

## Article

# Upholding Protocol — The Logic of Diagnosis — Tribute to E. M. Nicholls (1927–2011)

Alan E. Stark<sup>1</sup>  and Paulo A. Otto<sup>2</sup>

<sup>1</sup>School of Mathematics and Statistics, The University of Sydney, Sydney, New South Wales, Australia and <sup>2</sup>Department of Genetics, University of Sao Paulo, Sao Paulo, Brazil

## Abstract

Max Nicholls had an almost unique experience as a medical practitioner, researcher and teacher of medical genetics. An earlier paper described his contribution to the etiology of neurofibromatosis. This was followed by Nicholls' own experience as lecturer in the Faculty of Medicine, University of New South Wales, Australia. This note draws attention to his research in immunology. For example, he was instrumental in the study of the buffy coat leuko-agglutination (BCLA) test, a sensitive assay for cell-mediated immunity that he introduced to detect conditions (including cancer) in preclinical stages.

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In 2016 we (Stark & Otto, 2016) published in this journal a brief account of the important role played by Edward Maxwell ('Max') Nicholls (1927–2011) in the development of the two-hit theory of cancer development, calling the attention to the in-depth analysis of scientific priority allocation by Kern (2002), who showed that his (Nicholls's) ideas (N3, N4, N7) preceded those of Knudson (1971) by at least two years, despite the fact that only the latter was fully credited with the two-hit ideas. In order to keep the focus on the two-hit model of tumor formation, we left out his papers published after 1974, just commenting that Max's interests had shifted to other subjects, mainly to immunology issues.

The present note, a complement to our 2016 paper, aims to present a complete list of Nicholls' published papers, briefly commenting on his activities and importance on the subjects he dealt with after the two-hit hypothesis papers. All his publications took place when he was working at the Faculty of Medicine of the University of New South Wales (UNSW) in Sydney from 1964 to 1986 and at the Biomedical Engineering and Safety Science Departments of the Faculty of Engineering of UNSW from 1986 onwards. An interesting, candid, personal account of his experiences with genetics at UNSW was published by Stark (2020), who also pointed out that Dr Nicholls was a prominent figure in the formation of the Human Genetics Society of Australasia.

Although he concentrated his efforts on the area of immunology, a browsing of his list of publications makes absolutely clear that Nicholls never abandoned his attraction and interest for the study of the biology of tumor development.

For example, he was instrumental in the study of the buffy coat leuko-agglutination (BCLA) test, a sensitive assay for cell-mediated immunity he introduced to detect conditions (including cancer) in preclinical stages (N15, N23, N24, N25, N29, N31). No due credit was given him relative to this accomplishment, despite the fact that (1) he published his results and ideas in well-credited scientific periodicals; and that (2) direct descendants of the test are still essential and important tools in immunology and cancer research: for instance, it has been suggested recently that the analysis of molecular markers from circulating immune cells present in the buffy coat can be used to help the early diagnosis and treatment of different types of malignancies (Donzelli et al., 2016; Velez et al., 2021).

He also published short articles and reviews on nephroblastoma, the most common kidney malignant tumor affecting children (N11, N12, N13), histocompatibility testing (N16), pigmentation genetics (N17), and human gene mapping (N18), and authored or coauthored papers on several important subjects of practical and applied medicine (N22, N33, N34, N35, N36).

All other published papers deal with hypotheses on tumor immunity, autoimmune diseases and the evolution of the immune system (N19, N20, N21, N30) or with the immunology of pregnancy and embryonic development (N26, N27, N28, N32).

Most of Nicholls' ideas, discoveries and hypotheses were important at least at the time of their publication. While his seminal contributions on the theme of the two-hit cancer hypothesis might be already tacitly accepted (Kern, 2002; Stark & Otto, 2016), the ones developed after the two-hit hypothesis (despite revealing the author's pristine and immaculate qualities as an excellent and earnest scientist), submerged amid the incredibly vast plethora of exceptionally good papers dealing with practical and theoretical applications of immunology and cancer research. Unfortunately,

**Corresponding author:** Alan E. Stark; Email: [alans@exemail.com.au](mailto:alans@exemail.com.au)

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scientific papers have on average a very short half-life, irrespective of their scientific value, because science works exactly like everything else in this physical world, that is, on a trial and error basis, with a never-ending adjustment and/or accommodation motion, what straightforwardly justifies the phrase “Today’s science is tomorrow’s error”, a plain translation from ‘Die Wissenschaft von heute ist der Irrtum von morgen’, as stated by the famous German biologist Jakob von Uexküll in 1900 (Aschill, 2017).

We think that this note might be justified by pointing out how the scientific milieu in general and universities in particular fail at times to adequately recognize the exceptional talents of their more-than-prepared minds.

### Edward Maxwell (Max) Nicholls Publications

- N1 Cooper, D. W., Lewis, H. B. M., & Nicholls E. M. (1965a). Haptoglobin Johnson in Australian aborigines. *Nature*, 5011, 694.
- N2 Nicholls, E. M., Lewis, H. B., Cooper, D. W., & Bennett, J. H. (1965b). Blood group and serum protein differences in some central Australian aborigines. *American Journal of Human Genetics*, 17, 293–307.
- N3 Nicholls, E. M. (1968). Genetic susceptibility and somatic mutation in the production of freckles, birthmarks and moles. *Lancet*, 1, 71–73.
- N4 Nicholls, E. M. (1969a). Somatic variation and multiple neurofibromatosis. *Human Heredity*, 19, 473–479.
- N5 Nicholls, E. M. (1969b). The genetics of red hair. *Human Heredity*, 19, 36–42.
- N6 Nicholls, E. M. (1969c). Dopa and the red, brown and black pigments of hair and feathers. *Journal of Investigative Dermatology*, 53, 302–309.
- N7 Nicholls, E. M. (1970). Phacomatoses, the inheritance of cancer, and somatic mutation. *Clinical Genetics*, 1, 245–257.
- N8 Nicholls, E. M., & Stark, A. E. (1971a). Bayes’ theorem. *Medical Journal of Australia*, 2, 1335–1339.
- N9 Nicholls, E. M., & Rienits, K. G. (1971b). Tryptophan derivatives and pigment in hair of some Australian marsupials. *International Journal of Biochemistry*, 2, 593–603.
- N10 Nicholls, E. M. (1973a). Development and elimination of pigmented moles, and the anatomical distribution of primary malignant melanoma. *Cancer*, 32, 191–195.
- N11 Nicholls, E. M. (1973b). Nephroblastoma and genetic analysis. *Medical Journal of Australia*, 1, 457.
- N12 Nicholls, E. M. (1973c). Nephroblastoma. *Medical Journal of Australia*, 2, 660.
- N13 Nicholls, E. M. (1973d). Nephroblastoma. *Medical Journal of Australia*, 2, 1074.
- N14 Nicholls, E. M. (1973e). Pigment spotting in man and number of genes determining skin and eye color. *Human Heredity*, 23, 1–12.
- N15 Nicholls, E. M. (1974a). Aggregation of buffy-coat leucocytes. A simple, sensitive assay for cell-mediated immunity. *Clinical and Experimental Immunology*, 17, 673–680.
- N16 Nicholls, E. M. (1974b). Histocompatibility testing 1972. *Medical Journal of Australia*, 2, 308.
- N17 Nicholls, E. M. (1974c). Red hair, white skin, blue eyes — genetics of human pigmentation. *Annals of Human Biology*, 1, 111.
- N18 Nicholls, E. M. (1977a). Human gene mapping. *Medical Journal of Australia*, 2, 759.
- N19 Nicholls, E. M., Lazer, C. E., & Mitchell, N. R. (1977b). Tumor immunity — What should be monitored and why. *Medikon*, 7, 5–12.
- N20 Mitchell, N. R., & Nicholls, E. M. (1978). HLA and the genesis of autoimmune diseases. *Medical Hypotheses*, 4, 149–155.
- N21 Nicholls, E. M. (1979). The evolution of an immune system. *Medical Hypotheses*, 5, 225–235.
- N22 Nicholls, E. M. (1981). Cephalothin interferes in automated assays of plasma creatinine. *Clinical Chemistry*, 27, 1953–1954.

- N23 Lazer, C. E., & Nicholls, E. M. (1982a). Buffy coat leukoagglutination. 1. A simple assay for both cell-mediated immunity and serum leukoagglutination. *IRCS Medical Science Biochemistry*, 10, 772–773.
- N24 Lazer, C. E., & Nicholls, E. M. (1982b). Buffy coat leukoagglutination. 2. The leukocyte clumping phenomenon. *IRCS Medical Science Biochemistry*, 10, 774–775.
- N25 Lazer, C. E., & Nicholls, E. M. (1982c). Buffy coat leukoagglutination. 3. A simple monitor of the progress of cancer. *IRCS Medical Science Biochemistry*, 10, 776–777.
- N26 Griziotis, G., Markovic, B., & Nicholls, E. M. (1982d). Maternal lymphocytes in the embryo and a role for the placenta in preventing embryonic rejection. *IRCS Medical Science Biochemistry*, 10, 778–779.
- N27 Markovic, B., Griziotis, G., & Nicholls, E. M. (1983a). Phagocytosis of maternal lymphocytes by the foetal trophoblast and the immunology of pregnancy. *Medical Hypotheses*, 10, 337–345.
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- N29 Lazer, C. E., & Nicholls, E. M. (1983c). A blocking antibody in cancer easily assayed and of practical significance. *Medical and Pediatric Oncology*, 11, 199.
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- N31 Lazer, C. E., & Nicholls, E. M. (1986). The buffy coat leukoagglutination (BCLA) test. *Journal of Immunological Methods*, 92, 183–187.
- N32 Marcovic, B., & Nicholls, E. M. (1988a). Maternal effects — What is the role of the mother’s immune system in development. *Australian Paediatrics Journal*, 24, 87.
- N33 Nicolas, T., Nicholls, E. M., Robertson, R. D., Bonifacio, M., Sinosich, M., Field, B., & Saunders, D. M. (1988). The development of action lines in an Australian maternal serum alphafetoprotein screening service for neural tube defects. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 28, 12–16.
- N34 Sosula, L., Nicholls, E. M., & Skeen M. (1988c). Ultrastructure of *Campylobacter jejuni* in gamma-irradiated mouse jejunum. *American Journal of Pathology*, 131, 125–131.
- N35 Markovic, B., Kwan, Y. L., Nicholls, E. M., Walsh, C., & Crouch, R. L. (1992). A sensitive method for the detection of poly-A tails of mRNA using a biotin-labelled heteropolymer of dT:rA. *Journal of Pathology*, 167, 369–373.
- N36 Markovic, B., & Nicholls, E. M. (1993). The expression of cytokine messenger-rnas in clear cell acanthoma. *International Journal of Oncology*, 2, 519–522.

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