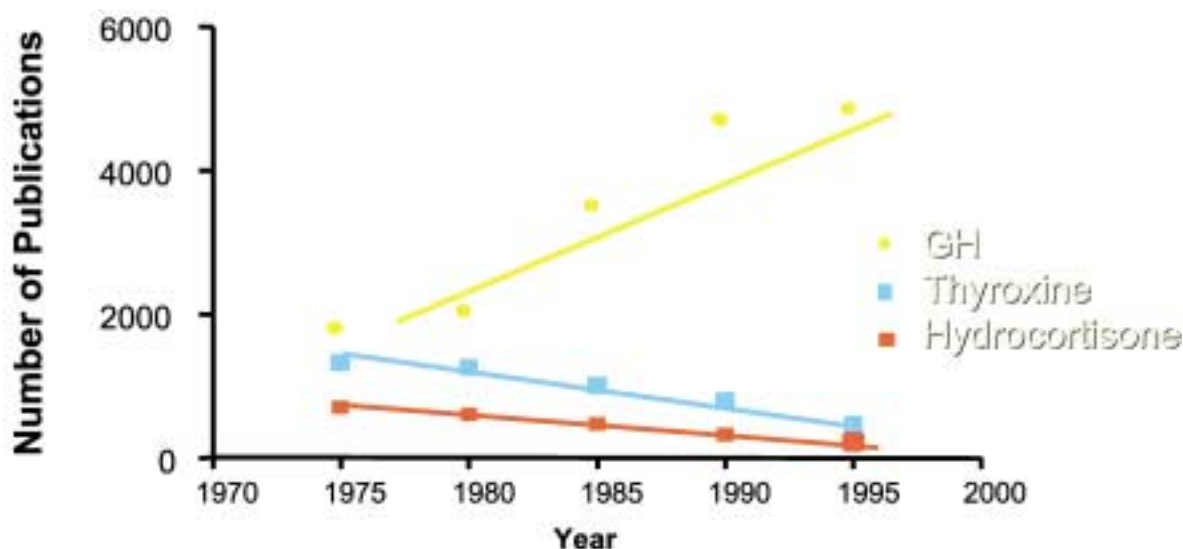


Figure 2 The number of publications in PubMed with hydrocortisone, thyroxine or growth hormone in the title (restricted to 5-year intervals).

and/or TSH and phenylalanine concentrations remain first choice, because the genotypic abnormalities do not adequately predict the phenotypic changes. Maturity-onset diabetes of the young (MODY) might be an example of a genetic disease in which the knowledge of specific gene mutations might be of importance to predict the course of disease progression, as well as the choice of optimal therapy (30, 31).

For the more frequently occurring hereditary endocrine and metabolic diseases which occur during adulthood, more and more doubts about the predictive value of determining the genetic abnormalities for the phenotypic expression are being reported. The actual chance of developing clinically significant consequences of iron deposition, even in homozygotically affected individuals with mutations in the HFE gene might be very low (32). The measurement of ferritin or iron saturation percentages of transferrin seem of comparable predictive clinical value for screening purposes. In the case of familial hypercholesterolemia also a discrepancy has become increasingly clear between the genotype and phenotype (33). Other modifying genes affecting high density lipoprotein (HDL)-cholesterol, triglyceride and/or homocystein levels, and especially life-style play a deciding role as to whether a certain mutation in the low density lipoprotein (LDL)-receptor gene results in clinically significant premature atherosclerosis (34–36).

Hereditary hemochromatosis and familial hypercholesterolemia are caused by germ-line mutations which inherit in a Mendelian fashion. These mutations have a high penetrance on the biochemical variables (iron saturation, LDL-cholesterol), but with unpredictable genotype–phenotype relationships. In most common endocrine diseases the hereditary component is even less strong, making them from a genetic standpoint

‘complex’ (37–39). Many ‘genocentric’ investigators predict that genetic markers for disease susceptibility will, in the immediate future, have a large impact in endocrinology and medicine (40). However, one should not forget that, in contrast to the rare high penetrance single gene disorders, gene polymorphisms which in large population studies have been associated with certain risks form an insufficient basis for (preventive) treatment. In most cases these ‘predictive’ polymorphic sites in susceptibility genes may not result in symptoms (hypertension, obesity, diabetes, fractures) for many years to come. In addition, their predictive power is at present in all cases insufficient to allow the start of premature medicalization in genetically defined individuals. In the near future, therefore, clinical endocrinologists will continue to use the well-known, more powerful predictive intermediates, like organ-specific autoantibodies, blood pressure, serum cholesterol concentrations, intima thickness of the carotid artery, smoking and dietary habits, body weight, and activity patterns in predictive models of these complex diseases. It might take years before genetic variants can be included in these predictive models, bringing secondary prevention on the basis of genetic analysis into the center of clinical endocrinology. For the time being, genetic analysis of blood or tissue in endocrinology remains reserved for a small number of rare diseases.

In the meantime, molecular endocrinology will continue to offer us new insights into the molecular basis of tissue regulation of hormone sensitivity, in the physiological functions of the many remaining orphan nuclear receptors, and in the pathophysiological role of the new hormones that are discovered every year. High-throughput genomics and proteomics with computer modeling will allow development of new drugs specifically interfering with hormone receptors.

The changing endocrine patient: the impact of life-style drugs and the prevention of aging

In a recent debate in the British Medical Journal on 'non-diseases' it was concluded that the concept of what is and what is not a disease has become slippery (41). It was observed that pharmaceutical companies have a clear interest in medicalizing life's problems and/or perceived shortcomings, for which they try to create designated medication (42).

The field of endocrinology seems especially prone to a tendency where new treatments are actively pursued by, but not offered to, otherwise healthy individuals. More and more people ask for medical intervention in life's normal processes, seeking to increase body height of their children (in normal short stature), to regulate appetite and body composition (e.g. overweight, obesity, muscle mass and strength), sexuality (libido and potency), reproduction (assisted reproduction later in life, gender preference for children), and to prevent baldness, wrinkles, as well as to delay the aging process. Increasing pressures from a growing population of affluent people, which have great expectations (partially based on browsing the internet) (43) are about to change the appearance, as well as the composition of the 'patient' population of the endocrine clinic. Much will now depend on the attitude, the interest, and the reaction of the individual endocrinologist, as well as of their national endocrine societies.

The medicalization of the reduction in bone mass which is a physiological part of the aging process is a tentative example of a risk factor which seems to have become conceptualized as a disease by many individuals. Is it advisable to measure bone mineral density in all healthy women after menopause? When should long-term preventive drug treatment be offered? A 4-year treatment of menopausal women with slightly lowered bone mineral density without fractures with a bisphosphonate lowered the incidence of vertebral fractures from 3.8% to 2.1% (44). One can look at these results in two ways: as a very slight decrease of the absolute risk by 1.7%, or as a very promising 44% relative risk reduction.

In 'the endocrinology of aging' the concepts of menopause, andropause, adrenopause, and somatopause have been investigated mainly in cross-sectional and occasionally in longitudinal population studies (45). In most instances, in randomized clinical trials the healthy elderly have been included for treatment with estrogens, testosterone, dihydroepiandrosterone or GH. These trials often lack powerful endpoints related to activities of daily life, independence or quality of life. They are often of short duration and they very often suffer from selection bias (45). In the case of estrogen replacement therapy this has resulted for many years in what now turns out to be false optimism (46). It is an absolute requirement that the general principles

of evidence-based medicine are fully implemented by providers of these medical interventions in the aging process. In several countries a tendency is noted in which a new type of clinical endocrinology is created, which promises 'eternal youth and beauty', but it remains uncertain at what price (financially, as well as with regard to unknown (long-term) adverse effects). The medicalization of old age is slowly entering the endocrine clinic of many of our mainly non-university based colleagues, and life-style medication for the affluent adult is about to enter the mainstream of endocrinology. The pressure from society is high, as are the financial benefits to the medical profession. It will be an enormous challenge to the endocrine community to adequately respond to this tendency to greater medical consumerism. Moreover, we should challenge the concept of insufficient endocrine function in aging. There are a large number of animal models which show that decreased hormone secretion and/or sensitivity (e.g. of GH) increase, rather than decrease longevity.

Infrastructure and education

Completely integrated endocrine laboratories in which highly specialized hormone assays, DNA diagnostics, nuclear medical diagnostics and therapeutics are integrated with the care offered by a group of endocrinologists remain necessary in order to provide the best care (47). However, such integrated care is in decline in Western Europe, even in the academic centers (1–5).

Clinical endocrinologists need a wide range of training in general internal medicine, but also a deep knowledge in basic science: apart from (molecular) cell biology, the understanding of hormonal regulation, feed-back loops and homeostatic mechanisms which involve the whole body and not just single cells, are especially essential. Also, it should be realized that research in the field of endocrinology is widely spread over many different disciplines including physiology, pharmacology, and cell biology on the one hand, but also gynecology, oncology, neurosciences, pediatrics, urology and other disciplines. Therefore, the scientific impact of endocrine research is often presented in a diluted manner diminishing its perceived significance.

A major challenge is to provide strong evidence that the quality of the care by clinical endocrinologists in the diagnosis and treatment of diseases of the thyroid, bone, pituitary, adrenals, but also of obesity, diabetes and atherosclerosis is clearly better as well as more cost-effective than that provided by non-endocrinologist physicians. In a recent study comparing the quality of care of diabetic patients provided by endocrinologists and internists working in primary care centers in the USA, no overall significant differences in care were found after the application of complex statistical methods related to case-mix and physician-level clustering.

However, the data provide clear evidence that better care was offered by endocrinologists if basic process and outcome measures like HbA_{1c}, lipid levels, urinary protein excretion, blood pressure, eye and foot examination were considered (48). Also, the satisfaction with the personal care offered by endocrinologists was rated higher by the patients. In an editorial, the inherent methodological difficulties of this type of study to measure quality of care were discussed (49). In our opinion it is an absolute priority for clinical endocrinology to optimize and repeat these types of studies, and to expand them to other endocrine disorders as well.

Another aspect of modern health care regulations which is about to take place in many Western European countries is the evaluation of endocrine clinical practice with regard to its costs and effectiveness. New evaluation techniques using health care technology assessment methods and specific questionnaires concerning the quality of life of our patients are currently developed and will have great impact on practical patient care in the coming years. Again, it is a great priority for Western European endocrine societies to take the lead in these developments, rather than to wait for external reviewers to develop these techniques.

Conclusions

Clinical endocrinology is very much alive and will remain so for many years to come. The 'chronic endocrine patient' will be replaced by more and more 'cured' patients, as knowledge about the pathophysiology of auto-immune diseases, reproduction and benign endocrine tumors expands. Also, hormone replacement therapy will be administered more precisely on the basis of genetic knowledge of the set-points of the endocrine axes in the individual patients. The evolution of endocrine concepts will enable a better perspective of the underlying pathophysiology and will result in better treatment of many unresolved endocrine diseases. As knowledge about the predictive value of genetic variations in the genes involved in the most common complex diseases, which are often 'endocrine' in nature, become better known, the role of the clinical endocrinologist in early risk identification and early primary or secondary prevention will expand. Finally, the application of all principles of evidence-based medicine will, without doubt, result in a certain degree of 'hormonal' medicalization, especially of the aging process. However, there will be increasing pressure from the public on clinical endocrinologists to help solve an increasing number of 'non-diseases' e.g. variations in life's normal processes (sexuality, body height, body composition, muscle strength, reproduction). It is an enormous challenge to endocrinology, to the clinical endocrinologist, and

to their respective national endocrine societies, to get this right.

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