For debate

The Need for a New Biological Model in Geratology

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Summary

Disease classes have hitherto been based on anatomical pathology and structural lesions belonging to an earlier ecological medical model involving classification. The diseases of ageing now coming to dominate clinical practice evolve across the clinical threshold in middle age parallel to changes occurring in the internal environment. The concept 'multiple pathology' used to describe the plural features of biological changes now requires new intellectual tools by which to understand overlap phenomena. Boolean algebra and Set Theory are proposed as the relevant enabling concepts, and their application to modern clinical practice is discussed.

Introduction

The infirmities of ageing are characterized by slow evolution and response to shifts in the internal environment. They emerge across the clinical threshold in middle age on a scale varying between apparent normality and gross disturbance. It is increasingly difficult to classify these conditions according to a conventional model based on anatomical pathology in which the identifying features held in common are considered more important than the variable features.

Pathological changes in elderly people must be conceptualized in ways that avoid 'diseases' and their classification. The multiplicity of features have overburdened the clinician in the task of identifying the critical features that can be used to assign cases to disease classes. Too much heterogeneity has been exposed among cases in the same disease class, and too many similarities have been exposed among cases in different disease classes. Nor is it helpful to have recourse to the vague concept of 'multiple pathology' with its implication of a meaningful aggregate. There are intellectual tools available to handle the common biopathological features of elderly patients, which is overlap. Feinstein [1] noted that instead of trying to abolish overlap it could be classified and preserved using Boolean algebra and Venn diagrams.

Set theory is a useful intellectual tool in geriatric medicine. A set is a collection of elements, or biopathological populations, having some common properties used to define the set and so identify its member elements. Elements need not have identical properties and in fact rarely do so. Obesity, for instance, can belong to many sets since in clinical medicine elements may be biomedical features. The set may include sub-sets, each of which is a set in itself. The identifying characteristic of sets that constitute biopathological populations or disorders may be an abnormal anatomical property such as osteoporosis or a concept of functional derangement, such as hypertensive disorder.

In 1986, from the cross-index of my morbidity register [2], I defined the eight diseases of ageing as: obesity, atherosclerosis, essential hypertension, type 2 diabetes, cancer, autoimmune disease, endogenous psychic depression and immunological failure. The most common finding in people aged over 60 was obesity, affecting 61% of women and 43% of men. Using the symbol of Boolean algebra, this can be expressed as x ∈ A meaning the element x belongs to the set A, i.e. to the set of obesity disorders. x ∈ B means that the element x belongs to the set B, i.e. to the set of hypertensive disorders.

The contents of the two sets can be brought together by the operation of union, represented by the symbol U. Thus S = A U B means that the new set S contains all the elements in set A and all those in B and the expression x ∈ (A U B) means that x belongs to the new set formed by the union of sets A and B and that x has the characteristic of A or of B or both.

By the operation of intersection, represented by the symbol ∩, is formed a new set containing all the elements that are members of both sets A and B. Thus S = A ∩ B means that the new set contains only those elements that belong to both A and B (obese hypertensives) and x ∈ (A ∩ B) means that x has the characteristics of both A and B. A set then is a class made up of members possessing the characteristic property that defines the set.
The operation of negation represented by the symbol \( \sim \) forms a new set that contains all the elements in the given universe that do not belong to the original set, as in the expression \( S = \sim A \) the new set \( S \) is said to be the complement of set \( A \) and \( x \in A \) means that \( x \) is a member of the universe to which the set \( A \) belongs but does not have the identifying characteristics of \( A \).

Biopathological sets are a useful substitute for the old mutually exclusive disease classes and subclasses because they allow for overlap. Overlap or non-overlap is made particularly clear by Venn diagrams in which the members of a set are represented by the contents of a geometric figure, usually circular or ovoid in shape. There are five possible relationships of set \( A \) and \( B \) to each other (Figure 1):

(a) mutually exclusive or disjoint (no member belongs to both sets);
(b) overlapping (a member may belong to \( A \) or to \( B \) or to both);
(c) subordinate (all members of \( B \) belong to \( A \) but only some of \( A \) belong also to \( B \));
(d) subordinate (all members of \( A \) belong to \( B \) but only some of \( B \) belong also to \( A \));
(e) identical (every member belongs to both \( A \) and \( B \)).

Two sets are said to be independent if each one contains members that are not in the other. Of the five relationships shown in Figure 1, disjoint (a) overlapping (b) sets are independent but subordinate (c and d) or identical (e) sets are not. In the union of set \( A \) with set \( B \), \( S = A U B \), the total membership of the new set \( S \) is the same as would be arrived at by the algebraic addition \( S = A + B \) but only when sets \( A \) and \( B \) are disjoint or mutually exclusive.

Since overlapping is the commonest and most important relationship among biopathological sets it is instructive to look at the membership of sub-sets represented in the operations of Boolean algebra in the Venn diagrams in Figure 2. The membership of each newly derived sub-set \( S \) is represented by a shaded area derived from the operations of Boolean algebra that represent collections of biomedical cases. For example \( A \) might be obesity and \( B \) essential hypertension:

(a) identifies a set of the obese, some of whom are also hypertensive;
(b) identifies a set of hypertensives, some of whom are also obese;
(c) is a set all of whose members are either obese or hypertensive or both;
(d) shows a sub-set of obese hypertensives;
(e) shows a sub-set of obese subjects who are not hypertensive;
(f) shows a sub-set of hypertensives who are not obese.

In the universe of diseases of ageing the set \( A U B U G \) might include elements \( A \) and \( B \) such as obesity and hypertension with an overlapping relationship, while \( G \) is disjoint as shown in Figure 3. The Table based on data from 100 female cases, shows the various sets represented in the Venn diagram of Figure 3 and the number of cases in each.

By the operations of intersection and intersection–complementation (negation), one can construct mutually exclusive sub-sets out of overlapping sets and algebraic addition can be applied to the sub-sets’ membership when their contents are joined by union. The total number of mutually exclusive sets that can be so derived depends on how sets overlap, the largest
number being produced by the full intersection of independent sets; that is where each set interacts with every other set. If \( n \) independent sets fully intersect, the maximum number of mutually exclusive sets so derived is \( (2^n - 1) \). Thus in Figure 4a there are seven \( (2^3 - 1) \) and in Figure 4b there are fifteen \( (2^4 - 1) \).

**Practical application to modern practice**

In Figure 4A sub-sets A, B and C might define obesity, atheroma and diabetes forming a set of cardiovascular risk factors. Whereas traditional classification cannot accommodate the true richness of similarities and differences between cases, set theory enables the clinician to handle such cases in terms of membership of overlapping biological populations. Old ways of thinking give diseases an ontological existence of their own. The domination of thought by nouns may make us see the patient with hypertension as if it were a feature that had become a part of his or her being. We should not allow the sense of order created in Western medicine by the analytical method to produce an artificial reality in our minds. In a society increasingly dominated by geriatric medicine there is a particular need to consider cases, which the rules of logical division formerly held to be distinct, in accordance with a synthetic model that allows for overlap. We should construct a biomedical order where overlapping pathological sets assign a case to as many sets and sub-sets as are indicated by the data, thus permitting a view of the patient in multiple contexts.

**An example of multiple contexts**

A very depressed 53-year-old woman complained of heavy perimenopausal bleeding. She weighed 89.5 kg and was 1.6 m in height, a Quetelet Index of 35 indicating severe obesity which had been present when she became pregnant at the age of 43. The child had weighed more than 4 kg and was hyperinsulinaemic at birth. The patient's blood pressure had been raised and was now 230/125 and she had heavy glycosuria. Random blood sugar was 15 mmol/l and haemoglobin was 11.5 g/dl. Thyroid autoantibodies were present. Apart from the paediatrician’s continued interest in her son she had not been followed-up and she could have been referred to a number of specialists. Because of the vaginal bleeding the decision was made to refer her to the gynaecologist who reported carcinoma of the corpus uteri requiring a Wertheim operation. This was complicated by a chest infection that proved difficult to treat.

Having all eight diseases of ageing I had defined from the chronologically old in my practice, this woman was considered biologically old and indeed died suddenly two years later from a myocardial infarction.

**Discussion**

The old medical model, ecological in principle, required doctors to learn hundreds of diseases and to classify them in various ways. In modern developed societies we are concerned particularly with the small number of diseases of ageing, of partly intrinsic origin, occurring on a scale from apparent normality to gross disturbance. The eight diseases of ageing cannot be cured and do not occur singly but overlap. They are present long before detection at the clinical threshold and defying separation and classification render the traditional approach of precise diagnosis and specific therapy inappropriate. Future medical progress will be concerned less with intervention than with assessment, monitoring and health promotion.

There is increasing awareness that age should be measured less from the date of birth than from likely death in older people. ‘Severity’ relates less to the presence of diseases expected in later life than to their rate of advance. The common features linking them suggest they are aspects of a 'super-disease', arising from some imbalance in the internal environment, leading to a state in which life can no longer be sustained. Hypertension is more common in diabetics but the varieties of correspondence between obesity, hypertension, depressive illness and cancer have long been recognized.

As life expectancy reaches the late 70s in developed countries, old concepts grouping cases according to pathological similarities that have allowed for comparison and classification no longer serve us intellectually.
So long as the common identifying features were considered more important than the variable features, disease classes seemed real enough, but a classification following the rule that logical division must be distinct needs to be replaced. The often stated concept that elderly people suffer from multiple pathology implies an aggregate that needs to be replaced by an approach that maps on to modern polygenic models of susceptibility loci [3].

References

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