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Adolescent development

Advice in ABC of adolescence is potentially misleading

Editor—Christie and Viner say that delayed puberty in boys can be quite distressing but is almost always a normal variant. They say that boys aged 15 or over with a testicular volume of 4 ml or more can be reassured that puberty is beginning and, by inference, do not require referral to a specialist. This advice is potentially misleading.

For all that it is a variant of normality, constitutional delay in growth and puberty can have adverse psychosocial and sexual consequences. To deny an apubertal teenager the opportunity to choose low dose androgen treatment until he is in his 16th year would be unusual by present standards. Given the likely ensuing timescale, his doctor might as well refer him straight to an endocrinologist instead of a paediatrician.

A testicular volume of 4 ml is well within the range found in boys with irreversible hypogonadotrophic hypogonadism and therefore by no means necessarily indicates that puberty is beginning. Many boys with hypogonadotrophic hypogonadism start puberty but fail to progress beyond the early stages. Moreover, a history of cryptorchidism (especially if bilateral) or anosmia should prompt an even earlier referral.

Neither does a family history of pubertal delay necessarily support a diagnosis of constitutional delay in growth and puberty, given the high prevalence of constitutional delay in growth and puberty among first degree relatives of patients with hypogonadotrophic hypogonadism. A recurring theme in the personal stories posted on the www.Kallmanns.org website by men with irreversible hypogonadotrophic hypogonadism is of just how difficult it was for them as teenagers to screw up the courage to go to see their family doctor about a lack of secondary sexual characteristics. On being told “not to worry, because it’s only pubertal delay,” many felt (or were made to feel) so crushed and foolish that they then put off seeing a doctor until many years later.

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Cognitive behaviour therapy for adolescents with chronic fatigue syndrome

Data are insufficient and conclusion inappropriate

Editor—I have concerns about the design and interpretation of the study reported by Stulemeijer et al on cognitive behaviour therapy for adolescents with chronic fatigue syndrome.1 The trial arms were not matched for the number of contacts with healthcare professionals. Experience from larger and more carefully controlled randomised interventional trials of patients with chronic fatigue syndrome has clearly shown that short term improvement in symptoms is related directly to the maintenance of regular contacts with healthcare professionals rather than the therapeutic effect of the intervention itself and consequently, the improvement is not sustained once the contact is lost.

The authors did not offer patients in their waiting list the opportunity to meet therapists regularly for five months but without having cognitive behaviour therapy. Few follow up data on patients in the intervention arm show that the specific treatment benefit was carried forward without regular contacts with the therapists. A cautious approach is essential in inferring direct benefit from cognitive behaviour therapy in the intervention arm (as opposed to short term benefit from close contact with therapists).

The level of activity in some of their participants whom the authors considered to be passive remained unclear.

In their summary points the authors claim that cognitive behaviour therapy was effective by challenging patients’ belief that activity aggravated symptoms. Epidemiological data, however, confirm that fatigue made worse by exercise is a characteristic feature of adolescents at risk of chronic fatigue syndrome.2 Encouraging activity in disabled patients is entirely different from challenging an accepted feature of the disease. A rhetorical approach towards a physically and emotionally challenging condition does not help recovery and only encourages therapeutic failure.

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from cognitive behaviour therapy and were all patients. We believe that our study clearly have one treatment that leads to recovery in distinction between physically passive and activities in a systematic and safe way. Our regulate and increase their physical and other is possible. Thus, patients are taught to term and maintains activity avoidance and the condition, is dysfunctional in the longer phase of fatigue is made worse by exercise. This cogni-

ments, although functional in the first phase of the condition, is dysfunctional in the longer term and maintains activity avoidance and symptoms. By challenging these and other activity related cognitions, activity regulation is possible. Thus, patients are taught to regulate and increase their physical and other activities in a systematic and safe way. Our results show that this is possible. The distinction between physically passive and relatively active patients, based on acotmery, is helpful to select the correct approach to help the patient.

As in other chronic conditions, we do not have one treatment that leads to recovery in all patients. We believe that our study clearly shows that many of the participants benefited from cognitive behaviour therapy and were able to function as normal adolescents again.

How to prevent caesarean deliveries deserves more study

Entring—Declerq et al bring to light “no indicated risk” as a new classification of caesarean delivery.1 Like other classes of caesarean delivery, annual rates of caesarean sections with no indicated risk have been increasing in the United States and around the world. In the context of these increases, we are surprised that methods of care that might prevent caesarean delivery have not been pursued more aggressively.

Caesarean delivery is strongly correlated to the age of the mother, parity, and increasing gestational age within the term period of pregnancy.1 If caesarean delivery is an adverse outcome worthy of prevention, if risk factors for caesarean delivery can be identified, and if a latent period exists between the identification of risk and the development of situations requiring caesarean delivery then perhaps a preventive approach—encourag-
ing patients with risk factors to enter labour before their risk can become disease—could lower caesarean delivery rates safely.

Our working group recently described the use of risk driven, prostat glandin assisted induction of labour, and this intervention was associated with a rate of caesarean delivery of only 4%. While Declerq et al think that research should be done to elucidate whether the risks of primary caesarean delivery in cases of no indicated risk will be offset by associated benefits, we hope that an equal amount of time and effort will be spent on developing and testing methods that might safely prevent, or lower, rates of caesarean delivery performed for this and the other more traditional indications.

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2 Caughey AB, Musci TJ. Complications of term pregnan-
3 Nicholson JM, Kellar LC, Cronholm PF, Macones GA. Active management of risk in pregnancy at term: an associa-

Early epidurals increase caesarean rate, meta-analysis shows

Entring—The study reported by Mayor in her news item uses the term “neuropsychal-
gnosis” and claims that early epidurals do not increase the rate of caesarean deliveries.1 2 This is confusing as the study was not of early epidural anaesthesia, and the oxytocin augmentation rate of 75% at first analgesia makes for lack of generalisability.

The claim that women need not worry that early epidurals will lead to increased caesareans is false.3 This trial was about two methods of helping women with pain in early labour. In the so called epidural arm, on their first request for analgesia, women received intrathecal fentanyl, and in the narcotic arm, hydromorphone. On their second request, almost two thirds of women in both arms were 4 cm or more dilated. In the intrathecal “epidural” arm, they received low dose epi-
dural; in the narcotic arm, hydromorphone.

This trial, as others that have contributed to the Cochrane meta-analysis,4 5 showed no increase in caesarean sections in the presence of epidural analgesia, but does not acknowl-
edge that most women were in active labour at randomisation, when most will do well. Wong et al, like Sharma et al, the major contributors to the Cochrane meta-analysis,4 have shown only that when women’s pain in the latent phase is managed with intrathecal, narcotic, or other pharmacological or non-pharmacological means, an epidural in the active phase of labour does not increase the rate of caesareans.

The role of an early epidural in contribut-
ing to increases in caesarean rates has yet to be studied in an randomised controlled trials, but the sensitivity analysis in the Cochrane meta-analysis, after removing late randomisation studies, shows that early epi-
durals to more than double caesarean rates.

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1 Mayor S. Epidurals do not lead to more caesarean sections, study shown. BMJ 2005;330:395. (19 February.)

Clomipramine and neuroleptic malignant syndrome

Klein—Haddow et al describe a severe adverse drug reaction but create an oxy-
moron in describing clomipramine induced “neuroleptic malignant syndrome.”

Clomipramine is not a neuroleptic and therefore by definition cannot cause this syndrome (any more than it can cause anti-
covulants or neuroleptics). The description is consistent with serotonin toxic-
ity, a well described adverse reaction to serotonergic antidepressants. In attempting to describe a new adverse drug reaction, Haddow et al have focused on non-specific clinical features that are present in many drug induced neuropsychiatric syndromes.2 Clomipramine, a potent serotonin reuptake inhibitor, has been associated with hyper-
thermia and was more correctly labelled as a neuroleptic.3 Muscle rigidity and raised muscle enzyme activities also occur in severe serotonin toxicity.4

Neuroleptic malignant syndrome is an idiosyncratic reaction to therapeutic doses of neuroleptic agents.5 A pragmatic clinical
description of the syndrome includes four primary features: autonomic lability, hyperthermia (pyrexia) without other cause, extrapyramidal syndrome (cog-wheel or lead pipe rigidity), and encephalopathy. Despite superficial clinical similarities between neuroleptic malignant syndrome and serotonin syndrome, they are usually easily differentiated on the basis of careful neurological examination. Neuroleptic malignant syndrome is associated with lead pipe rigidity, bradykinesia, and other extrapyramidal features. Conversely in serotonin syndrome there is hyperkinesia, hyperreflexia, and clonus.

Descriptions of adverse reactions to psychotropic drugs need detailed clinical descriptions of neuromuscular, central, and autonomic features. Using ambiguous or non-specific criteria to label adverse reactions as a particular syndrome while ignoring the pharmacology of the implicated drug may lead to false associations between particular drugs and clinical syndromes and to inappropriate treatment.

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Authors’ reply

Enzor—Clomipramine is not a neuroleptic and is classed as an “antidepressant.” However, as mentioned in our article, this drug has an appreciable blocking effect at dopamine receptor sites, the traditional domain of the neuroleptic drug. This is a weak effect, but it is more potent than several other antidepressant agents. This action is recognised in the current edition of the BNF, which says that neuroleptic malignant syndrome may, very rarely, arise in the course of antidepressant treatment.

Reference to 50 worldwide reports received regarding clomipramine and neuroleptic malignant syndrome or suspected neuroleptic malignant syndrome, in addition to four reports received by the Committee on Safety of Medicines and two published case reports.

We agree that we should have made clear that this patient’s muscle rigidity was of the lead pipe variety, although some widely accepted diagnostic criteria require only severe muscle rigidity. The diagnostic criteria that we tabulated were based on Levinson and Sternbach and referenced in our article.

We described in this patient an earlier diagnosed episode of serotonin syndrome, and no clinical evidence of rigidity was found on that occasion.

In view of the action at dopamine sites of clomipramine, and the statement in the BNF from the BMA and the Royal Pharmaceutical Society of Great Britain, we would continue to support our diagnosis of neuroleptic malignant syndrome in this informative case.

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Need for expertise based randomised controlled trials

Expertise based design has shortfalls

Editor—Devereaux et al discussed the need for expertise based randomised controlled trials for surgical procedures.

Firstly, the use of expertise based designs does not necessarily enhance the validity of a surgical trial. Surgical outcome does not depend solely on the operation; other factors that influence the results of an operation are heterogeneous and immeasurable (postoperative management, the surgical team, equipment). A different bias is introduced by the expertise based design, the influence of the overall performance of surgeon A > B, and in this regard, expertise based design is not necessarily a more valid comparison of operation A vs B.

Secondly, the use of expertise based designs does not necessarily enhance the applicability of a surgical trial. The expertise based design assumes that an operation will only be performed by a select few. This is rarely the case, and hence the results will not reflect the true performance of an operation introduced to the general public (performed by a variety of surgeons).

Moreover, the results of expertise based design trials do not take into account any learning curve that exists when a new operation is introduced. The initial rates of adverse outcomes are higher when a surgeon refines an existing operative technique, never mind a new one.

A solution is to perform a randomised trial that has a balanced surgical expertise in

Artwork of gene therapy

Editor—Kimmelman provided a comprehensive discussion about the risks and ethics of gene therapy. We certainly cannot predict the future, but the risks should be weighed against the complete lack of alternative options for many of the diseases discussed.

The two cases of T cell leukaemia in the X linked severe combined immunodeficiency gene therapy trial are presented as typical examples of malignant transformation. However, that treatment entailed the modification of immature stem cells, which may present additional risks.

Much work is being done in vector design to lessen these risks. Relative risks and toxicities are also likely to be linked to the disease type and target cell. For non-lethal disorders such as the inherited retinal dystrophies, minimising risk is of even more importance. However, gene transfer to a post-mitotic cell such as a photoreceptor by using a vector with limited genomic integrative potential, such as recombinant adeno-associated virus, is much less likely to be mutagenic.

The risks of gene therapy must be weighed carefully against the risks and efficacy of existing treatment. Conventional treatments such as organ transplantation, which are no longer considered experimental, are associated with substantial morbidity and mortality. The difficult balance is to steer a path between the ethical application of new untested strategies with the potential to improve health care, and a position of caution. As with conventional medicines, the risks and ethics of gene therapy should probably be reflected in this light.

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both arms in proportions reflective of the population that will perform the operations. Academics can analyse the “expertise subtraction” while the rest of us can look at the overall results to determine how an operation will really perform.

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**Surgical research shares many similarities with psychotherapy research**

**Editor**—Of course the expertise based randomized trial, mooted for surgical procedures by Devereaux et al., is the norm in psychotherapy research when comparing two different psychotherapies. A similar debate on the interpretation of such trials occurred in the psychotherapy literature. Research in surgery and psychotherapy share other similarities beyond having to account for practitioner expertise. There is the issue of blindness—hard to achieve for both patient and doctor in these disciplines—as well as the “why test it, it’s obvious it makes a difference” argument. Both disciplines could learn from each other about the design and analysis of clinical research.

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**Old docs and new tricks**

**Seasoned doctors may be better than young doctors at some things**

**Editor**—Spurgeon reports that the doctors’ standards of care drop with years in practice. When I began clinical practice in the late 1980s I thought that one key to being a “good doc” was keeping up with the latest drugs and technologies. I was dismayed to see seasoned colleagues who were slow to change. I then saw many new drugs get pulled from the market (rofeconib is not the first non-steroidal anti-inflammatory drug to be withdrawn) and various medical fads come and go. Evidence based medicine appropriately shed light on the poor evidence available to support most things that physicians do.

Armed with this keener analytical approach, I came to realise that most claims were exaggerated compared with absolute incremental changes and that most patients are not like trial subjects. Although an intervention might benefit a population, it is much less certain that it will benefit the patient who sits before me.

I suspect that seasoned doctors are better than their junior colleagues at some things, and worse at others. Maybe the ability to see the big picture, diagnostically and therapeutically, is enhanced by experience. Meanwhile the emphasis on the newest treatment detail might wane. Perhaps that is a reason why I have conflicting opinions about whether doctors get better with time.

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**Efficiency is important**

**Editor**—In British general practice, where everyday demand exceeds capacity, the efficient general practitioner is king. That is one thing that experience should bring. If all general practitioners followed every guideline the system would collapse, and although a few patients would have exemplary care, many would have no care at all as they would just not get seen because they would find the wait intolerable. Perhaps this is what happens now in secondary care, where care delivered is often very good but access is less and less. An accepted practice is often developed for a “one issue patient.” Reality means multi-issue patients, who themselves have limited ability to follow all the investigation and treatment recommended by the single issue academic establishment. Many indications for treatment are immediately met with contraindications. Experience allows general practitioners to cut back on too much excess investigation and treatment while still striving to meet the guidelines.

Protecting the patient from the iatrogenic harm of excess health care used to be a core skill of the general practitioner. Is this being taken away from us as well? A system that fails to value the soft end points and often efficient and effective care that experience brings will have to restructure to meet the demand and that inevitably will lead to a hugely expanded system with resource implications. I am not disputing the findings of the paper reported by Spurgeon, that the standard of care may drop with years spent in practice, but the immediate common sense illogic of its hypothesis and conclusions make me advise to proceed down this route with caution. Being a doctor is already a difficult job. Being advised that all your thoughtful patient experience has actually made you a worse doctor is demotivating. Perhaps experienced doctors and patients would have a different set of criteria about what good care is?

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