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Eva Lerner

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have sets of reference values, utilising fractiles or S.D. units.
system has the great advantages that most measurements
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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
limits (e.g., below -2 S.D. for blood-lipids).
The complex problems of reference values are being dis-
cussed 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 recom-
mendation shortly and can already distribute some unofficial
normal. An editorial¹ in *Clinical Chemistry* provides useful
information.

Expert Panel on the Theory of Reference Values, I.F.C.C.
Research
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RALPH GRÄSBECK

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

Sir,—Dr Wright (Dec. 20, p. 1261), Professor Lennox
(Dec. 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 phys-
icians to the need for the wheel in matters methodologi-
cal, normalisation offers 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
attractive enough to be made mandatory. As a standard
method for reporting (and thereby storing) data in the litera-
ture 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 ± 2

Sir,—It is not surprising 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
at 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
first 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 Underman, R. W., Jr. *Clin. Chem.* 1975, 21, 1673.
² Lennox, H. *Lancet*, 1975, ii, 1085.
³ Krentz, H. M. *ibid.* p. 1261.

Much of clinical medicine is now committed to using labora-
tories for monitoring a patient's condition rather than for
diagnostic purposes. Is there a normal haemoglobin for a neph-
rotic 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 nor-
mality. 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 fabri-
cate 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 per-
sons employed in extruding, moulding, cutting, and turning or
otherwise machining plastics,¹ which includes P.V.C. fabri-
cators, 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 plas-
tics 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 sig-
nificant 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 pro-
portional-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 expo-
sure.

Death certificates for male plastics workers, 1970-72, were
coded by the O.P.C.S. according to the International Classifi-
cation of Diseases, eighth revision. Age-standardised propor-
tional-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 In-
spectorate 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: occupa-
tional mortality tables*. H.M. Stationery Office, 1971.
3. Registrar General. *Statistical Reviews of England and Wales for 1970, 1971,
and 1972: part 1, tables, medical*. H.M. Stationery Office.
4. Office of Population Censuses and Surveys. *Census 1971, Great Britain: eco-
nomic activity tables part III, 107 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)	1	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
Endocr/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
Bronchus (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,¹ as well as angiosarcoma of the liver and other liver diseases.² 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.^{3,4}

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1. Monson, R. R., Peters, J. M., Johnson, M. N. *Lancet*, 1974, ii, 397.
2. Thomas, L. B., Popper, H., Berk, P. D., Seikoff, I., Falk, H. *New Engl. J. Med.* 1975, 292, 17.
3. Duck, B. W., Carter, J. T., Coombes, E. J. *Lancet*, 1975, ii, 1197.
4. Fox, A. J., Collier, P. F. The Mortality Experience of Workers Exposed to Vinyl Chloride Monomer in the Manufacture of Polyvinyl Chloride in Great Britain. (Unpublished).

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.^{8,9} 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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S. C. FREN

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SELECTIVE IgA DEFICIENCY

SIR,—You state¹³ 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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1. Lee, F. L., Harry, D. S. *Lancet*, 1974, i, 1316.
2. *British Medical Journal*, 1974, i, 590.
3. *British Medical Journal*, 1974, iv, 486.
4. Falk, H., Creech, J. L., Heath, C. W., Johnson, M. N., Key, M. N. *J. Am. med. Ass.* 1974, 230, 59.
5. Creech, J. C., Johnson, M. N. *J. occup. Med.* 1974, 16, 150.
6. Lange, C. E., Jübe, S., Veltman, G. *De med. Wiskr.* 1974, 99, 1598.
7. Ravier, E., Diter, J. M., Piat, J. *Arch. Mal. prof. Med. trav.* 1975, 36, 171.
8. Roth, F. *Zentralbl. Path. path. Anat.* 1955, 93, 424.
9. Regelson, W., Kim, U., Aspin, J., Holland, J. F. *Cancer*, 1968, 21, 514.
10. MacMahon, H. G., Murphy, A. S., Bates, B. I. *Am. J. Path.* 1947, 23, 585.
11. Telsuk, H., Nordin, W. A. *Arch. Path.* 1955, 60, 493.
12. Rein, F. R., Huth, F. *Int. Arch. Arbeitsmed.* 1975, 34, 237.
13. *Lancet*, 1975, ii, 1291.

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