relationships, or among individuals with HIV infection—requires measured clinical judgment until further studies are available. Furthermore, the vexed question remains of whether the notable reduction in transmission provided by valaciclovir would be achieved by other antiviral drugs, such as aciclovir or famciclovir, and if so, at what dose? Without comparative data, individual prescribing decisions in specific healthcare settings will need to be made on the basis of factors including availability, potential adherence, and cost.

That no evidence of viral resistance was detected in those individuals who became infected in this study is reassuring. That some susceptible individuals did become infected reinforces the message that valaciclovir reduced the frequency of HSV reactivation, subclinical shedding, and transmission of genital herpes, but it did not eliminate it. Antiviral treatment is thus not a substitute for other methods to control the spread of sexually transmitted infections but an additional tool. Patients should also be advised to continue using condoms, practise safer sex, and inform their partner about transmissible infections they have. The risk of transmitting genital herpes will not be removed, but patients can be assured that they are doing everything they can to reduce the risk of infecting a loved one.

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Schizophrenia: a genetic disorder of the synapse?

Glutamatergic synapses might be the site of primary abnormalities

Understanding the cause and pathogenesis of schizophrenia remains one of the great challenges in psychiatry. Progress has been slow, but one of the few certainties is that individual differences in liability are predominantly genetic.[1] This information has, however, not been useful neurobiologically because the genes themselves had not been identified. This situation is beginning to change, allowing a reappraisal of existing hypotheses of pathogenesis.

Until recently the two leading hypotheses concerned dopamine and neurodevelopment. The classic dopamine hypothesis, which attributed schizophrenia to a hyperdopaminergic state, arose from the ability of dopaminergic drugs to induce a psychosis, and the realisation that the potency of antipsychotic drugs is proportional to their ability to block dopamine receptors.[2] Refinements of the hypothesis indicate a more complex picture—increased dopaminergic transmission in the basal ganglia may underlie acute psychosis,[3] but a prefrontal cortical dopamine deficit is associated with neurocognitive impairments.[4] The dopaminergic changes are probably secondary to altered cortical glutamatergic transmission,[5] but compelling evidence for a primary causative abnormality in neurotransmission does not exist.

Whatever the fundamental causes of schizophrenia, clinical, epidemiological and neuroimaging studies clearly show that their influences are exerted from early in life and well before the changes in neurotransmission at the onset of acute psychosis.[6 7] Given robust findings that a number of brain regions are reduced in size, the absence of any pathological evidence for neurodegeneration is also consistent, albeit by default, with a neurodevelopmental model of schizophrenia.[8]

The positive findings from neuropathological studies are not conclusive, but now reasonable evidence exists for alterations in the cytoarchitecture of several brain areas, notably the hippocampus, the prefrontal cortex, and the dorsal thalamus where neurons, dendrites, synapses, and oligodendrocytes are affected.[8] Taken together, the findings imply an alteration in cortical circuitry, which may represent the anatomical basis of aberrant connectivity that has been inferred from neuropsychological and functional imaging studies.

These and other hypotheses of schizophrenia have been frustratingly vague, and although they provide clues to proximal causes of symptoms, they do not specify the causal molecular events. The situation, however, is now changing rapidly as several putative susceptibility genes have been discovered. Evidence for associations between DNA polymorphisms and schizophrenia has been reported and, more importantly, replicated for some of these genes.[9 10] The degree of agreement between studies sets these findings apart from numerous other claims made on the basis of single studies and makes it timely to consider how they affect the biology of the disease.

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The genes most clearly implicated all code for proteins that potentially have an impact, directly or indirectly, on the function of glutamate synapses.[11] The genes include dysbindin-1, neuregulin-1 (NRG1), D-amino acid oxidase (DAO), its activator DAOA (previously known as G72), and regulator of G protein signalling 4 (RGS4). For example, dysbindin-1 may influence the uptake of glutamate into synaptic vesicles, NRG1 is released from glutamate terminals and regulates NMDA glutamate receptors, and DAO, which is activated by DAOA, oxidises D-serine, an endogenous modulator of NMDA receptors.[10] These functions imply that synapses, particularly glutamatergic ones, might be the site of primary abnormalities in schizophrenia, with downstream disruption of neural circuitry.[10]

The synaptic hypothesis of schizophrenia had already been attracting interest and, given these genetic clues, is likely to become a major research focus and a point of convergence between the genetics of schizophrenia and its neurobiology. Despite exciting recent findings we need to remain cautious in a field notorious for premature claims. The genetic evidence itself is incomplete, particularly for the genes with the most direct synaptic implications (DAO, DAOA, RGS4). The more strongly supported genes, however, especially NRG1, encode proteins with multiple functions, which could be relevant to schizophrenia without specifically involving the synapse.[12] Although the desire to fit the data into a unified pathophysiological theory is attractive and parsimonious, it may therefore be misguided. Schizophrenia is not a disorder where simple ideas generally prove to be true, and we should not slow down the hunt for novel schizophrenia genes. At the same time, we need to identify the specific mechanisms by which the current crop of genes alters risk of schizophrenia and the molecular processes that link these primary events to altered function—synaptic or otherwise. We can then look forward to novel treatments that surpass the efficacy of existing medication, ameliorate the neglected cognitive and negative symptoms, and begin to modify the disease process itself.

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Would regional government have been good for your health?

England may have missed an opportunity to improve public health

The resounding "no" vote for a regional assembly in the North East of England has firmly put the lid on the prospect of elected regional government for the foreseeable future. There is considerable debate in the North East as to the reasons for the rejection of the proposal, which may have come down to a distaste for having more politicians, a suspected higher council tax, intraregional rivalries, too few powers, or perhaps a mix of these. In the white paper announcing the regional referendums, assemblies would not have any direct responsibility for health care,[1] although many would have liked to have seen such an outcome in the spirit of the government's devolution policy and commitment to localism.[2] But the assemblies would have had a specific remit for public health.

The white paper announcing the regional referendums pointed out the high impact that housing, transport, and economic development have on public health and promoted the joining up of these policies to reduce health inequalities. Nevertheless, it remained a cautious document, produced against a background of little interest in the issue of elected regional assemblies.[3]

A public health presence already exists at regional level—a process that began with the *NHS Plan* and the move of regional directors of public health to the nine regional government offices in 2002. This was designed to enable the regeneration of regions to embrace health as well as environment, transport, and inward investment.[4]

What, if any, would have been the health benefits of regional government? Integrating public health with regional activities in social and economic development and inclusion would go some way towards meeting Derek Wanless's view that good health is also good economics.[5] Regional development agencies are already investing in the regions, and an even closer

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