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EVA LENNOX

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are sets of reference values, utilising fractiles or S.D. units. The system has the great advantages that most measurements can be expressed in the same way and that the results of different examinations can be combined into a single value.
Caution: "cut-off limits" or "discrimination limits" such as ± 2 S.D. are arbitrary. In some cases it may be good for the patient to have a value falling outside the limits (e.g., below -2 S.D. for blood-lipids).
The complex problems of reference values are being discussed by the Expert Panel on the Theory of Reference Values of the International Federation of Clinical Chemistry. The panel welcomes suggestions on the use of reference values and will be glad for the discussion to spread to haematologists and clinical physiologists. The panel hopes to publish a recommendation shortly and can already distribute some unofficial material. An editorial in *Clinical Chemistry* provides useful information.

Panel on the Theory of Reference Values, I.F.C.C.
Ralph Gräsbeck

RALPH GRÄSBECK

Panel on the Theory of Reference Values, I.F.C.C.

Sir,—Dr Wright (Dec. 20, p. 1261), Professor Lennox (Nov. 29, p. 1085), and others have written on the subject of normalisation and units in laboratory medicine. Apart from the difficulties entailed in educating clinical and research physicians to the correct use of the wheel in matters methodological, normalisation suffers from a serious built-in disadvantage: it depends upon the availability of a normal mean value which is universally accepted.

We must accept the fact that normal mean values are liable to change with time. Further, it is not unusual to find normal mean values differing from country to country and from region to region within a country—even from hospital to hospital within a given city.

As a technique for evaluating, interpreting, and extracting full information from clinical data, normalisation is useful and instructive enough to be made mandatory. As a standard method for reporting (and thereby storing) data in the literature it is not acceptable because the data become derived, rather than directly measured, quantities that are dependent upon a consensus definition of normal mean values which can change with time.

Two useful functions are at stake here—and what serves one may very well not serve the other.

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BERNARD J. RANSIL

NORMAL = 10 $\pm$ 2

Sir,—It is troubling to have such a rigidly defined concept of normality as so lucidly expressed by Professor Lennox¹ and supported by Dr Wright.² To take the normal of haemoglobin as 100 because it was good historical precedent does not make a right now. It is a particularly interesting unit of normality, as it was originated by Haldane in a rather small series ("My future lab boy"—though this oxonian quotation may be apocryphal). Dr Wright suggests that if certain biographical data are presented to the laboratory, then normal ranges for sex and age may also be computed. This is, in fact, how biochemical data are reported in this institution, and the system is trouble-free.

¹ Wadman, H. W. *Jr. Clin. Chem.* 1975, 21, 1673.
² Lennox, H. *Lancet*, 1975, ii, 1085.
³ Wright, H. M. *ibid.* p. 1261.

Much of clinical medicine is now committed to using laboratories for monitoring a patient's condition rather than for diagnostic purposes. Is there a normal haemoglobin for a nephrotic patient or one with chronic lung disease? Changes in absolute values or trends are far more cause for concern or rejoicing than their relationships to statistical or mythical normality. The need for an absolute value may be founded on groundless fears, but this proviso was placed in Dr Wright's opinion poll.

Medical literature is likely to become chaotic, while half the world will be using SI units with the rest hardly even knowing what they are! With deep respect to my colleagues, I should like to suggest that we do not need yet another frame of reference with which to assess our patients.

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ANGIOSARCOMA OF THE LIVER IN P.V.C. FABRICATORS

Sir,—Since the beginning of 1974 a number of cases of the rare tumour angiosarcoma of the liver have been reported amongst workers exposed to high concentrations of vinyl chloride, a chemical used to manufacture the plastic polyvinyl chloride (P.V.C.). Exposure to much smaller amounts of vinyl chloride may also occur when the raw P.V.C. is used to fabricate plastic articles, as residual amounts of untreated vinyl chloride may then be released. Epidemiological studies of P.V.C. manufacturers have been set up in several countries, and the risk of occupational exposure to different levels of vinyl chloride will eventually be evaluated, but it is not known whether there is any risk to P.V.C. fabricators. The Office of Population Censuses and Surveys (O.P.C.S.) categorises persons employed in extruding, moulding, cutting, and turning or otherwise machining plastics,¹ which includes P.V.C. fabricators, under the title of "workers in plastics" (occupational unit code 90). An analysis of death certificates for workers in this category should be a guide to the mortality pattern of plastics workers overall and, by inference, to the effects of vinyl chloride in P.V.C. fabricators.

The last published rates for plastics workers showed no significant excess of deaths in any of the given disease categories, the standardised mortality ratio being 78.² Because the figures for 1971 are not yet available we decided to undertake a proportional-mortality study using death certificates for 1970-72 to detect any recent change in the pattern of mortality which may have occurred and be ascribable to vinyl-chloride exposure.

Death certificates for male plastics workers, 1970-72, were coded by the O.P.C.S. according to the International Classification of Diseases, eighth revision. Age-standardised proportional-mortality ratios were calculated for each cause of death in ten-year age-groups, expected rates being obtained from mortality data for England and Wales for each year under study.³ Approximately 60 000 men were recorded as plastics workers at the last England and Wales population Census.⁴ About 35 000 of these (60%) are thought to be partly or wholly engaged in working with P.V.C. (based on H.M. Factory Inspectorate records for 1975).

As shown in the table the only statistically significant

1. Office of Population Censuses and Surveys. *Classification of Occupations*. H.M. Stationery Office, 1970.
2. Registrar General. *Decennial Supplement England and Wales 1961: occupational mortality tables*. H.M. Stationery Office, 1971.
3. Registrar General. *Statistical Reviews of England and Wales for 1970, 1971, and 1972: part I, tables, medical*. H.M. Stationery Office.
4. Office of Population Censuses and Surveys. *Census 1971, Great Britain: economic activity tables part III, 10% sample*. H.M. Stationery Office, 1975.

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excesses for the causes of death were stomach cancer and diseases of the urogenital system. The number of deaths due to all cancers were slightly higher than expected but there was a deficit of lung cancer and only 1 death from liver cancer (certified as primary carcinoma). There were 3 deaths from liver disease, with 3-6 expected. The deaths from diseases of the urogenital system were analysed further into those due to nephritis and nephrosis (I.C.D. 580-584); there were 10 deaths in this category with 5-6 expected, a difference which did not quite attain significance at the 5% level. Fewer deaths than expected were attributed to neoplasms of lymphatic and haemopoietic tissue.

The excess deaths from cancer of the stomach and diseases of the urogenital system were surprising because vinyl

MALE PLASTICS WORKERS: DEATHS FROM ALL CAUSES 1970-72

Cause of death (I.C.D. no.)	Obs. (O)	Exp. (E)	O/E
All cancers (140-239)	204	185.9	1.1
Stomach (151)	24	16.4	1.5
Liver (155)	3	1.1	0.9
Lung (162-1)	88	99.3	0.9
Brain (191)	5	5.0	1.0
Lymphatic/haemopoietic (200-207)	3	15.2	0.2
Endo/nutr./metabolic (240-279)	4	6.2	0.6
Circulatory (390-458)	345	336.0	1.0
Ischaemic (410-414)	229	228.0	1.0
Respiratory (460-519)	77	80.0	1.0
Bronchitis (490-491)	42	54.4	0.8
Digestive (520-571)	14	17.1	0.8
Liver (570-573)	3	3.6	0.8
Urogenital* (580-629)	15	8.1	1.9
Accidents (E800-949)	24	36.8	0.6
Suicides (E950-959)	5	11.8	0.4
All other causes	19	25.1	0.8
All	707	707.0	1.0

*p<0.05.

chloride has not so far been linked with either of these conditions. However, a wide range of other chemical substances is used in the plastics industry, some of which may eventually prove to be carcinogenic or nephrotoxic and giving rise to these excesses. When interpreting a study of this kind it must be remembered that a proportional excess in a disease category may not reflect a real increase in death-rates over a comparative population, but may also arise if there is a deficiency of deaths in other categories in the study group.

Vinyl chloride has been suggested as causing cancer of the lung and brain,² as well as angiosarcoma of the liver and other liver diseases.³ In this study the observed numbers of deaths from these causes were not in excess of those expected. Any excess mortality from these causes which may be present in p.v.c. fabricators is consequently not large enough to be detected amongst plastics workers as a group. This is not to say that there is no excess risk; this study was undertaken to assess the order of magnitude of any excess risk as quickly as possible. However, recent studies of p.v.c. manufacturers also show little indication of an excess risk of lung and brain cancer associated with exposure to vinyl chloride.⁷

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ANGIOSARCOMA OF THE LIVER

SIR,—The reports of haemangiosarcoma of the liver in people exposed to vinyl chloride¹⁻⁷ led us to investigate the situation in Holland.

We asked all pathology laboratories throughout the country to allow us to study their cases diagnosed as angiosarcoma (or allied conditions). This yielded information on and tissues of 27 adults seen since 1950. There were only 8 definite (7 men and 1 possible) angiosarcomas of the liver. In addition 1 angiosarcoma was present in a woman on long-term arsenic medication—a well-known association.⁸ Angiosarcomas associated with 'Thorotrast'^{10,11} were not considered. 2 other angiosarcomas originated in the spleen. There were 14 non-vascular tumours of miscellaneous origin, and in 1 case no tumour was seen. Histopathological details will be given elsewhere. Age at death of the 8 angiosarcoma patients varied between 46 and 73. One man (aged 56), who had worked for 15 years with zinc-chromate primers under primitive circumstances, had a seminoma at the end of this period and a malignant liver tumour of uncertain histogenesis more than 10 years later. The incidence of liver angiosarcoma is difficult to estimate. Rein and Huth¹² had 6 cases in 30 079 necropsies. Our 8 cases occurred in a fluctuating population of 10-14 million, with at least 40 000 necropsies. Remarkably, none of our 27 patients had any traceable contact with vinyl chloride.

We are grateful to all pathologists, surgeons, internists, and general practitioners who cooperated in compiling the data on the 27 patients.

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G. BRAS

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SELECTIVE IgA DEFICIENCY

SIR,—You state¹ that there is no difference in the frequency of sinopulmonary infection in healthy serum-IgA-deficient people and healthy blood-donors. There are two different forms of IgA, one in the serum and the other in secretions such as saliva, gastric juice, tears, and colostrum. They differ in that the secretory form is produced locally by the plasma-cells in the submucosal tissues of exocrine glands, whereas serum IgA is produced by circulating plasma-cells. The local plasma-cells continue to function independently of circulating plasma-cells. The IgA produced locally differs from serum IgA in that it contains an extra antigenic chain known as the secretory or transport piece as well as the heavy and light chains normally present in serum IgA. The transport piece is secreted by the columnar cells and joined to the IgA molecules as they pass between the cells. Because of these differences, I think it would be unwise to suggest that IgA deficiency is not associated with recurrent infection unless local secretory IgA activity in patients with low-serum-IgA has been assessed.

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