Correspondence

Benefits and limitations of pathology databases to cancer registries

In a recent article, Brewster et al presented data on estimated completeness of case ascertainment for 2335 cases of malignancy. Results are given for all subjects and for each of 36 anatomical sites. In each case, the observed percentage completeness is given, together with what purports to be a 95% confidence interval. A glance at these intervals is sufficient to suggest they are so narrow as to constitute wishful thinking.

On closer examination, it is evident that the authors intended to use the simplest method for calculating a confidence interval for a proportion, \( p = \frac{\text{no.}}{\text{denom.}} \), viz. \( \pm z \cdot \sqrt{\frac{p \cdot (1 - p)}{\text{denom.}}} \) where \( z = 1.96 \) for a 95% interval. In fact they have failed to take into account that, in the denominator inside the square root, with the result that the intervals are narrower than intended, by a factor \( n \), which can be large. Moreover, this method is a very poor one, in several respects: it gives an inappropriate zero width interval when \( p = 0 \) or 1 (as in the article); when the numerator \( r \) is very small, the calculated lower limit can be an absurd value less than 0, with corresponding violation of the boundary at \( f \) when \( n - r \) is very small; and the average coverage of what is claimed to be a 95% interval is only around 88%.

The accompanying table shows confidence intervals calculated by the currently accepted standard method.1 These intervals may be obtained from Geigy scientific tables for small to moderate \( n \); they are not as yet, particularly accessible to researchers, but can be accessed by statistical software including MINITAB and SAS indirectly via the inverse of the \( z \) integral. An alternative, accepted method is that of central form and the readily programmed is \( (2n^2 + x^2 \pm 2z)^2 / (2(n + x)^2)\). Furthermore, it is difficult to appraise whether the heterogeneity of observed completeness rates is any greater than would be expected on the basis of chance variation; it is noteworthy that the lowest rates tend to have small denominators. A hypothesis test would be helpful here—it would necessitate a judicious, anatomically or pathologically meaningful combination of groups into broad categories each containing 100 cases or more.

ROBERT G NEWCOMBE
Department of Medical Computing and Statistics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4EE


Dr Brewster comments:
We are grateful to Robert Newcombe for drawing our attention to the error in our calculation of confidence intervals which was replicated by the use of a spreadsheet and which, in retrospect, we should have identified ourselves. We are also persuaded by his arguments for using other methods of calculating confidence intervals in this situation. Nevertheless, the recalculation of confidence intervals, by whatever method, does not alter the substance or conclusions of our paper.

Histological patchiness and sparing of the rectum in ulcerative colitis: refuting the dogma

We were delighted to see that Levine et al have confirmed the findings of our prospective study reported in 1995. Thus, refuted is the conventional wisdom that ulcerative colitis is always diffuse and most severe in the rectum, and that it tapers in severity proximally. Our findings were welcomed by many of our colleagues who knew this from their clinical experience but were often dismayed

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Estimated completeness of case ascertainment by the Scottish Cancer Registration Scheme, based on an independent comparison with pathology data, 1992

<table>
<thead>
<tr>
<th>ICD-9 code</th>
<th>Site</th>
<th>No of cases (%)</th>
<th>No of completely missed cases (%)</th>
<th>Estimated % completeness (x/100)</th>
<th>95% Confidence intervals (Lower, Upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>140-149</td>
<td>Lip, oral cavity, and pharynx</td>
<td>39</td>
<td>1</td>
<td>97.5</td>
<td>86.8, 99.9</td>
</tr>
<tr>
<td>150</td>
<td>Oesophagus</td>
<td>58</td>
<td>0</td>
<td>100.0</td>
<td>93.8, 100.0</td>
</tr>
<tr>
<td>151</td>
<td>Stomach</td>
<td>89</td>
<td>0</td>
<td>98.0</td>
<td>94.0, 100.0</td>
</tr>
<tr>
<td>153, 154</td>
<td>Colon, rectum</td>
<td>192</td>
<td>20</td>
<td>90.6</td>
<td>85.8, 94.1</td>
</tr>
<tr>
<td>155, 156</td>
<td>Liver, gall bladder</td>
<td>30</td>
<td>0</td>
<td>100.0</td>
<td>88.4, 100.0</td>
</tr>
<tr>
<td>157</td>
<td>Pancreas</td>
<td>57</td>
<td>1</td>
<td>98.3</td>
<td>90.8, 100.0</td>
</tr>
<tr>
<td>152, 158, 159</td>
<td>Small intestine, retroperitoneum, other digestive sites</td>
<td>14</td>
<td>0</td>
<td>100.0</td>
<td>76.8, 100.0</td>
</tr>
<tr>
<td>160</td>
<td>Nasal cavities, middle ear, sinuses</td>
<td>1</td>
<td>0</td>
<td>100.0</td>
<td>69.2, 100.0</td>
</tr>
<tr>
<td>161</td>
<td>Larynx</td>
<td>21</td>
<td>1</td>
<td>95.5</td>
<td>77.2, 99.9</td>
</tr>
<tr>
<td>162</td>
<td>Trachea, bronchus, lung</td>
<td>360</td>
<td>2</td>
<td>99.4</td>
<td>98.0, 99.9</td>
</tr>
<tr>
<td>163</td>
<td>Pleura</td>
<td>10</td>
<td>0</td>
<td>100.0</td>
<td>69.2, 100.0</td>
</tr>
<tr>
<td>170, 171</td>
<td>Bone, connective tissue</td>
<td>9</td>
<td>0</td>
<td>100.0</td>
<td>66.4, 100.0</td>
</tr>
<tr>
<td>172</td>
<td>Skin (melanoma)</td>
<td>41</td>
<td>0</td>
<td>100.0</td>
<td>91.4, 100.0</td>
</tr>
<tr>
<td>173 (M-807)</td>
<td>Skin (squamous cell)</td>
<td>103</td>
<td>12</td>
<td>89.6</td>
<td>82.5, 94.5</td>
</tr>
<tr>
<td>173 (M-809)</td>
<td>Skin (basal cell)</td>
<td>330</td>
<td>46</td>
<td>87.8</td>
<td>84.0, 90.9</td>
</tr>
<tr>
<td>173 (M-8832)</td>
<td>Skin (dermatofibrosarcoma)</td>
<td>1</td>
<td>1</td>
<td>50.0</td>
<td>1.3, 98.7</td>
</tr>
<tr>
<td>174, 175</td>
<td>Breast (female/male)</td>
<td>247</td>
<td>13</td>
<td>95.0</td>
<td>91.6, 97.3</td>
</tr>
<tr>
<td>179</td>
<td>Uterus</td>
<td>2</td>
<td>1</td>
<td>66.7</td>
<td>9.4, 99.2</td>
</tr>
<tr>
<td>180</td>
<td>Cervix uteri</td>
<td>33</td>
<td>6</td>
<td>84.6</td>
<td>69.5, 94.1</td>
</tr>
<tr>
<td>182</td>
<td>Corpus uteri</td>
<td>24</td>
<td>2</td>
<td>92.3</td>
<td>74.9, 99.1</td>
</tr>
<tr>
<td>183</td>
<td>Ovary</td>
<td>46</td>
<td>1</td>
<td>97.9</td>
<td>88.7, 99.9</td>
</tr>
<tr>
<td>184</td>
<td>Other, unspecified genital organs</td>
<td>11</td>
<td>0</td>
<td>100.0</td>
<td>71.5, 100.0</td>
</tr>
<tr>
<td>185</td>
<td>Prostate</td>
<td>86</td>
<td>6</td>
<td>93.5</td>
<td>86.3, 97.6</td>
</tr>
<tr>
<td>186</td>
<td>Testis</td>
<td>11</td>
<td>0</td>
<td>100.0</td>
<td>71.5, 100.0</td>
</tr>
<tr>
<td>187</td>
<td>Penis</td>
<td>2</td>
<td>0</td>
<td>100.0</td>
<td>15.8, 99.9</td>
</tr>
<tr>
<td>188</td>
<td>Bladder</td>
<td>115</td>
<td>11</td>
<td>98.3</td>
<td>94.0, 99.8</td>
</tr>
<tr>
<td>189</td>
<td>Kidney</td>
<td>29</td>
<td>0</td>
<td>100.0</td>
<td>88.1, 100.0</td>
</tr>
<tr>
<td>190</td>
<td>Eye</td>
<td>2</td>
<td>0</td>
<td>100.0</td>
<td>15.8, 100.0</td>
</tr>
<tr>
<td>191, 192</td>
<td>Brain, central nervous system</td>
<td>30</td>
<td>0</td>
<td>100.0</td>
<td>88.4, 100.0</td>
</tr>
<tr>
<td>193</td>
<td>Thyroid gland</td>
<td>6</td>
<td>1</td>
<td>85.7</td>
<td>42.1, 99.6</td>
</tr>
<tr>
<td>194</td>
<td>Endocrine glands</td>
<td>1</td>
<td>0</td>
<td>100.0</td>
<td>2.5, 100.0</td>
</tr>
<tr>
<td>196-199</td>
<td>Secondary sites</td>
<td>83</td>
<td>0</td>
<td>100.0</td>
<td>95.7, 100.0</td>
</tr>
<tr>
<td>200, 201</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>53</td>
<td>8</td>
<td>86.9</td>
<td>75.8, 94.2</td>
</tr>
<tr>
<td>201</td>
<td>Hodgkin’s disease</td>
<td>8</td>
<td>1</td>
<td>88.9</td>
<td>51.8, 98.7</td>
</tr>
<tr>
<td>203</td>
<td>Multiple myeloma</td>
<td>16</td>
<td>2</td>
<td>88.9</td>
<td>65.3, 98.6</td>
</tr>
<tr>
<td>204-208</td>
<td>Leukaemia</td>
<td>42</td>
<td>4</td>
<td>91.3</td>
<td>79.2, 97.6</td>
</tr>
<tr>
<td>140-208</td>
<td>All malignant sites</td>
<td>2202</td>
<td>133</td>
<td>94.3</td>
<td>93.3, 95.2</td>
</tr>
</tbody>
</table>
when: pathologists used this finding of patchiness as a strong mandate for the diagnosis of Crohn's disease; or surgeons became reluctant to do proctocolectomies in ulcerative colitis cases that were indicated clinically, because they were fearful that patchiness of involvement meant Crohn's disease. As the arena of available modulatory drugs expands, more specific to one disease than the other, it is critical to recognise this important diagnostic feature of ulcerative colitis.

Our findings were in patients with documented ulcerative colitis whereas Levine et al found predominately normal or borderline biopsies among patients with ulcerative proctitis (10 of 11 cases) rather than ulcerative colitis. Although we have shown that over time rectal biopsies from patients with ulcerative proctitis are indistinguishable from biopsies from patients with ulcerative colitis,1 it remains a possibility that these diseases may have different pathophysiology. Nonetheless, it is important to realise that in ulcerative proctitis, rectal biopsies may normalise over time. The presence of frankly normal rectal histology in patients with longstanding diagnoses of ulcerative colitis or proctitis often raises the issue of the accuracy of the initial diagnoses. We support Levine et al in their contention that these diseases are dynamic in their expression patterns, and this fact should now be accepted into the new diagnostic dogma of ulcerative colitis.

Why has the conventional wisdom of absolute rectal involvement, and absolute disease continuity in ulcerative colitis persisted so long? We believe that it points to the selectivity of human observation. We only look for what we believe we should find. Patchy rectosigmoid involvement in ulcerative colitis is one example, and even more compelling one is how Helicobacter pylori could be missed in gastric biopsy tissue sections for so long, by so many!

CHARLES N BERNSTEIN
Section of Gastroenterology,
University of Manitoba,
Winnipeg, Manitoba, Canada

FERGUS SHANAHAN
Department of Medicine,
University of Cork,
Cork, Ireland

WILFRED M WEINSTEIN
Division of Digestive Diseases,
UCLA School of Medicine,
Los Angeles, California, USA

Proliferation indexes—a comparison between cutaneous basal and squamous cell carcinomas

We read with interest the article by Al-Sader et al that compared cell proliferation indexes in cutaneous basal cell carcinomas (BCC) and squamous cell carcinomas (SCC).1 We have evaluated silver-stained nuclear organiser region (Ag-NOR) and PCNA labelling index, and mitotic index in the corresponding spontaneous canine cutaneous tumours obtaining comparable results.2 However, more recently, in an attempt to explain the paradoxical clinical behaviour of canine cutaneous BCC, we obtained interesting results studying the combined behaviour of mitotic index, apoptotic index, and mitotic phase distribution in the aforementioned tumours.3 In fact, in accordance with Brown and Gatter for human BCC, our results strongly suggest that a prolonged “M phase” of the cell cycle plays an important role in maintaining a slow rate of growth in canine BCC. The strong similarity between canine and human BCC and SCC support the opinion that spontaneous animal tumours could represent useful models for human disease.


CHARLES N BERNSTEIN
Section of Gastroenterology,
University of Manitoba,
Winnipeg, Manitoba, Canada

FERGUS SHANAHAN
Department of Medicine,
University of Cork,
Cork, Ireland

WILFRED M WEINSTEIN
Division of Digestive Diseases,
UCLA School of Medicine,
Los Angeles, California, USA

P MAIOLINO
G DE VICO
Dipartimento di Patologia di Profilassi e di Ispedizione degli Alimenti
Sezione di Anatomia Patologica
Facoltà di Medicina Veterinaria
Università degli Studi di Napoli "Federico II"
Via F Delpino, 1–80137, Napoli
Italy

Brain tissue banks in psychiatric and neurological research

We welcomed the article by Cairns and Lanto on brain tissue banks.1 The importance of such facilities in psychiatric and neurological research has not been adequately appreciated by the wider clinical community, perhaps because collection and storage of postmortem tissue for research is not as an emotive issue as requesting organs for donation. However, without such tissue banks little would be known about many debilitating conditions.

The South West Brain Bank in Bristol was established over 10 years ago to collect brain tissue from people suffering from dementia. It is from this experience that we write to emphasise certain points that need to be made not only to potential donors and their relatives but also to the physicians requesting the donation, and those using the tissue for research.

Making the decision to donate tissue for research can be a very difficult one for most people. This can be made even more difficult if it is left to the time when loved ones are close to death or have died. It is far preferable that all arrangements are made in advance of the event, and it is helpful if potential donors and their families can be given information about the procedures involved in a donation (perhaps in the form of a leaflet). The details can be assimilated and discussed within the family and with the coordinator of the facility at a time before bereavement does not cloud the issue. We have found the role of the brain bank coordinator to be a crucial one at this stage. We have one person acting as the coordinator, an MLSO trained in neuropathology. She deals with the donation from the initial arrangements through to processing of the tissue for histological assessment.

Before a histological diagnosis is made, the neuropathologist is provided with as complete a clinical history as possible. This is obtained, using a standardised protocol, from all available hospital and general practitioner notes.

The continuing acquisition of tissue for research purposes relies heavily on an understanding of the importance of such donations by the medical practitioners who must make the request and, perhaps more importantly, by their patients and relatives. The responsibility for giving potential donors and their families the necessary information and support regarding a donation lies with the brain banks who must approach this with compassion and sensitivity.

G K WILCOCK
S MATTHEWS
S H MACGOWAN
Department of Care of the Elderly
Frenchay Hospital, Bristol BS16 1LE

Correspondence, Book reviews, Notices, Corrections

no explanatory text would have difficulty in understanding it. Equally, I found a completely new system of numbering diseases based on the chapter number unnecessarily confusing. Metabolic disease has its own jargon and abbreviations, more are not required.

It is important that metabolic disease is considered as part of differential diagnosis but I doubt whether its investigation could be effectively done using this book alone. Surely the laboratory has a role to play. The tests are usually performed in specialist centres that not only do the analysis but offer interpretation and can put the general clinician in touch with the appropriate expert.

This book is not for reading and it fails in my opinion to reach its target audience. Perhaps it would have been better to drop the first word of the title. Nevertheless, it contains a lot of useful information much of which is not easily found in other textbooks or sources. It could sit comfortably on a shelf next to The Metabolic and Molecular Bases of Inherited Disease in a library or in the specialist paediatricians office, and even the general laboratory.

G M ADDISON


You don't need to get as far as page 1 to realise that the sixth edition of Greenfield is the result of a major overhaul, and is essentially a new book. Gone is the short fat, unwieldy volume that very quickly got separated from its covers; the book is now in two manageable volumes in larger format, each around 1000 pages long. The silver print on the outside announces completely new chapters: "schizophrenia", "prion diseases", "movement disorders", and, most notably, "tumours" (previously excluded because they were dealt with in the companion volume by Russell and Rubinstein, from the same publishers). Inside, the list of contributors is impressive: well over half the 64 names are those of overseas authors, many of them leading names in their field, many of them clinicians. About a third of the chapters are completely new; all have been extensively rewritten.

So how can one do justice to such a book in 500 words? In brief: it is brilliant. No longer merely an anthology of macroscopic and microscopic morbid anatomy, the book aims to set classic descriptive neuropathology within the framework of molecular and cellular events. As a result, this edition has a much wider appeal than earlier ones. Neurosurgeons and neurologists will find it an invaluable reference work, while for neuroradiologists—whose imaging techniques have made them into neuropathologists, whether they like it or not—it should be required reading. I found the most successful chapters to be those that integrated normal anatomy, physiology, and cellular pathology with clinical information and neuropathology. Special mention must go to the masterly discussion of modern concepts of rising intracranial pressure, brain swelling and oedema in the chapter by Miller and Ironside; the timely update on the pathophysiology of traumatic brain injury by Graham and Gennarelli; the chapter on hypoxia, which includes an excellent account of events in hypoglycaemia, by Auer and Benveniste; and the clear and succinct discussion of malformations by Harding and Copp.

However, such selection is invidious. Almost all the contributions are of exceptionally high quality, and the information is as up to date as is possible in a large textbook such as this. What reservations do I have? A few, centring on the wisdom of including tumours. There are already a number of excellent texts on the subject, and the long chapter by Lantos and colleagues falls short of being useful as a reference work for surgical neuropathology. However, where the authors are not dealing with macroscopic and microscopic pathology of the tumours, as in the sections on molecular biology and cytogenetics, and in their long discussions of oligodendrogliomas and meningiomas, they give us much valuable information unobtainable elsewhere.

In summary, I really cannot fault this new edition. It has regained its place as the leading textbook of neuropathology, and should be in the libraries of the histopathology and neuroscience departments of every teaching hospital. It is unfortunate that the huge pricetag will prevent it from being part of many personal collections.

J F GEDDES

Correspondence, Book reviews, Correction


Square root symbols were inadvertantly omitted from three places in this letter. The second paragraph should have read:

On closer examination, it is evident that the authors intended to use the simplest method for calculating a confidence interval for a proportion, \( p = r/n \), viz.

\[
 p \pm z \sqrt{(p (1-p)/n)} \quad \text{where} \quad z = 1.96 \quad \text{for a 95\% interval. In fact they have failed to take the n appearing in the denominator inside the square root, with the result that the intervals are narrower than intended, by a factor } \sqrt{n}, \text{ which can be large.}
\]

The equation in the fourth paragraph should have read:

\[
(2\sqrt{p} + z + z^\prime \sqrt{(z^\prime + 4np (1-p))/32n})
\]

These errors are regretted.