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Law notes

Case pending before the European Court of Justice

Nancy Fern Olivieri vs. the European Commission. Luxemburg, 17 November 1999.

A highly unusual case, which whatever its outcome is likely to be of great importance to the issue of safe medical treatment, is being heard by the European Court of Justice at Luxemburg from November 1999 onwards. It relates essentially to the standard of practice of the European Commission and certain of its advisory bodies in granting authorization for new drugs to be sold throughout the Community.

Patients suffering from Thalassaemia Major owe their survival to long-term blood transfusions. Such intensive transfusion brings with it an unavoidable iron load on the body which in turn can lead to severe adverse effects, involving particularly the liver and the heart. To counter this problem, the chelating agent deferoxamine was introduced some 25 years ago. It is generally well tolerated and results in long-term survival of these patients, but it has to be administered by infusion.

Deferiprone, a new chelating agent which promised to be effective when administered orally, was developed in London in the 'eighties. Much of the clinical investigation was carried out in Canada by Dr Nancy Fern Olivieri at the Hospital for Sick Children in Toronto, Ontario. Two investigations, one of them a controlled comparative study of the drug's efficacy, examined alongside deferoxamine, were carried out directly at Toronto. A third (uncontrolled) study, primarily designed to investigate the drug's safety, was set up in Italy, where Thalassaemia is more widespread; Dr Olivieri and her colleague, Dr Brittenham, jointly chaired a Steering Committee for the Italian study. Whereas the clinical work had initially been funded by the Medical Research Council of Canada, funding was progressively assumed by the Canadian drug manufacturer Apotex.

In the course of 1998, the two trials in Canada were suspended by Apotex; almost at the same time, Dr Olivieri was dismissed from the Steering Committee of the Italian study; Dr Brittenham then resigned in protest. The reasons for these developments appear to be disputed. The manufacturer for his part seems to consider that there had been protocol violations. The investigator points out however that she had found evidence that the efficacy of Deferiprone was declining as treatment continued, and that it might actually increase the risk of organic damage; this evidence, which she subsequently published in a peer reviewed journal, led the hospital authorities to provide new warnings to the parents of the patients involved. It was immediately after these warnings had been issued that Apotex acutely stopped the study.

Subsequently Apotex submitted to the European authorities an application for Market Authorization for the drug. The advisory "Committee for Proprietary Medicinal Products" issued a positive recommendation, and a Marketing Authorization was duly issued by the European Commission in August 1999. In April 1999, having been apprised of the positive CPMP recommendation, Dr Olivieri approached the European authorities in writing, pointing out *inter alia* that:

- Apotex had abruptly, prematurely and unilaterally terminated the two Canadian trials which comprised the pivotal studies of the drug's efficacy and safety.
- She had reasonable grounds to believe that Apotex's application for marketing authorization contained information that was inaccurate and incomplete on material points. In particular, she noted that the Italian study was wrongly represented to the authorities as "pivotal", whereas in fact this

was only a safety study in which the only measure for efficacy was serum ferritin, the reliability of which was to be regarded as highly questionable. The data from the two incomplete trials had also been wrongly interpreted. In her submission, too, certain serious adverse reactions had not been reported to the European authorities.

Following Dr Olivieri's communication, the CPMP requested the Commission to delay issuing the marketing authorization while these issues were investigated. Dr Olivieri had a telephone conference with certain officials of the authorities, and her written materials were examined. Subsequently the Marketing Authorization was indeed granted, though with a number of additional obligations regarding supplementary investigation which was to be carried out by the manufacturer subsequent to marketing.

In the present case before the Court at Luxemburg, the applicant seeks an injunction to suspend the marketing authorization, and thereafter annulment by the Court of the marketing authorization in its entirety. The grounds adduced relate to alleged errors both of fact and law by the Commission's advisory body.

Comment. Most national regimes for the licensing of medicinal products provide for an appeal procedure, either on issues of fact or of law. The European procedure does not; the only corrective mechanism available is to follow the relatively cumbersome routing through the Court at Luxemburg. Even where appeal procedures exist, however, they are primarily conceived (and regularly used) as means by which an aggrieved manufacturer can challenge a negative or restrictive decision. This reflects the concept of drug control as a mechanism in which the authorities are dealing primarily with applicants, i.e., manufacturers and importers, and are held to do so fairly and openly. However correct this may be, it is only one side of the picture. It overlooks the basic fact that drug control is instituted and maintained primarily in the interests of the public; it is therefore at the very least curious that if a positive decision is taken incorrectly, resulting in the licensing of a potentially dangerous or ineffective drug, there is no readily available means by which the public or its representatives can recognize the error and appeal against the decision. In theory, at least at the national level, consumers or health professionals could make use of existing appeal procedures for this purpose, but in fact they are as a rule so incompletely informed of the facts of a particular matter that they have no means of recognizing incorrect decisions when they occur. Most of the investigational material available when an application is granted is, after all, unpublished and remains known only to the authorities on the one hand and the manufacturer on the other.

The present case could only be brought because the appellant was an investigator who had been involved in the studies with Deferiprone from the start, and was thus in the possession of much of the scientific material. Even she, however, has presumably no access to the final documents as presented by Apotex to the authorities. Unless they are released through a legal process of discovery, it is hard to see how the case can be conducted in a manner fair to all parties.

On the basis of the information available to date, it is difficult to predict how the case might be decided, either as regards the issuing of an injunction or definitive annulment of the licence. It is however of the greatest importance that such a case be heard and investigated thoroughly. By all accounts it is the first time that a positive European regulatory decision in this field has been challenged in a court of law. Whatever the outcome it is likely to cause drug regulatory authorities to review carefully the extent to which they are currently dependent – perhaps seriously over-dependent – upon the information and conclusions provided to them by interested manufacturers.

European Public Assessment Report: Ferriprox. European Agency for the Evaluation of Medicinal Products, London, August 25th 1999.

Doctors for Research Integrity: Press Release. Toronto, November 18th 1999.
Anon: Group seeks review of EC's drug backing. Toronto Globe and Mail, November 18th 1999.

Medical error; calculation of damages (England)

Windyk vs. Wigan Health Authority. High Court: April 26th–29th and May 7th 1999. [1999 MLC 0088.]

As a result of premature birth and resultant retinopathy, a young man was blind in his right eye and had only extremely limited vision on the left. He succeeded however in leading a relatively normal and enjoyable existence. At the age of 27 a medical practitioner ill-advisedly recommended operation on the left eye, and as a result he became almost entirely blind. The physician admitted that his advice had been incorrect and that he (or in fact the health authority which employed him) was liable for the injury. The present case turned on the level of damages which could be awarded against him for negligence.

The defence argued that the patient's limited vision was in any case tending to deteriorate prior to operation, and that even in the absence of surgery he would have become blind within a period which might have ranged from five to twenty years. For that reason, damages must be calculated only with respect to the additional disability resulting from the operation.

The evidence of progressive deterioration of vision prior to surgery was disputed. Entries in the nursing records indeed suggested that in earlier years the plaintiff had been able to see hand movements and perhaps to count fingers, whereas in the period leading up to the operation he had only perception of light. For plaintiff the view was advanced that these measures of visual ability were very inexact, and that the level of vision could have been determined more reliably in other ways, perhaps simply by questioning the patient. The nurse who entered the records had in fact been primarily concerned with the question as to whether he still had perception of light and was not systematically studying the level of vision. The plaintiff and his mother both argued that his vision had in fact been stable from childhood, with no evidence of decline; the operation had reduced visual ability almost to zero as well as producing physical disfiguration. Experts for the plaintiff produced published evidence that when patients who suffered impaired vision as a result of retinopathy of prematurity showed any subsequent deterioration, this tended to occur by the mid-twenties, vision thereafter remaining stable.

In arguing the level of damages, the plaintiff submitted evidence of rehabilitation needs amounting to as much as 34 hours of care weekly, whereas a medical expert for the defence expert held that only six hours of care would be needed. Evidence of the prospects for gainful employment prior to and following the operation was similarly conflicting,

The Court held that the prospects for employment even prior to surgery were negligible, but it accepted the plaintiff's estimate for the extent of care now needed. A total award was made of 376,534 pounds sterling, comprising the costs of care, special accommodation, appropriate computer equipment and travel needs.

Comments. It is normal when calculating damages for injury resulting from medical negligence to take into account the level of health and ability which a patient would have enjoyed had the negligent act not occurred. One point raised by this case is that, where treatment is offered to a patient already suffering from a severe degree of physical impairment in the hope of relieving it, the existing level of disability should be examined and recorded as exactly as possible, as a baseline for assessing the results of treatment, whether these are favourable or (as in this case) very unfavourable; this is a sound medical principle, quite apart from the medicolegal importance of such a record.

A surprising element in the view adopted by the Court is that a blind person has virtually no prospects for gainful employment. Involvement of the blind in paid work has developed markedly in recent years. The plaintiff in this case had already received training in computer operation, a field in which the blind can achieve a great deal, given properly adapted equipment.

Obligatory testing of pregnant women to obtain evidence for prosecution (USA)

Ferguson vs. Charleston. 186 F.3d 469 (4th Cir. 1999).

During the 1980's, there was evidence of an increase in the use of cocaine by pregnant women in South Carolina. In that state, a foetus potentially is considered a "person" and a woman who takes cocaine after the 24th week of her pregnancy can therefore be considered guilty of the offence of distributing a controlled substance to a minor. The Medical University of South Carolina, working together with the police and the district solicitor, therefore ordained that any woman attending the University's Obstetrics Clinic and in whom there was reason to suspect cocaine abuse would be subject to urine testing. If the outcome were positive, the woman would be offered the alternative of drug counselling or arrest for distribution to a minor. Ten women who had been tested under this programme brought an action against the University and the other parties involved, on the grounds that such testing violated their rights under the Fourth Amendment to the US Constitution to be free of unreasonable searches and seizures; it was also claimed that it violated their constitutional right to privacy and certain other legal instruments. The district court rejected their claims, and in second instance the US Court of Appeals for the Fourth Circuit confirmed the judgement.

The Court of Appeals recognized that the urine testing constituted "searches" without a warrant but held that such testing was reasonable under the doctrine of "special needs searches"; the latter provides for searching to meet "special governmental needs", beyond the normal need for law enforcement. The degree of intrusion was minimal (testing of urine only), the testing was performed only in women in whom there already was reason to suspect cocaine use, and the motivation for the testing related to the government's need to reduce maternal use of cocaine, which was both a health hazard and a drain on public resources.

As to the question of privacy, the Court held that, *even if* the women had a right to privacy regarding their medical records (a point on which it did not give a direct opinion) this would be outweighed by the government's strong interest in disclosure as a basis for law enforcement. The Court stressed in this connection that in the present instance disclosure would be only to government agencies; the findings would not enter the public domain.

Comments. One special element in this case is that in the United States the Supreme Court has still taken no decision as to whether a person has a constitutional right to privacy as regards his or her medical records, a matter which the Fourth Circuit Court succeeded in circumventing in its judgement; this is in marked distinction to the situation in many other countries. Another particular element is the fact that South Carolina is the only State where a viable foetus is regarded as a "person". The above judgement has elicited some vigorous protests from health professionals in the US on the grounds that, if women tested at obstetric clinics can be prosecuted in the light of the tests to which they are subjected, this may deter women from attending such clinics at all. It may be noted that in 1994 the Medical University of South Carolina, under threat of sanctions from the Office of Civil Rights of the (Federal) Department of Health and Human Services as well as the Federal "Office of Protection from Research Risks" has abandoned its

cocaine testing programme. OPRR held that it constituted a form of human research performed without the necessary approval of the relevant institutional review board. Whether the University will attempt to reinstate its testing programme in the light of the Fourth Circuit's judgement is not yet clear.

Delayed litigation in drug injury cases (England)

In early 1987, Roberts, a young lady then aged 19, was found to be suffering from depression and was prescribed amitriptyline in a standard dose by her general practitioner. In December of that year her condition relapsed and her depression was by now more severe; she was referred to the consultant psychiatrist Winbow who admitted her to hospital and prescribed a higher dose of amitriptyline, which he subsequently increased further. Shortly afterwards, on January 6th 1988, she was in addition prescribed the tranquillizer temazepam, which was replaced by carbamazepine in mid-January. On January 18th, once her condition had improved, she was given lithium. She thereafter developed a rash which Winbow initially diagnosed as drug-induced urticaria; he decided to continue treatment. Her skin condition deteriorated and on February 19th she was admitted to another hospital with a diagnosis of Stevens–Johnson syndrome attributable to hypersensitivity to carbamazepine, a serious condition which resulted in her remaining hospitalized for three weeks,

Shortly after her discharge, in March 1988, she again sought medical advice since she was now experiencing difficulty in swallowing. An oesophageal stricture was found and over a period of a year she had to undergo repeated dilatation. The cause of the stricture was unknown, though the possibility of caustic irritation of the oesophagus was mentioned.

During this period Roberts developed the suspicion that her oesophageal condition might be due to one of the drugs which she had been prescribed, though she had no medical evidence for this and did not know which drug to suspect. In April 1989 she consulted a lawyer who examined the possibility of bringing an action in negligence against the consultant Winbow, and in this connection he sought expert advice from a clinical pharmacologist. The latter's expert report was not received until June 20th 1992, but it concluded that the stricture was due to the use of carbamazepine. Legal proceedings against the consultant Winbow were therefore commenced, beginning in January 1995.

The defence pleaded that proceedings had been initiated too late, since the maximum delay allowed under the Limitation Act must be considered to run from the point in time at which she developed her suspicion of drug-induced injury and consulted a lawyer, i.e., 1988–1989. In the court of first instance, this defence was rejected on the grounds that her knowledge that the drug could have induced the injury dated only from the date of the expert report, i.e., June 20th 1992. Winbow appealed against this ruling.

The Court of Appeal essentially accepted the view of Winbow's counsel that by April 1989 Roberts' suspicion was sufficient to constitute actual knowledge, particularly because of her acute Stevens–Johnson reaction in 1988. The Court however exercised its discretion, as permitted under Section 33 of the Limitation Act, to allow the plaintiff to proceed with the action, primarily because of the serious consequences for the plaintiff of not so allowing; Winbow on the other hand would still have the opportunity to defend himself on the merits of the case.

Comment. All legal systems impose a period of limitation, so as to ensure that legal actions are brought within a reasonable period of the events to which they relate. This is intended to avoid the difficulties that inevitably arise in assessing events from the distant past, but also to promote legal certainty; there must be some assurance that, at a given moment, life can carry on and bygones can be considered bygones, even in a court of law.

A common problem is however to determine the date from which such a period of limitation can be considered to run. Some forms of injury are immediately evident; a patient who is paralyzed as a result of surgical error is aware of the accident as soon as he recovers from the anaesthetic. In the case of drugs, however, a considerable time may elapse between the postulated causal event and the realization of injury. There are various reasons for this. *Firstly*, a long latent period may in the case of some drugs elapse between the time when it is administered and the date of occurrence of the complication. The radiopharmaceutical thorium dioxide proved capable of inducing tumours in some patients forty years after they had been treated with it; oestrogens given in pregnancy can produce serious complications which manifest themselves only when the second or even the third generation come to maturity. *Secondly*, the fact that a particular drug may cause a particular type of complication may only become known to science or to the community generally after the drug has been marketed for years; aspirin had been sold for seventy years before it became clear that it could cause Reye's syndrome in children. *Thirdly*, even where the link between a drug and a particular complication is known to medical science, it may still not be known to the individual concerned; only when he or she is alerted to the known link will the patient realize that some adverse event from which he once suffered could have been due to a drug, and could give rise to a claim.

Statutes such as the United Kingdom's Limitation Act allow Courts a degree of discretion in allowing proceedings at a late date if there is some such reasonable explanation for the delay in instituting them. A more general discretion may be exercised (as it was in this case) if disallowing the proceedings would result in gross unfairness to one of the parties.

It can be particularly difficult to determine the date from which the period of limitation should run if the knowledge on which an action might be based has emerged only slowly and progressively. A rule – though one which it is not always easy to apply – was laid down in English law by Lord Justice Brooke in 1997: "A plaintiff has the requisite knowledge when she knows enough to make it reasonable for her to begin to investigate whether or not she has a case against the defendant"[1]. Both Brooke and other judges have also pointed out that the date at which a plaintiff has consulted a solicitor can be helpful in confirming that he or she has by this date attained the requisite state of knowledge. Such rulings seem to show that in English law the period of limitation will start running at a relatively early point, and that patients and their lawyers must tackle their cases efficiently and rapidly. In this case it took six years from the postulated "date of requisite knowledge" for the solicitors to obtain an expert report on Roberts' case and to institute proceedings; only thanks to the leniency of the Court of Appeals was she able to proceed with her case. Fortunately the Limitations Act (and analogous provisions in some other legal systems) provides considerable latitude for a Court to take account of the special circumstances which often unavoidably delay the initiation of drug litigation.

For a more detailed consideration of the situation as it is developing specifically in English law see S. Elliman, *Med. Litigation* **5**(3–4) (1999).

Device injury: generic versus specific evidence (Australia, NSW)

Denzin et al. vs. Nutrasweet Company et al. (1999) MLC 0087.

Nine Australian women who had been fitted with copper-containing intra-uterine contraceptive devices (Gravigard, Mini-Gravigard) and who developed pelvic inflammatory disease brought actions in

[1] [1997] 8 Med LR 125.

negligence against the manufacturer, alleging that the devices were responsible for their illness. For the plaintiffs it was argued that the polypropylene "tail" attached to the device was prone to fray as a result of strains to which it had been subject during manufacturing, and that this damage significantly increased the risk of ascending infection.

The Supreme Court of New South Wales considered both scientific data as to the process by which such a device might contribute to the induction of pelvic inflammation and epidemiological evidence from the period 1975–1994 as to the presence or absence of an increased risk of inflammation in users of such devices generally. The defence argued that the epidemiological literature did not point to any general causal link between these devices and the complication concerned.

The Court found that neither the epidemiological nor the scientific evidence were sufficient to establish a general causal link between the use of copper-containing intra-uterine devices and the occurrence of pelvic inflammatory disease. Nor did any of the clinical observations adduced by the plaintiffs prove a causal connection. The plaintiffs themselves had provided no case-specific evidence that in their own situation there had been a causal connection. The clinical literature showed that pelvic inflammatory disease did occur in some users of intra-uterine devices, but that it also occurred in the general population not using such devices. Since the law required plaintiffs to demonstrate that the negligence of the defendants was either "the cause" or a "probable" cause of their injury, their case must fail.

Comment. In cases involving alleged injury by medical products, it is normal for a Court to consider both "generic" evidence ("can the product cause this type of injury") and "specific" evidence ("did the product contribute to the injury in this actual case?"). The two types of evidence are complementary, though general evidence alone is only likely to be sufficient to prove a case if the nature of the injury is entirely characteristic for the product (e.g., phocomelia induced by thalidomide). In these cases, it could not be claimed that pelvic inflammatory disease was so characteristic of the use of these devices as to render individual causation probable; the clinical literature, though disputed, did not even point to a clear increase in the risk concerned when these devices were used.

Evidence of individual causation is always difficult to adduce, unless the time of occurrence of the event is highly characteristic, or there has been successful rechallenge and rechallenge.