removes all clothing from above the waist. Most of us find it difficult enough to examine the jugular venous pulse, for example, without the added encumbrance of a "pulled-up nightie", acting like a scarf round the patient's neck.

Surely the point that Dr Wright is making is that one should perform as dignified and thorough examination in an elderly person as one would in any other patient.

16 Angelis Meadow, Ashwell, Baldock, Herts. D. Rowley Jones

RADIOIMMUNOASSAY FOR NORTRIPTYLINE AND AMITRIPTYLINE

Sir,—Dr Aherne and his colleagues (June 4, p. 1214) correctly draw attention to the advantages of their radioimmunoassay (R.I.A.) for estimation of plasma concentrations of nortriptyline and amitriptyline in monitoring response of patients receiving these drugs. However, a wide range of monoamine-reuptake-inhibiting drugs is now used in treatment of depressive illness, and an advantage of some other analytical methods, such as the gas-liquid chromatography method described by Gifford et al.,1 is that they can readily estimate most of these drugs and their main metabolites as well as identify some other centrally acting drugs such as benzodiazepines which the patient may be taking. For example, in a comparative study of two antidepressive drugs, we found that some patients had been given the wrong drug and some were found to be taking benzodiazepines, for part or all of the trial period. Chromatographic and R.I.A. methods both have their analytical roles according to the clinical or research problem being investigated.

Department of Clinical Pharmacology, St. Bartholomew's Hospital Medical College, London EC1A 7BE Paul Turner

GOALS AND OBJECTIVES IN MEDICAL EDUCATION

Sir,—Your editorial (May 7, p. 985) left me with a profound sense of déjà vu. The vocabulary is all too familiar: goals, objectives, facilitation of educational planning, learning activities, feedback. The same jargon has filled many North American medical journals for years. Big business and government in the U.S.A. have long been sending their executives and high-ranking civil servants to management courses that are repetitive.

Despite these criticisms Dr Sircus concedes that the deduc-
tion, that the capacity to secrete acid increases with increasing duration of symptoms, is consistent with his earlier observations. Standardisation of secretory data for age or lean body mass, or more appropriately for height,12 is necessary before the relationship between M.A.O. and duration of symptoms can be demonstrated in retrospective studies. Appropriate standardisation of secretory data should therefore be achieved before the data from retrospective studies, such as those of Petrillo et al.,13 can be accepted as evidence against the existence of such a relationship.

Dr Sircus draws attention to the unusually large proportion of low secretors in our control subjects. This unusually large proportion of low secretors may reflect the relatively poor incidence of recurrent ulcers when in fact we clearly state that our incidence was 7.8%. In addition to his disregarding these many facts Dr Sircus misquotes our paper, claiming that we had a preposterous 21% incidence of recurrent ulcers when in fact we clearly state that our incidence was 7.8%.

RISK OF ULCERATION EXPRESSED AS PERCENTAGE/10 YEARS IN SUBJECTS WITH EQUIVALENT CAPACITIES TO SECRETE ACID

Percentage risk in "normals" and post-vagotomy patients computed on the assumption that 1-7% of all normal individuals and 7-8% of all post-vagotomy patients develop an ulcer in 10 years. (Patients with M.A.O. >40 meq/h have been included in this table.)

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V + D: vagotomy and drainage
V + A: vagotomy and antrectomy

Percentage risk in "normals" and post-vagotomy patients computed on the assumption that 1.7% of all normal individuals and 7-8% of all post-vagotomy patients develop an ulcer in 10 years. (Patients with M.A.O. >40 meq/h have been included in this table.)

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Both Dr Sircus and Dr Prescott question the validity of the conclusions in our paper on the M.A.O. and risk of ulceration on statistical grounds. Such criticism is inappropriate for the retrospective nature of the study, the incomplete follow-up, and the assumptions that we had to make in order to calculate the risks of ulceration prevented us from using statistical comparisons to support our conclusions. Unfortunately it is most unlikely that a prospective study of sufficient magnitude to test the validity of our conclusions or of the views of Dr Sircus and Dr Prescott will ever be performed. Fig. 3 and the succeeding figures, to which Dr Prescott refers were derived from values obtained from the regression equation between the M.A.O. and the incidence of recurrent ulcers. The points, which these figures were intended to portray, are emphasised in the accompanying table which includes details of the patients treated by Dr Sircus and Dr Prescott. The table shows the striking difference between the calculated risk of recurrence following vagotomy and drainage and the calculated risk of ulceration in normal individuals with the same M.A.O. The difference is consistent with the deduction that ulcers are not caused by an abnormal capacity to secrete acid and does not support the deduction that ulcers are caused by an abnormal capacity to secrete acid.

Acknowledging the fact that duodenal ulcers may develop in patients who have a normal capacity to secrete acid, Dr Sircus suggests that ulcers may be caused by the inappropriate secretion of acid that has been demonstrated in patients with duodenal ulcers. This may be so, but, in the absence of data from similar experiments in patients with gastric ulcers, this evidence cannot be accepted as support for the belief that duodenal and gastric ulcers are different diseases. The accompanying table illustrates the striking similarity between the actual incidence of recurrence following vagotomy and antrectomy and the calculated incidence of ulceration in normal individuals with the same capacity to secrete acid. These data form the basis for our deduction that antrectomy tends to cure patients of their ulcer disease. Dr Sircus questions this deduction on the grounds that a Billroth-I antrectomy is ineffective treatment for duodenal ulceration but overlooks the evidence that Billroth-I antrectomy is effective treatment for duodenal ulceration provided that sufficient antrum is removed.15,16 Even so, in terms of the hypothesis I presented, a gastrojejunostomy does have a theoretical advantage over a gastroduodenal anastomosis for it impairs the release of duodenal gastrin by food. The impairment may account for the relative success of gastrojejunostomy in the treatment of duodenal ulceration. How does Dr Sircus account for a therapeutic success of a gastrojejunostomy?

The hypothesis I proposed is illustrated in the accompanying figure. All the abnormalities which have been described in peptic ulceration can be explained by postulating that the release of chalone is impaired and that ulcers form in areas that are primarily determined by each individual's capacity to secrete acid. As Schaffalizky de Muckadell et al. observed it may not be possible to demonstrate an impaired release of secretin in peptic ulceration by perfusing acid into the duodenum. In most instances the abnormal responses to

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Hypothsis for peptic ulceration (see text).

duodenal acidification, to which I have referred in my hypo-
thesis, have been observed in response to pharmacological
amounts of acid. The pathophysiological significance of an
abnormal response induced by a pharmacological stimulus
may be questioned but it is well established that provocative
stimuli are sometimes necessary to demonstrate hormonal ab-
normalities in other endocrine disorders. As indicated in my
hypothesis, the abnormal release of secretin may only be part
of the abnormal response to duodenal acidification. It is per-
haps more appropriate to refer to the hormone or hormones,
whose release appears to be impaired in peptic ulceration,
as chalones. In looking for a chalone whose release is impaired
in peptic ulceration we should not overlook the possibility that
an impaired release may be manifest as an impairment of basal
release rather than of stimulated release. Furthermore we
should not overlook the possibility that basal concentrations of
immunoreactive chalone may not reflect the biological activity
of the chalone in its basal state.

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Ann Arbor, Michigan 48109, U.S.A.

RICHARD G. FIDDIAN-GREEN

Sir,—We were fascinated, and rather perplexed, by Dr Fid-
rian-Green's interpretation and statistical treatment of our
acid secretory data.10 His views have perturbed some of our
colleagues1 who, like ourselves, have championed the view that
acid-pepsin aggression is a major aetiological factor in duodenal
ulcer, and impaired mucosal resistance an important cause of
gastric ulcer. However, fundamental similarities between gas-
tric and duodenal ulcers have also been noted8 and recent
complicated statistical studies by Hobson et al.9 have pur-
ported to show that duodenal ulceration is the cause, rather
than the result, of acid hypersecretion. Dr Fiddian-Green can
hardly be blamed for choosing to extend this concept by exam-
ining our data for evidence of similarities, rather than dif-
fences, in the pathogenesis of peptic ulcers. In this respect,
many of the current views on the pathophysiology of peptic
ulceration require almost as much "further study" as do those
of Dr Fiddian-Green. Guth10 believes that the role of antral
gastritis and bile reflux in gastric ulceration is suggestive
rather than proven, and studies showing increased parietal-cell
sensitivity to gastrin in duodenal ulcer11 and, indeed, other
findings on hormonal and homeostatic differences between
duodenal-ulcer and control subjects do not exclude the pos-
sibility that at least part of the ulceration is due to prepyloric
ulceration. Dr Fiddian-Green's unitarian hypothesis is in
keeping with the suggestion that gastric ulcers be regarded
as duodenal ulcers in the wrong place,12 and his evi-
dence that the acid secretory capacity of the stomach in-
fluences the position in which an ulcer may develop gives sta-
tistical expression to the time-honoured concept of the gradient
of mucosal vulnerability to peptic ulceration.5

It is unfortunate that many workers draw conclusions from
conventional and, it seems, questionable statistical correla-
tions which lean heavily on acid secretory data standardised

1. Fiddian-Green, R. G., Bank, S., Marks, I. N., Louw, J. H. Lancet, 1976, ii,
1387.
6. Grossman, M. I., Guth, P. H., Eisenberg, J. I., Passaro, E. P., Roth, B. E.,
1975, 55, 330.
8. Illeg Worth, C. Personal communication.

for either height, weight, lean body mass (L.B.M.), or age. Sig-
nificant correlations, usually with lower values, have been
shown to exist between the M.A.O. and one or more of these
measures in control subjects13,14,15 but the correlation
between M.A.O. and body habitus in D.U. patients is more
tenuous.16,17,18 To date, there is no consensus about which of
the indices of body habitus offer the best correlation with
M.A.O.19,20 Hassan and Hobson17 found that I.B.M. offered the
better correlation with acid secretion "corrected for pyloric
loss", whereas Novis et al.21 noted that the correlation between
body weight and M.A.O. was slightly better than that between
M.A.O. and I.B.M. in a large group of students of relatively uni-
form age. In any event, Hobson et al.22 "corrected" their secre-
tory data for height, Fiddian-Green et al. calculated age-stan-
dardised acid outputs, and Sircus23,24 simply expressed his data
in terms of acid output per kg body-weight. Dr Fiddian-Green
is clearly in good company, although we must concede that his
use of age-standardised M.A.O.s in correlating M.A.O. with
duration of symptoms was perhaps unwise.

Dr Sircus's comments are, in the main, well taken, but it is
only fair that we, too, should be confused by his data pertain-
ing to the possible influence of duration of symptoms on M.A.O.

The data on his 200 D.U. patients in the table suggest that the mean M.A.O., expressed in mmol/kg T.B.W./h, remains con-
stant irrespective of the duration of symptoms. This is in striking
contrast not only to his earlier findings20 in 176 D.U. pa-
ients where M.A.O. was expressed in meq/kg but also to his later
study29 on 339 patients in which M.A.O. was expressed in
mmol/kg T.B.W./h. This study, interestingly enough, showed
that the M.A.O. increased progressively with duration, that
there was no "fall-off" in M.A.O. in the groups of patients with
symptoms of more than 19 years' duration, and that the pro-
gressive and significant increases in M.A.O. with duration
applied equally to "normosecretor" and "hypersecretor" type
of D.U. patients.

Perspective regarding the influence of duration on M.A.O. in
D.U. patients and its pathophysiological implications may per-
haps be gained from data from a study carried out some 20
years ago in 63 D.U. patients with no clinical, radiological, or
surgical evidence of stenosis.28 No significant correlation was
found between M.H.R. (maximal histamine response expressed
in meq/30 minutes) and duration of symptoms for the entire
group of 63 patients, but a significant positive linear correla-
tion between M.H.R. and duration was found in the subgroup
of 49 patients with a history of up to 12 years' duration
(r=0.305, p<0.05). A multiple regression of M.H.R. on body-
weight, age, and duration in this subgroup was also found to
be significant (r=0.35, p<0.05) and M.H.R. increased as the
duration of symptoms increased. The data, in contrast to those
of Fiddian-Green et al.29, showed no significant correlation be-
 tween M.H.R. and duration in the subgroup of patients with
symptoms of more than 19 years' duration, and that the pro-
gressive and significant increases in M.A.O. with duration
applied equally to "normosecretor" and "hypersecretor" type
of D.U. patients.

Further statistical scrutiny of the data in the entire group of
63 patients including the 14 with a duration of more than 12 years,
showed that the correlation between M.H.R. and duration could
be better fitted to a cubic polynomial (r=0.43, p<0.01) than to a linear
regression. However, only 22% of the total variance in M.H.R.
could be accounted for by consideration of sex and the quad-
ratic and linear terms for duration. Age and body-weight again
showed no significant contribution to the regression. The data,
while supporting the contention that the M.H.R. tends to in-
crease with duration in D.U. patients,2,3,4 emphasised the point
that factors other than duration, sex, and the negligible effects
of body-weight and age are responsible for the magnitude of
the M.H.R. in the vast majority of duodenal-ulcer patients, and

The reluctant coauthors feel that his avant-garde approach to ulcer pathogenesis is not, we believe, a subject for reproach.

A. TORSOLI
R. CARRATU
A. TORSOLI
P. BERTHELOT

CONSTITUTIONAL UNCONJUGATED HYPERBILIRUBINÆMIA
Sir,—Dr Bailey and his colleagues (April 30, p. 391) suggest that the hyperbilirubinæmia found in Gilbert’s syndrome is not a real disease but rather constitutes the upper end of the normal range. This view implies that all patients with unconjugated hyperbilirubinæmia in the absence of overt bilirubin overproduction belong to a homogeneous group, which is neither our experience nor that of others.1

Over the past five years we have investigated 39 patients with chronic unconjugated hyperbilirubinæmia which could not be explained by overt dyserythroplasia or haemolysis. 36 of these patients closely resembled each other in having a normal (slightly reduced in 2 cases) plasma disappearance-rate of bromsulphthalein and much reduced hepatic bilirubin/uridine-bisphosphate glucuronosyltransferase activity (B.-G.T.A.), a finding reported by others.2,3 The B.-G.T.A. in these patients was 0.25±0.17 (S.D.) mg bilirubin conjugated/h/g liver, the normal value in our laboratory being 1.3±0.44. However, chronic unconjugated hyperbilirubinæmia was also observed in 3 brothers whose features were different from the other 36. Their plasma disappearance-rates of bromsulphthalein were dramatically reduced (0.04, 0.05, and 0.05) compared with our normal value of 0.14±0.02, while the B.-G.T.A., measured in one brother, was normal (0.874). Such patients resemble those described by Martin et al.,4 who also had unconjugated hyperbilirubinæmia and very low disappearance-rates of bromsulphthalein; B.-G.T.A. was not measured.

These findings demonstrate that there are at least two types of constitutional unconjugated hyperbilirubinæmia—one associated with a reduced B.-G.T.A., while the other, a rare condition, seems to be primarily related to a defect in hepatic uptake. People with constitutional unconjugated hyperbilirubinæmia therefore form a heterogeneous population, a factor not considered by Dr Bailey and his colleagues.

J. M. M. SARLE
D. DHUMEAUX
C. GIESSELBRECHT
A. M. PREAUD
P. BERTHELOT

GYNÆCOMASTIA WITH CIMETIDINE
Sir,—Hall1 and Sharpe and Hawkins1 have reported breast pain and gynæcomastia when treating Zollinger-Ellison syndrome and peptic ulcer disease with H₂-receptor antagonists. In two cases thorough endocrine studies were done, including prolactin assay, but no abnormalities were found.1 We have measured the plasma-prolactin by radioimmunoassay in six patients with duodenal or post partial gastrectomy anastomotic ulcers or Zollinger-Ellison syndrome. Plasma-prolactin was measured before and at the end of 2 months’ cimetidine treatment (0.4 g by mouth, four times daily). Patients were not receiving any other drug.

The results obtained are shown in the figure. Pre-treatment values were normal (5–15 ng/ml in males and 5–20 ng/ml in females). At the end of the treatment the plasma-prolactin had risen by 50–112%. One patient had gynaecomastia and a young woman had galactorrhoea.

These results offer a possible explanation for the side-effects of H₂-receptor antagonists at mammary-gland level. The mechanism responsible for the increase of prolactin is unknown.

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4. Waggoner, H. Presented to the annual meeting of American Society for Clinical Pharmacology and Therapeutics, held in Dallas, Texas, in 1977.