Relations between Season of Birth and Subsequent Seasons

Periods	Calendar Months of Birth	No. of Months Exposed to:	
		Winter Conditions (Oct.-March)*	Summer Conditions Apr.-September)*
Neonatal	January-June	3	3
	July-December	3	3
	April-September	—	6
	October-March	6	—
1-5 months	January-June	6	24
	July-December	24	6
	April-September	15	15
	October-March	15	15
6-11 months	January-June	27	9
	July-December	9	27
	April-September	15	21
	October-March	21	15

*Northern Hemisphere only.

between 1 and 6 months than children who are born in other seasons (see table); and (b) because respiratory infections are twice as common in winter as in summer and cause twice as many deaths between 1 and 6 months as during the rest of infancy.²

The first study revealed a deficit of childhood leukaemias among the O.S.C.C. twins who were not x-rayed before birth which affected like-sex twins (60% deficit) more than opposite-sex twins (30%);³ also second deliveries (62%) more than first deliveries (34%).⁴

In the second (unpublished) study⁴ the O.S.C.C. cases were compared with children whose deaths were either unexpected and unexplained (cot deaths) or were ascribed to pulmonary infections. The relevant findings relate to deaths within six months of birth because this is the period most affected by the switch from passive to active immunity and also the period when the risk of an infection death is most strongly influenced by season of birth (see table). Among the cancer deaths in this age range there was a deficit of births in the second half of the year which affected leukaemias (54% deficit) and lymphomas (46%) far more than other cancers (3%). And among the other deaths there was a deficit of births during the first half of the year which affected the unexplained deaths (47%) more than the deaths which were obviously caused by infections (35%).

Finally, the unpublished O.S.C.C. data⁴ showed that there was a rapid replacement of myeloid by lymphatic leukaemias after the second month of life. For deaths within two months of birth the myeloid to lymphatic ratio was 3.50; for deaths between two and six months the ratio was 0.69; and for later deaths it was 0.41.

To sum up, it clearly requires more than epidemiological data to establish the existence of a group of haemopoietic neoplasms which are associated with such profound disturbances of the reticuloendothelial system as to be causes of unexpected and unexplained stillbirths and infant deaths. There are, however, indications that myeloid leukaemia has remained a rare cause of childhood deaths only because cases with embryonic origins are exceptionally difficult to recognize; also indications that it is only during the period when passive immunity is operative that there is any relaxation of these diagnostic difficulties.—I am, etc.,

ALICE STEWART

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² Registrar General's Statistical Review for England and Wales for 1970, Tables, pt. I Medical. London, H.M.S.O., 1972.

³ Stewart, A. M., *British Journal of Cancer*, 1973, 27, 465.

⁴ Oxford Survey, U.S. Public Health Service and the Medical Research Council. Unpublished data.

Septic Abortion and the Dalkon Shield

SIR,—The Dalkon Shield intrauterine device has now been on the market in the U.K. for approximately three years and for one year longer in the U.S.A. and up to the present time approximately 2½m. insertions have taken place.

Recently it has come to the attention of my parent company in the U.S.A. that there has been an apparent increase in the number of cases of septic abortions, many mid-trimester in timing, occurring in patients purportedly wearing the Dalkon Shield. Four fatalities have been reported but there is no evidence of a direct cause-and-effect relationship between the wearing of the Dalkon Shield and the occurrence of septicemia. I am certain that the apparent increase is due more to the increased number of physicians and women who prefer this method of contraception than to any inherent fault in the Dalkon Shield itself.

We are of course exploring every reasonable approach to determine whether any unique relationship exists between the Dalkon Shield and septic abortions and in this connexion I would be most grateful if any cases which occur in patients could be reported to me with as full details as possible. In the meantime I feel that the following precautionary steps should be followed in the management of patients:

(1) Every patient who misses a menstrual period should have a pregnancy test.

(2) As soon as a pregnancy is confirmed the device should be removed if it is possible to do so by traction with the string.

(3) If the device cannot be so readily removed serious consideration should be given to offering the patient a therapeutic abortion.

(4) If the pregnancy is allowed to continue, whether or not the device is removed, the patient should be followed very closely for early signs which will alert the physician to potential severe complications.

It is suggested that all patients in whom a Dalkon Shield is considered for contraceptive purposes, should be advised prior to insertion that a therapeutic abortion may be recommended in the event of an accidental pregnancy.—I am, etc.,

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Can I Have an Ambulance, Doctor?

SIR,—Dr. D. E. Ford (4 May, p. 278) suggests, on the basis of our paper (9 February, p. 226) that outpatient physiotherapy at Northwick Park Hospital is likely to be ineffective because of its infrequency. This raises several points.

First of all, this was not physiotherapy at Northwick Park Hospital, but was in fact physiotherapy at the Harrow Physical Treatment Centre. Because we had the opportunity to take over this unit for a short time before the opening of the physiotherapy department at Northwick Park Hospital, it seemed to us to be an excellent opportunity to carry out a number of surveys.

Secondly, of course, we were referring to the minority (12% of patients) who require ambulance transport. These tend to be the elderly (50% were over the age of 65).

A further point is that it has never been convincingly demonstrated that the presumed effectiveness of physiotherapy depends upon its frequency of application by the therapist. On the contrary, in an ongoing trial concerning the value of outpatients with strokes this appears to be not so. Well-instructed patients who do not attend the department seem to be doing at least as well as those who are attending five whole days per week.

Until Dr. Ford and his colleagues have demonstrated the comparative value of his basic 47-hour week (37 hours in the department and 10 travelling), despite the resultant social inconvenience, we would prefer to emphasize the teaching role of the physiotherapist at the present for this type of patient.—We are, etc.,

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Assessment of Surgical Treatment

SIR,—Your leading article "Do We Know What We Are Doing?" (13 April, p. 73) on the supposed continuing difference between physicians and surgeons was at least more restrained than the American article to which it referred.¹ Cast more in the style of a hospital pantomime than in the language of a scientific journal this asserted that there was a double standard, both in practice and in clinical journals, in regard to the assessment of medical as distinct from surgical treatment. But is the distinction really as clear-cut as that?

In medically developed countries well-balanced teams of physicians and surgeons are now the rule, at least where major specialist enterprises are being undertaken. I have recently pointed out that the physicians in such teams are often the enthusiasts who are pressing reluctant surgeons to operate.² Surgeons deserve sympathy rather than scolding, because their position is peculiarly difficult. They are exposed to pressure for action from both colleagues and patients; any surgical operation is still a dramatic experience for the individual who undergoes it, and patients naturally cherish high expectations of its result. In spite of these difficulties academic surgeons of standing frequently undertake controlled trials when the value of an

¹ Kneale, G. W., *British Journal of Preventive and Social Medicine*, 1971, 25, 152.

operation is in serious doubt. Such surgeons are prepared to make random allocation of matched groups to surgical or other treatment or to alternative surgical techniques. Moreover they often accept that the outcome is more reliably assessed by doctors who were not concerned with the initial treatment and who, if possible, remain "blind" as to what kind of surgery was done, if any.

To go further than this in scientific objectivity and to accede to Dr. Spodick's demand for sham operations in order to exclude placebo effects¹ would surely be unwise and unrealistic. This is not to deny such an effect of surgery nor to question the importance of Beecher's classic study³ which demonstrated how powerful this may be. But in the light of recent developments in ethical attitudes it is doubtful whether such studies could now be repeated, let alone recommended as a requirement before any new surgical procedure was regarded as effective. Would Dr. Spodick expose his patients with coronary artery disease to sham operations, with the small but undeniable risks of anaesthesia, of wound infection, and of other postoperative hazards? Many patients with serious conditions would accept such risks if there was even a small chance of benefit. But would they do so if they knew the odds were only 50-50 that they would be given even that chance?

I hesitate to prolong a controversy which is almost as dated as debating whether women are fit to vote. But having recently exhorted my fellow-surgeons to be more critical about their work, I may perhaps risk reminding my medical colleagues of a statement made by one of their own kind last year.⁴ Pointing out that every clinician spends much time in activities which give little if any benefit, that most patients who have maladies susceptible to dramatic (medical) treatment have already been given it by their family doctor, and that many patients in medical wards are there largely for nursing and general care, the author concluded that "only surgeons spend much time actually giving benefit."—I am, etc.,

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¹ Spodick, D. M., *American Heart Journal*, 1973, 85, 579.

² Jennett, B., *Journal of the Royal College of Surgeons of Edinburgh*, 1974, 19, 1.

³ Beecher, H. K., *Journal of the American Medical Association*, 1961, 176, 1102.

⁴ Todd, J. W., *Lancet*, 1973, 1, 1106.

Late Onset of C.N.S. Leukaemia

SIR,—There is no doubt that the incidence of leukaemia of the central nervous system in acute lymphoblastic leukaemia can be greatly reduced by prophylactic radiotherapy and intrathecal chemotherapy, and such prophylaxis is now regularly included in the management of children with this disease. There must still be a number of children, however, diagnosed perhaps 2-3 years ago or more and still in their first remission, who have not received the benefit of early craniospinal prophylaxis. We write to draw attention to the risk of late onset of C.N.S. leukaemia and to suggest that there is still a place for prophylaxis in such cases, even after three years from diagnosis.

The incidence of C.N.S. involvement in children with acute lymphoblastic leukaemia seen at this hospital from 1958 to 1970 was approximately constant for the first 2½ years after diagnosis but then fell sharply.¹ A similar fall in incidence has also been observed by Evans *et al.*² For this reason, when the benefits of C.N.S. prophylaxis became apparent it was not felt justifiable to advise "late prophylaxis" for children who had already remained in complete remission for longer than 2½ years.

However, of 42 children with acute lymphoblastic leukaemia diagnosed during 1970-1—the last two years before the introduction of routine C.N.S. prophylaxis in this hospital—30 have so far developed C.N.S. leukaemia at times ranging up to 188 weeks after diagnosis. In contrast to our previous experience there has been no decline in incidence after 130 weeks; four children have had a C.N.S. relapse after this time, including two who had stopped systemic chemotherapy. This accords with experience in the St. Jude's Total IV programme, in which C.N.S. relapse occurred in five of eight patients who had not received prophylaxis and in whom chemotherapy was subsequently discontinued.³ This prolongation of the incidence curve of C.N.S. leukaemia may be an effect of improvements in the control of bone marrow disease by chemotherapy. Whether or not that is the case, it is clear that any child remaining in complete remission, even 3-4 years after diagnosis, who has not already had C.N.S. prophylaxis should be given it as soon as possible.—We are, etc.,

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¹ West, R. J., *et al.*, *British Medical Journal*, 1972, 3, 311.

² Evans, A. E., Gilbert, E. S., and Zandstra, R., *Cancer*, 1970, 26, 404.

³ Simone, J., *Seminars in Hematology*, 1974, 11, 25.

Gentamicin-resistant *Escherichia coli*

SIR,—As gentamicin is widely relied upon in the treatment of serious Gram-negative infections we report two cases of *Escherichia coli* meningitis in which a strain of *E. coli* initially sensitive to gentamicin, developed resistance during therapy.

An 8-week-old girl developed *E. coli* septicaemia and meningitis. The organism isolated from blood and cerebrospinal fluid was resistant to ampicillin, chloramphenicol, co-trimoxazole, and kanamycin but sensitive to cephaloridine, gentamicin, and polymyxin B. The minimum inhibitory concentration of gentamicin for the organism was 1.2 µg/ml. She was treated with intravenous and intraventricular gentamicin at dosage giving pre-injection C.S.F. gentamicin levels of 10 µg/ml. After 10 days of gentamicin therapy two colonial variants were present in cultures from the C.S.F. The larger colonies were similar to those of the original culture but were very scanty and still sensitive to gentamicin. The smaller colonies were numerous and gentamicin-resistant but sensitive to cephaloridine and polymyxin B. Both large and small colonial forms were of serotype O20K. Treatment was changed to intraventricular cephaloridine and polymyxin B with intravenous cephalothin and 20 days after the onset of illness the C.S.F. became sterile.

A 2-week-old boy developed *E. coli* septicaemia and meningitis. The organism was resistant to ampicillin but sensitive to gentamicin, cephaloridine, and chloramphenicol. After four days' treatment with intramuscular cephaloridine 25 mg/kg

day and gentamicin 1.5 mg/kg/day he was transferred and treated with intravenous gentamicin 8 mg/kg/day and intraventricular gentamicin 2 mg/day, giving pre-injection C.S.F. gentamicin levels of 10 µg/ml. Four days later a small colonial variant resistant to gentamicin was present in C.S.F. cultures, while the original larger forms (still sensitive to gentamicin) were reduced in number. Despite treatment with intraventricular cephaloridine and intravenous chloramphenicol and cephalothin the patient died.

Thus two organisms, initially sensitive to gentamicin, developed resistance to the antibiotic during therapy. This phenomenon among *E. coli* has not hitherto been a clinical problem at this hospital and we have not heard of it elsewhere. Acquired gentamicin resistance is well documented for *Pseudomonas aeruginosa*, particularly in patients who have been given oral gentamicin.¹ Both infants were treated intensively with gentamicin alone for a time and the second infant was initially treated with low-dose gentamicin, which might have helped the emergence of a resistant strain. Clearly indiscriminate use of gentamicin is undesirable, and if it is to be used it should be given in amounts which give adequate levels in the infected tissue.—We are, etc.,

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¹ Greene, W. H., *et al.*, *Annals of Internal Medicine*, 1973, 79, 684.

Renal Damage Caused by Gentamicin

SIR,—It came to our attention during a study of the urinary excretion of cytoplasmic enzymes in patients who had received renal homografts that there was an increased excretion of the marker enzymes N-acetyl-β-D-glucosaminidase and β-galactosidase not only during rejection episodes¹ but also during treatment with gentamicin. Electron microscopy of proximal tubular epithelium of renal homografts revealed lipid droplets and dense laminated bodies in the cytoplasm. Similar laminae'd bodies have been found in the urine deposit of patients with other diseases treated with gentamicin.

Rats given daily intramuscular injections of gentamicin at dosages varying from 5 mg/kg/day (corresponding to human therapeutic dosage) to 100 mg/kg/day showed elevation of urinary enzymes similar to that found in man. Proximal tubular epithelial cell damage varied from cytoplasmic inclusion of lipid and laminated bodies at low dosage to tubular necrosis at high dosage. These changes occurred 5-21 days after commencing therapy.

It is not widely appreciated that gentamicin in therapeutic dosage may produce these biochemical and morphological changes in renal tubular epithelium, and this should be considered before higher dosage is given.—We are, etc.,

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¹ Wellwood, J. M., *et al.*, *British Medical Journal*, 1973, 2, 261.