Discrimination in Life, Science and Medicine

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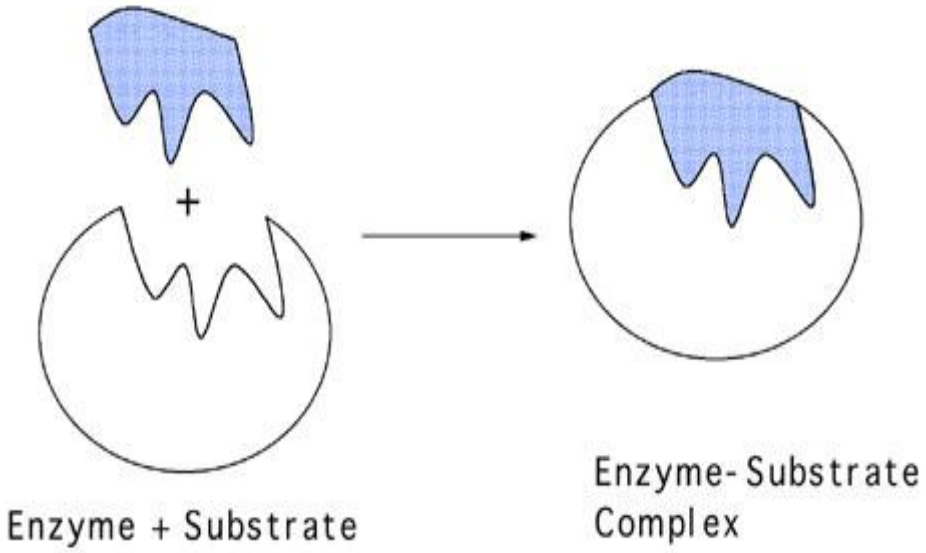
Being a biochemist, you will expect me to talk about biochemical things, but this is also to show how ordinary people and doctors can and must choose or decide, by recognizing patterns; and what we mean by that.

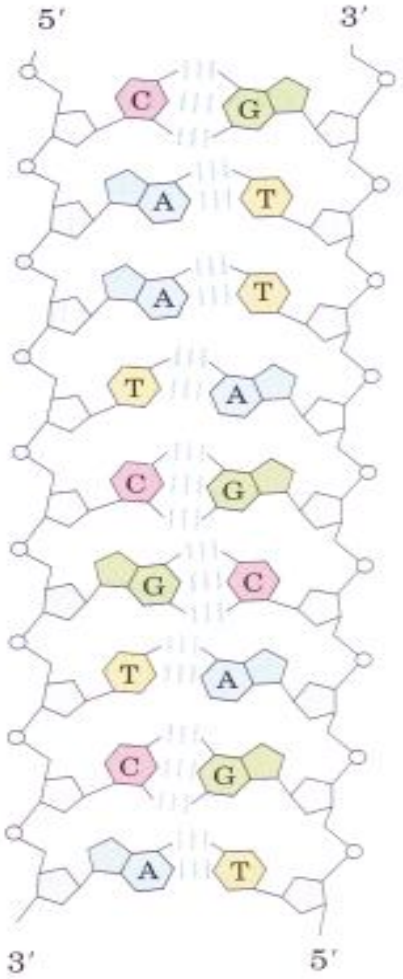
An Enzyme

…. shows remarkable specificity for its substrate, by which is meant that it selects that molecule out from all others, shall we say by shape or pattern.

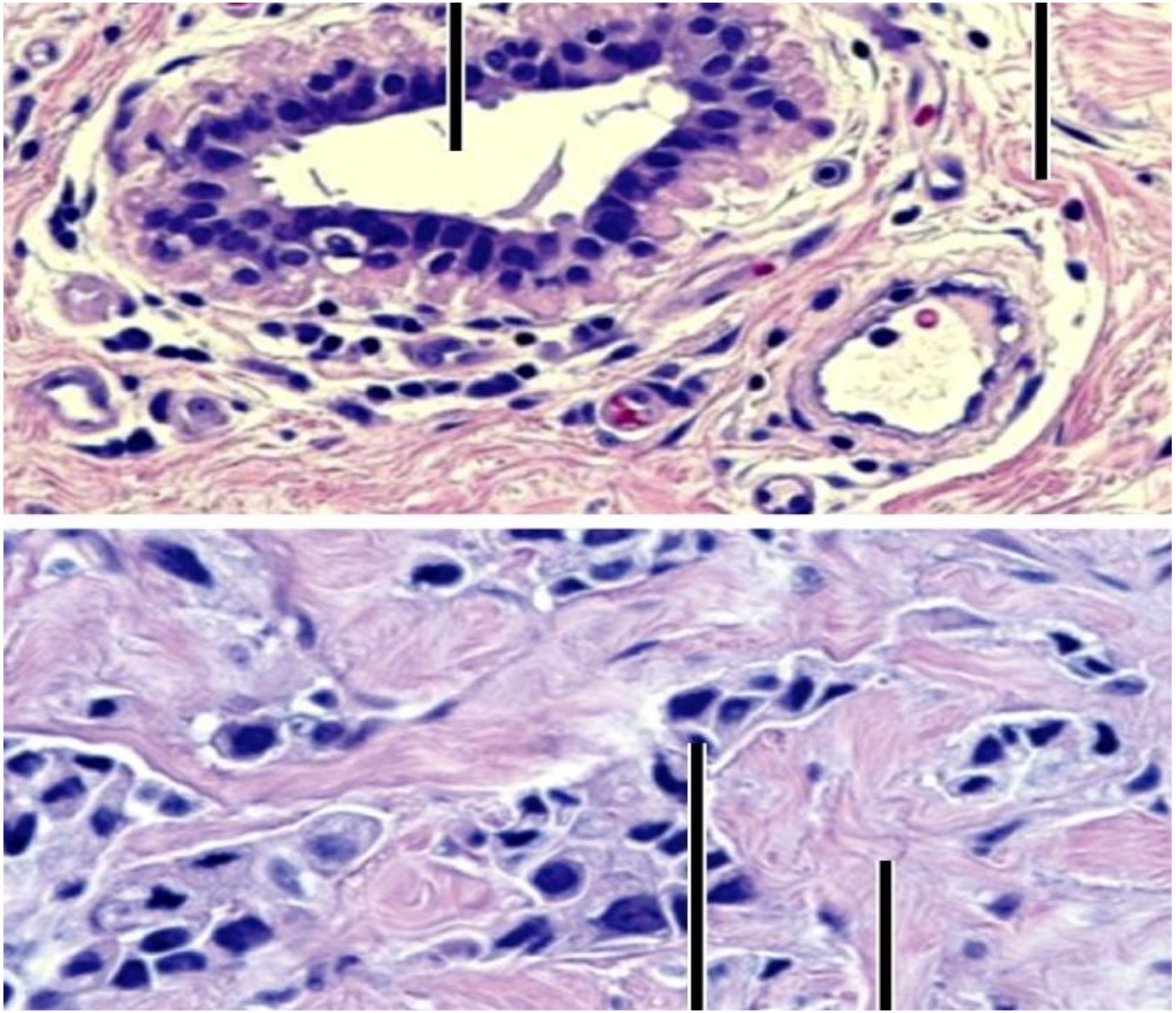


Hybridization of nucleic acids

is even more selective



A histopathologist looks for characteristic features…



Hippocratic method

… and in much the same way a clinician recognises a pattern to make the diagnosis. This is proudly named the Hippocratic method, which really means that we know it's an elephant because we've seen one before. It is a good method, and might be carried a little further, shall we say to the diagnosis of cats ….

At night

All cats

Look alike

But **not if we use >1 criterion**

- **Well, obviously they were three different cats. The third one cannot be the same cat as the first picture because it has white feet, and it cannot be the second one either because it has a white chin.**

- **The point is, our test for gingerness in cats can be made as rigorous as you like; still it will not discriminate between cats if all you are testing for is gingerness.**

- **You need extra criteria, like what we are supposed to when making a diagnosis of rheumatoid arthritis or to match the NICE requirements for rituximab treatment.**

Old-fashioned Medicine

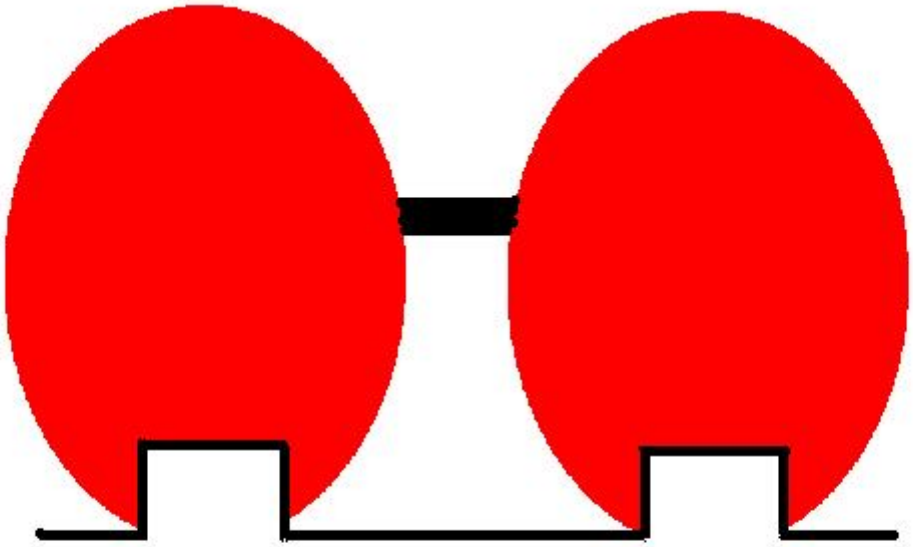
- **A died-in-the-wool clinician is going to say, “I don’t need these artificial listings and box-tickings; my experience and clinical judgement are better than all of them”. No contest, but what is he or she really doing? In brief, it is to unconsciously assemble a whole swathe of criteria that together justify the diagnosis or the decision. In my cat example, it is ‘obvious’ that they are different – actually, we don’t even need to look at the colour of their feet.**

- **More broadly, there is ample mathematical proof that the brain routinely does pattern recognition like no computer ever will, as Alan Turing knew perfectly well although many people seem to believe that he proved the opposite. The important points are, several different criteria; not one, maybe not even two or three, but as many as you need to do the job.**

- **And in medicine, for goodness sake look at the whole patient.**

An antibody

Returning to our biochemical interests, this picture symbolizes a bivalent antibody binding to its target. We could divide the picture down the middle; to show a single binding site and epitope, but real antibodies have at least 2 binding sites. Why?



Why is an antibody polyvalent?

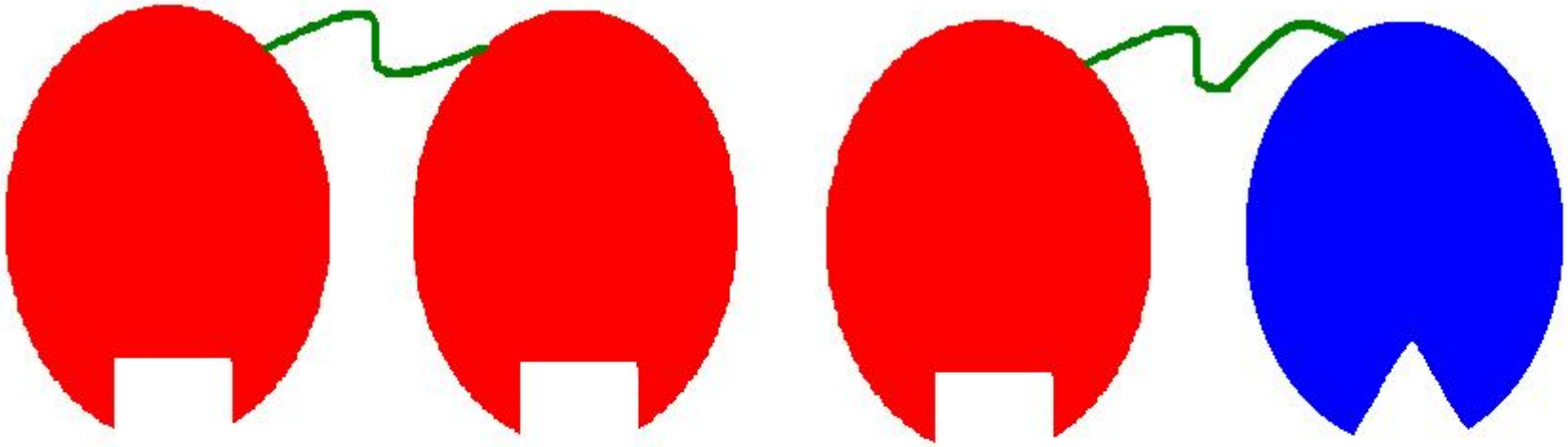
- **My answer is that the real-life target of an antibody is always polyvalent, homopolyvalent, and an antibody is selective not so much for the solitary epitope but for the presence of two or more identical epitopes side by side - as it were for twin ginger cats, or a whole litter of ginger kittens.**

- **This classic molecular structure gives an increase in affinity (for the polyvalent target!) measured for the first time in 1965 by Greenbury, Moore & Nunn – a piece of work deserving the highest praise and even more so because it was done in the path lab of an ordinary NHS hospital (Stoke Mandeville - which once was a place of pilgrimage but then fell into the hands of some very ordinary managers indeed).**

Co-bodies, co-selectivity

Suppose we could artificially combine two binding sites?

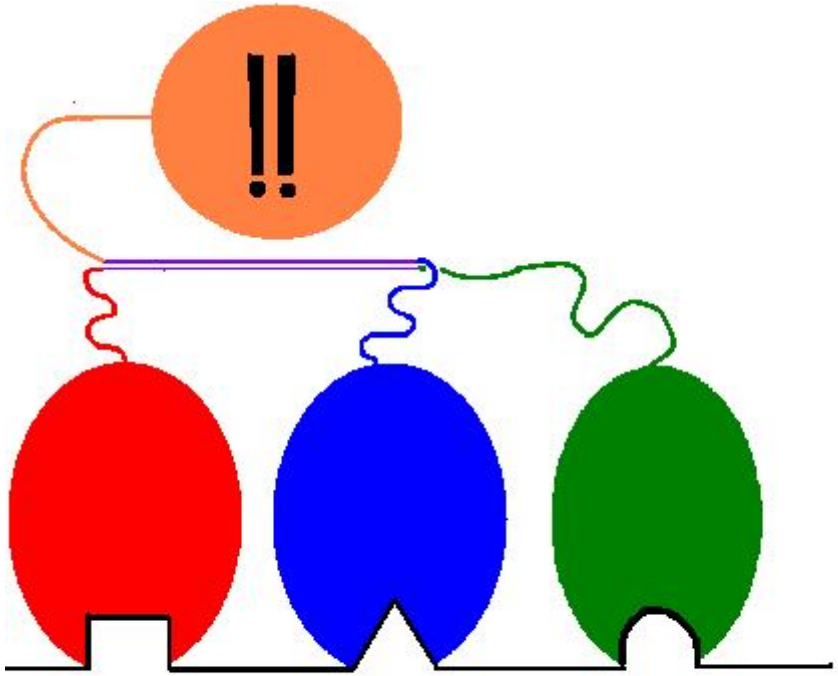
Here are models in which the binding sites act against two epitopes which may be the same (as in nature, on the left), or different (on the right … as it were one type for gingerness and one for white feet).



And why only two binding sites?

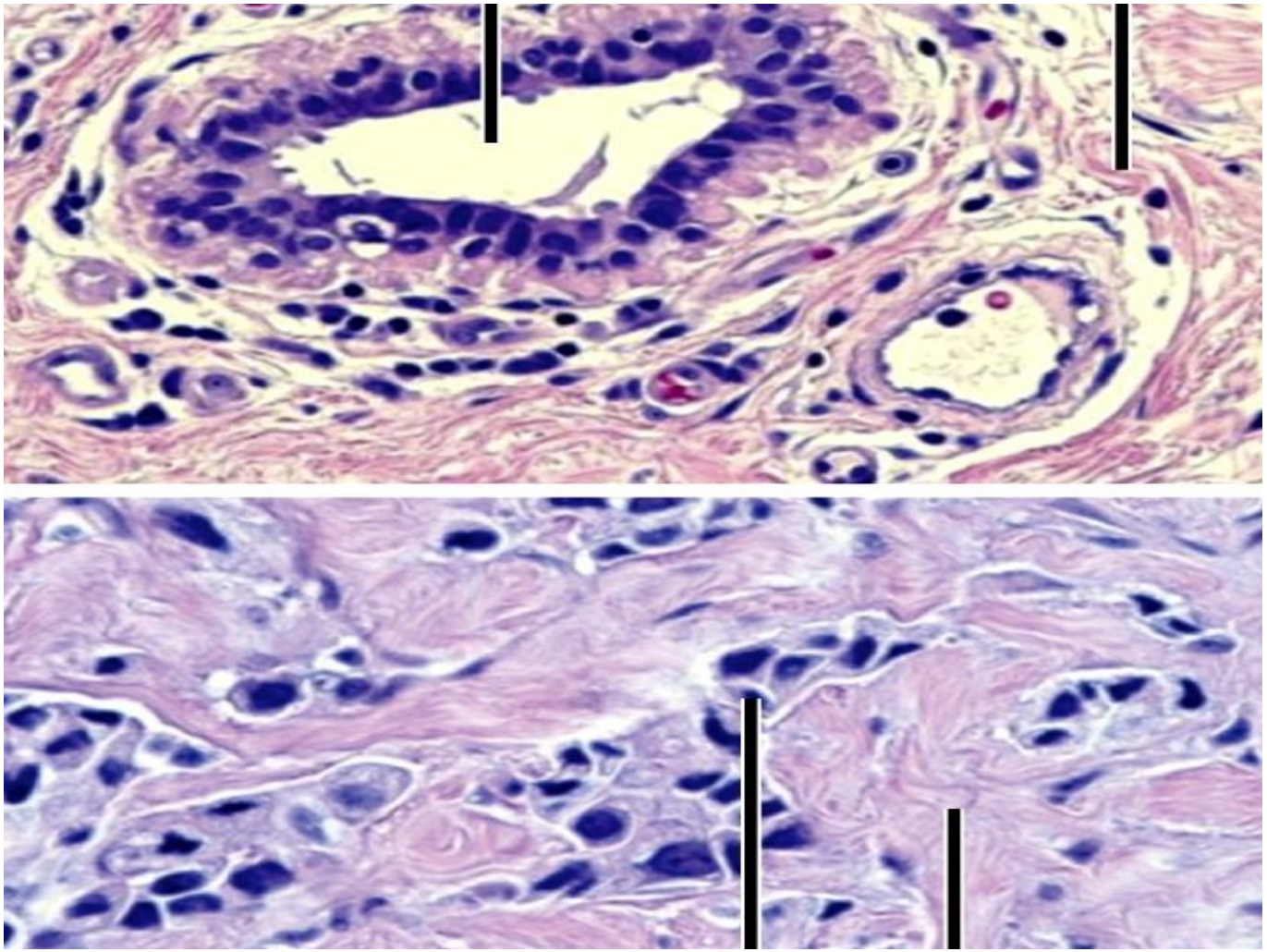
The construct shown here will select on the basis of co-existence of THREE distinct epi-types. The principle is extendable indefinitely, given semi-rigid DNA linking components. It isn't used yet, but it will be, and you heard about it first in Rome.

And the construct carries with a signalling or cytotoxic group

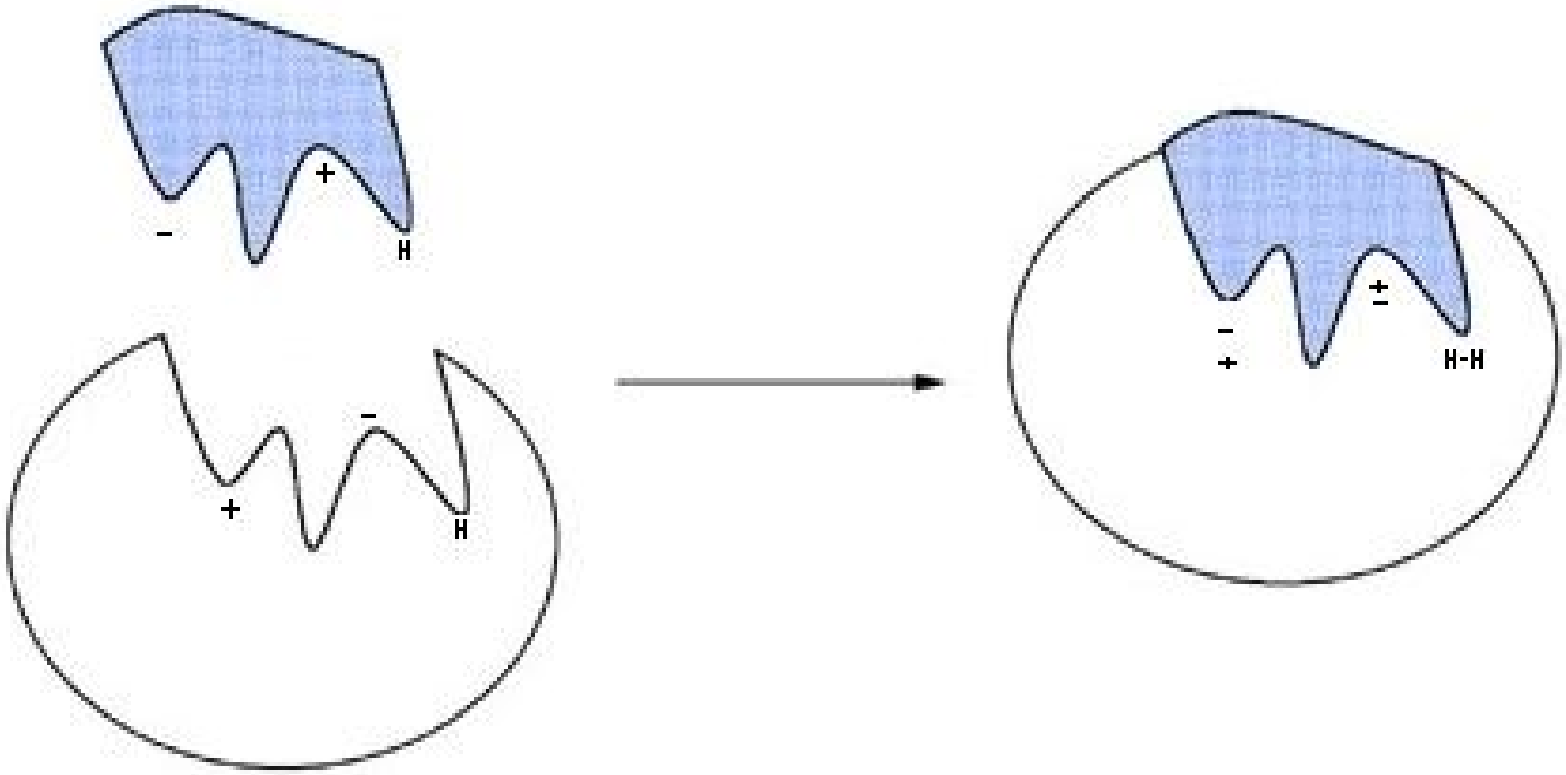


Co-selection is not so unusual.

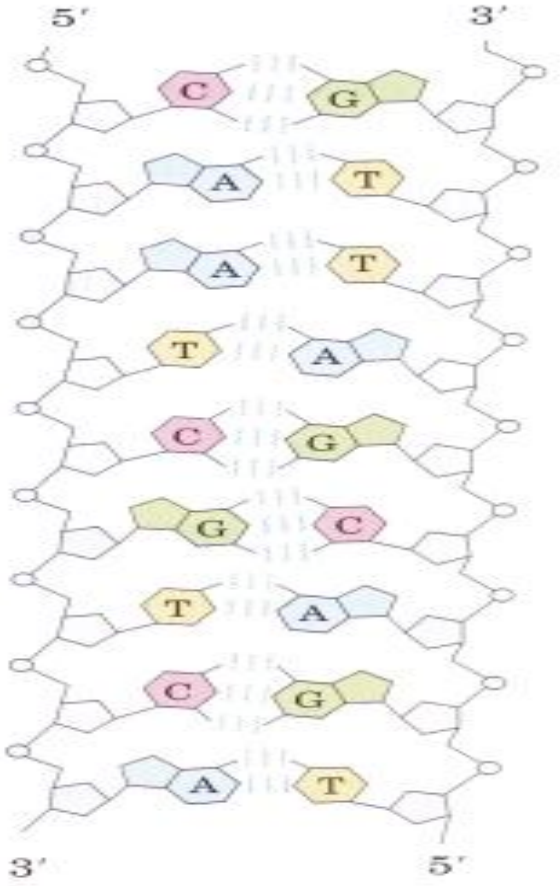
The histopathologist recognizes malignancy by looking for loss of normal architecture, invasion and nuclear abnormalities - three criteria at least.



Likewise, when an enzyme binds its substrate or an antibody to the corresponding epitope, there are actually many matches, not only shape but also in charge distribution (positive opposite negative) and mutual bonding potential



In the best example of all, **paired nucleic acid strands offer each other matched H-bonding opportunities. This example can best be reckoned as eight matches, not just one, and the degree of discrimination varies with how many matches – too few and the thing falls apart. Combined selection in action, CO-SELECTIVITY.**



Co-selectivity

- **So combined discrimination (co-selection) is a real phenomenon, a scientific subject worthy of study in its own right, capable of development (using co-bodies) to applications far beyond what we know today.**

- **The principles have been used in Medicine for thousands of years.**

- **And it happens in ordinary life as well ….**

Red cars can be quaint, square, naff or sleek. Choose the one you want, but it is not enough to say that the car must be red.

Discrimination in Life, Science and Medicine. Recap and Conclusions

T.R.C. Boyde, IDF ROME, 9TH OCTOBER 2010

- Why are natural antisera so very good at what they do even though the binding properties of individual antibodies are nothing special? In part it is because antibodies join together so that the heterogeneous assembly reacts with multiple different epitopes on the target cells. We may call this *hetero-co-selectivity* to distinguish it from the combined operation of identical binding sites.
- Though the mathematics is not finished, we may generalise from these ideas to a theory of how real people make choices and diagnoses, including about marriage. We talk about 'patterns' and when trying to formalize the concept we make lists of what to look for, namely a *multiplicity* of *different, independent* criteria. A few examples: Ginger cats may be distinguished from each other by the presence of white feet, red cars by shape, size and decoration; an enzyme matches its substrate not only in shape but also by how charge and reactivity are distributed in the active site; cancer is diagnosed by the simultaneous presence of disturbed architecture, invasion and nuclear abnormalities. An old-fashioned clinician makes a diagnosis "instinctively" by unconscious assessment of a whole range of criteria, which is how Hippocrates did it and still a good method two thousand years later. From the work of Gödel, Turing and Penrose we know that in this area the human brain can easily solve problems that are impossible for all computers, for ever.
- Coming back to antibodies and similar things; the binding energy of a single binding site (a) is amplified in the *homo-co-selectivity* of natural bivalent antibodies, if both sites are able to bind at the same time (b). Even the slightest strain or mismatch diminishes this "bivalent advantage".
- If two or more *different* sites are linked artificially *and flexibly* (c) there is a completely new combined specificity and enhanced affinity. These new reagents - *co-bodies* - will revolutionise both laboratory work and medical treatment, through their *hetero-co-selectivity*.
- You heard it first in Rome!!