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He was awarded the Fellowship of the Royal College of Pathologists in 2001. Dr. Wakefield is involved in many scientific research collaborations in the United States and abroad centering on the immunologic, metabolic, and pathologic changes occurring in inflammatory bowel diseases such as autistic enterocolitis, links between intestinal disease and neurologic injury in children, and the possible relationship of these conditions to environmental causes, such as childhood vaccines. During the course of his work on childhood developmental disorders, Dr. Wakefield was increasingly convinced of the need for a research-oriented, integrated biomedical and educational approach to these disorders, in order to translate clinical benefits for affected children into measurable developmental progress; this is the driving aim of Thoughtful House Center for Children in Austin, Texas. He has published over 130 original scientific articles, book chapters, and invited scientific commentaries.

The Devil's in the Detail

By Andrew Wakefield, MB, BS, FRCS, FRCPath

The General Medical Council vs. Wakefield, Walker-Smith, and Murch

The research reported by you in *The Lancet* was substantially different from that for which approval was granted by the Ethical Practices Sub-Committee in that it related to:

i) Children with a diagnosis of autism and not disintegrative disorder ...

Your actions were ... inappropriate, not in the best interests of patients, not in accordance with your professional ethical obligations, likely to bring the medical profession into disrepute, and fell seriously below the standard of conduct expected of a registered medical practitioner.

Blake Dobson
Assistant Registrar
General Medical Council

The foregoing is a charge made by the General Medical Council in 2004. The subject matter was "That Paper" (see also *The Autism File*, 2009; Issue 33) – *The Lancet* paper of 1998 that first reported intestinal disease in children with developmental regression. Notwithstanding the fact that in his enthusiasm Mr. Dobson got the wrong Ethical Sub-Committee approval¹ and the wrong research protocol for the wrong children...

...there is so much more to this esoteric charge than meets the eye, and the "more" deserves scrutiny. Let's rewind to 1995-7, armed with the enduring adage "if in doubt examine the patient." Among the presenting clinical features of *The Lancet* children were some that were apparently uncharacteristic of autism, at least as it was generally understood at that time. For all 12 children, these included normal or near-normal early development, a clearly delineated onset of behavioral/developmental symptoms, and loss of previously acquired skills. In addition, four children had become incontinent after previously having been potty-trained, while seven children had developed obvious clumsiness (ataxia), a motor symptom clearly indicative of central nervous system dysfunction (encephalopathy). In contrast with the cold,

aloof child described by Kanner, many of these children were affectionate, to the extent that doctors had sometimes been unwilling to make an autism diagnosis.

The combination of these atypical features along with the fact that, for the majority, there was onset following an infectious (vaccine) exposure, led our colleagues in the Department of Child Psychiatry at the Royal Free Hospital to suggest that what we were dealing with was not Kanner's autism, but Childhood Disintegrative Disorder [Panel 1].

Childhood Disintegrative Disorder

In 1908, many years before the publication of Kanner's seminal case-series on autism, Theodore Heller, a remedial educator in Vienna, described a new syndrome – *dementia infantilis* (later to become CDD) – in the *Journal for Research and Treatment of Juvenile Feeble-mindedness*.²

CDD is a Pervasive Developmental Disorder that fulfills behavioral criteria for Childhood Autism/Autistic Disorder, but where the pattern of onset is different. CDD requires documented normal or near-normal development³ up to 24 months of age with subsequent regression and loss of skills in at least two of the following: expressive/receptive language, play, social/

adaptive skills, continence, and motor skills [Panel 1].

You might reasonably ask, “But isn’t CDD just autism with a later onset and regression?” Later onset following a period of normal development means there are skills to be lost. If the onset occurs after a child is potty-trained, for example, continence may be one of the skills that suffer. And where did 24 months come from? Surely this is entirely arbitrary – an artifact created to satisfy a need to categorize in the absence of a better understanding of the origins of the disease? What do the experts have to say?

- Hill and Rosenbloom noted that, “Unlike the vast majority of children with early infantile autism [children with CDD] undoubtedly showed a period of early normal development, including the acquisition of normal language and normal social relationships.”⁴
- They observed that the child usually “comes to look very autistic, such that the clinical presentation, but not the history [i.e., regression] is then typical of a child with autism.”³ Rosenbloom cites Professor Sir Michael Rutter as making age of onset a major criterion for diagnosis of CDD³ in distinguishing it from autism.
- In defiance of Rutter, Malhotra and Gupta noted that “at closer look the age range has varied from 1.2 years (Evans-Jones and Rosenbloom, 1978) to 9 years (Corbett et al., 1977).”⁵ Accordingly, they conclude, “it can be hypothesized that disintegrative disorder [CDD] may be a late-onset variant of autism.”
- Russo and colleagues reinforce this view: “Indeed, in many aspects the clinical features [of CDD] are indistinguishable from those of autism, and the differentiating factor is the period of normal early development.”⁶
- Malhotra and Gupta noted that “It has been observed that children with CDD have a clearly delineated onset and regression, especially for loss of previously acquired skills, which is absent from autistic disorders.”⁵
- The International Classification of Disease [ICD]-10 itself acknowledges the current “...uncertainty about the extent to which this condition [CDD] differs from autism...”⁷
- The final word goes to Hendry who, in a detailed review of the subject, concluded



that “the variables upon which CDD is currently distinguished from Autistic Disorder are not well substantiated.”⁸ She continued, “CDD should not yet be considered distinct from Autistic Disorder, as not enough information exists to justify it as a separate diagnostic category.” Further, she stated that “pervasive developmental disorders could be regarded as a continuum, or spectrum disorder and CDD could be considered a point or range of points along this continuum of behavioural expressions.”

In fact, the presenting features of CDD are identical to those of autism with respect to the core symptoms. The key difference lies in the history of normal or near-normal development and regression. The symptoms of CDD fit *The Lancet* 12 very well.

So, while opinions differ, any residual distinction appears to hang on the flimsy contrivance of age of onset. For Rutter, as a key prosecution witness at the GMC hearing, however, the matter was black and white. When asked whether “in embarking on a study of children with behavioral disorder, would [he] expect a distinction between CDD and autism to be made,” he replied, “Yes.” He continued, “and the literature would support drawing a clear distinction at the time [1996].” It is somewhat surprising, therefore, to find that he had earlier written⁹ that “The clinical

CDD or Heller’s Disease

From around the age of 2 through 10, acquired skills are lost almost completely in at least two of the following six functional areas:

- Language skills
- Receptive language skills
- Social skills & self-care skills
- Control over bowel and bladder
- Play skills
- Motor skills

Lack of normal function or impairment also occurs in at least two of the following three areas:

- Social interaction
- Communication
- Repetitive behavior & interest patterns

Panel 1

Measles – bowel – behavior – gluten

Dr. Guy Daynes. Bread and Tears – Naughtiness, depression, and fits due to wheat sensitivity.

Royal Society of Medicine
February 15, 1956

“Typically a child between 1 and 5 years becomes naughty and difficult a few days after the onset of an acute infectious illness... such as measles or gastroenteritis.

He is irritable, negativistic, and spiteful, sleep is disturbed and he wakes up in thse night and often screams; his appetite is poor, he fails to gain weight, his abdomen is often distended and the stools may become bulky, pale and offensive. This condition, if left untreated, usually rights itself after a month or two, but it may last for much longer in which case slight *petit mal* attacks may develop in addition to worsening of the other symptoms.

I have been placing these children on a gluten-free diet at the earliest opportunity and the symptoms respond dramatically, usually within two or three days. They relapse if a premature return to a normal diet is made.

Study of over 40 cases has led me to formulate a syndrome – pre-coeliac syndrome.”

Panel 2

picture [in CDD] after the phase of regression is often somewhat similar to autism and the differentiation may be difficult, **if not impossible**, in cases with an onset before 30 months.” It is notable that regression and onset before 30 months applies to virtually all of *The Lancet 12*.

Also notable among the other clinical features of CDD evident in *The Lancet 12* are loss of coordination, secondary incontinence, and, in contrast with “classical” autism, expression of affection.^{2,6} Might it simply be that affection, for example, does not make CDD a distinct disease because, unlike the child with classical autism, the child with CDD has had several years of normal development in which to experience and enjoy affection?

It would seem that Rutter is somewhat isolated in his categorization of childhood developmental disorders by age of onset. Indeed, it is arguably naïve to conceptualize disease in this way, when age of onset may simply better explain differences in presentation. In arguing for splitting autism and CDD, he stated that “although the onset differs from that which is usual in autism, the clinical picture in the two groups of conditions shows many similarities. Nevertheless... for the moment it seems highly desirable to retain [CDD] as a separate category because it is important (a) to recognise that often the syndrome is caused by organic brain disease (b) to appreciate that in some cases the aetiology remains quite unknown; and (c) to accept that the nature and extent of the overlap [with atypical autism] is unknown.”⁹

Rutter’s reasoning is curious; all three points apply equally to autism – atypical or not – and CDD. Both may be caused by organic brain pathology; in most cases of CDD and autism the cause is unknown; and, since “the nature and extent of the overlap is unknown,” there is little justification for categorizing them separately.

And even now the concept of regression itself appears to be morphing. Whereas, in the past, regression appeared to have been a key distinguishing feature between autism and CDD, Rutter now maintains that regression has always been a common feature of autism.

During his expert evidence at the GMC¹⁰, Rutter expressed the opinion that for autism “a transient period of regression occurs in 25-30% of cases and is usually temporary.” This appears to be at odds with the prior claim that regression was not seen “for the vast majority of children with infantile autism.”⁴ Rutter may have been referring to temporary loss of language in autism, although this was not clear from his testimony that appeared to focus on *The Lancet*¹².

The data often quoted in support of this position are those of Kurita et al. who reported loss of language in 30% of children with autism.¹¹ Interestingly, in a second study, Kurita went on to show that the children with regressive autism (the 30% with language loss) were clinically indistinguishable from CDD.¹² In light of their findings, Kurita et al. argued that the validity of CDD being a distinct entity from Autistic Disorder was unproven and “remains to be studied.”

Sadly, for *The Lancet 12*, developmental regression was pervasive – not confined to language alone. Neither was it temporary.

CDD, Autism, and Causation

“If autism is a consequence
of vaccination it should
have been a consequence of
natural infection”

Paul Offit, in interview with
Melanie Howard, *Babytalk* magazine

At the heart of the GMC hearing is a defense of the MMR vaccine. Stepping back from the pernicious lies, the political angst and the cries for blood, it may be valuable to gain some historical vantage point from which to judge scientific concerns about measles virus, vaccines, and developmental disorders. Take for example the presentation of Dr. Daynes to the Royal Society of Medicine in 1956 [Panel 2]. Herein he describes, for all the world, what we see in a clinical setting on a daily basis; apparently there is nothing new.

It is perhaps unsurprising that a further common denominator for some cases of autism and CDD is the causal role of measles virus. This virus, either in its natural or vaccine forms, has been causally linked to childhood developmental disorders, including autism¹³⁻¹⁶ and developmental regression.¹⁷

In utero exposure to measles is associated with autism. Deykin and MacMahon compared exposure patterns of 183 children with autism and 355 sibling controls to the encephalitogenic (causing brain inflammation) viruses, measles, mumps, rubella, and chickenpox. They found that “total autistic symptomatology seems to be associated with prenatal experience with measles and mumps.”¹³

In support of a causal role for prenatal measles in autism, Ring et al., used sophisticated statistical modeling of the



number of autism births in Israel compared with epidemics of measles, rubella, poliomyelitis, viral meningitis (inflammation of the lining of the brain) and viral encephalitis (inflammation of the brain) and found that peaks in the number of births of children with autism followed peaks of epidemics of measles and viral meningitis.¹⁴

The authors concluded that “Autistic birth patterns are partially explained by the rates of measles and viral meningitis [incidentally a frequent feature of measles¹⁸] in the general population. There is a statistically significant environmental association between autism and both viral meningitis and measles that should be further investigated.”¹⁴

CDD has been reported following natural measles infection, and cases have been reported in association with subacute sclerosing panencephalitis, a measles-related encephalitis.¹⁹

In the case of CDD and measles, Rutter himself wrote that profound regression and behavioral disintegration is often accompanied by a “premonitory period of vague illness, [when] the child becomes restive, irritable, anxious and overactive. . . Sometimes these conditions come on after measles, encephalitis or other clear-cut organic illnesses.”²⁰

Among five children who fit the criteria for CDD, Volkmar et al. described a child with onset of behavioral decline following measles encephalitis.²¹ Hudolin reported that, prior to regression, a 15-year-old boy with limited speech, stereotyped and repetitive play, and poor self-care skills, etc., suffered from an unknown strain of measles and high fever at approximately 30 months.²² Malhotra and Gupta confirm that many cases have been associated with some medical condition such as measles.⁵

Vaccines have been associated with CDD; for example, in a report of 12 cases in India seen between 1989 and 1998, Malhotra and Gupta noted onset in four cases with onset following either fever with seizures, acute gastroenteritis, and vaccination. The type of vaccine was not stated.²³

Dwelling briefly upon the clinical features of ataxia in combination with developmental regression, potentially novel adverse events associated with the combined MMR vaccine, rather than the monovalent component vaccines, have emerged from Plesner’s Danish study of ataxia following MMR.²⁴ Earlier studies had indicated that ataxia with gait disturbance might occur in up to 1 in 1000–4000 recipients of MMR.^{25,26} In Denmark this association had

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“ It is entirely plausible that measles, in combination with two other viruses which have themselves been linked independently to autism – as MMR – may increase the risk for this condition in certain children. ”

not been detected with any other vaccine administered to children of the same age prior to the introduction of MMR in 1987. In a follow up of the mandatory passive reporting system for vaccine adverse events operated in Denmark, Plesner not only confirmed this association but also indicated that the more severe ataxias following MMR may be associated with residual cognitive deficits in some children,²⁴ a finding of specific relevance to the MMR-autism debate.

Rutter remains steadfast, however. On behalf of the defendants in U.S. vaccine court and elsewhere, he has taken the position that vaccines are not a cause of autism. Given his pre-eminence, this position is likely to have been highly influential. Meanwhile, the first reported association between vaccines and autism came, not in 1998 with *The Lancet* paper, but in 1993.^{27,28} This earlier report took a robust position on the vaccine's likely culpability, certainly compared with the restrained statements in *The Lancet* paper of 1998. In 1993, the authors described 11 children with autism who were excluded from a genetic study based on their having a “medical condition of possible aetiological [causal] importance.” The authors stated,

“Only eight of the cases can be regarded as having a **probably causal** medical condition, [including] a child with epilepsy and a temporal lobe focus on the EEG who had an **onset following immunization.**”^{27,28} While the hopes of many desperate parents lie dashed upon the cold marble of the courthouse, it is but an ironic postscript that Professor Sir Michael Rutter, FRS was the senior author of that paper.

Conclusion

It is proposed that autism and CDD are on the same continuum of clinical disease. Measles virus exposure has been linked to both CDD and autism. The timing of this exposure – i.e., early (*in utero*) or later, in childhood – may determine the clinical presentation, including the presence and extent of regression. Infantile autism without regression may be linked to early exposure, whereas CDD with regression may be linked to later exposure. It is entirely plausible that measles, in combination with two other viruses which have themselves been linked independently to autism – as MMR – may increase the risk for this condition in certain children. Whether or not MMR is guilty as charged remains to be determined.

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