

generation: I wished the reader had been told what is the primary defect which has now been recognized. I cannot imagine that a low caeruloplasmin level is the primary defect you are referring to. As everyone knows, there is a definite though small number of patients with Wilson's disease who have normal caeruloplasmin levels. The opposite, of course, also holds true.

I am left wondering whether abnormal copper metabolism is the primary defect you have in mind. With regard to that one could recall that patients have been reported<sup>1-3</sup> who had a frankly or questionably positive copper balance and who, to all intents and purposes, were not instances of Wilson's disease. But then, is dopamine deficiency the primary defect of Parkinson's disease? To be sure, knowledge of a dopamine deficiency and of a positive copper balance has notably advanced our understanding of paralysis agitans and Wilson's disease respectively. I think, however, that we have a long way to go before we can ever say that the "primary defect" of Wilson's disease has been recognized. Perhaps the beginning of that long way could be sighted in some recently published work,<sup>4</sup> should the reported findings be conclusively established.—I am, etc.,

A. P. ANZIL

Max-Planck-Institut für Psychiatrie,  
Munich

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### Coxsackie B Viruses and Diabetes Mellitus

SIR,—Several studies have suggested that there may be a relationship between Coxsackie virus infections and diabetes mellitus.<sup>1</sup> In 1951 Pappenheimer *et al.*<sup>2</sup> found that Coxsackie B viruses caused acinar pancreatitis in mice with sparing of the islets of Langerhans. However, Burch *et al.*<sup>3,4</sup> reported that Coxsackie B1 and B4 also damaged the beta-cells of the pancreas. More recently Coleman *et al.*<sup>5</sup> found abnormal glucose levels in six of 14 mice infected with Coxsackie B4. In our laboratory prototype strains of Coxsackie B1, B3, B4, and B5 produced hyperamylasaemia and a decrease in the amylase content of the pancreas, but non-fasting glucose levels and glucose tolerance tests were normal under a variety of experimental conditions.<sup>6</sup>

The present experiments were initiated to see whether fresh Coxsackie virus isolates (rather than prototype viruses that have been passaged numerous times in tissue culture and neonatal mice) were capable of producing hyperglycemia in mice. Fourteen human isolates, passaged two or three times in monkey kidney cells, were kindly supplied by Dr. Edwin H. Lennette of the Viral and Rickettsial Disease Laboratory, California State Department of Health. Each virus preparation, containing about 10<sup>5</sup> median tissue culture infective doses (TCID<sub>50</sub>), was injected intraperitoneally into 15 CD-1 male mice 6-9 weeks of age. Serum amylase levels were determined by the blue starch substrate method and blood glucose levels by the glucose oxidase method.<sup>6</sup>

The fresh isolates all caused acinar pancreatitis manifested by hyperamylasaemia ( $P < 0.01$  for all but one of the strains of virus). The histological changes of acinar pancreatitis were indistinguishable from those found with prototype Coxsackie B viruses.<sup>3,4</sup> The mean non-fasting glucose levels

were not significantly elevated; more important, none of the 200 mice tested had blood glucose levels more than three standard deviations above normal. Glucose tolerance tests<sup>8</sup> performed on 10 mice from each group about 14 days after infection revealed that none of the mice had elevated glucose levels. Histologically, the islets of Langerhans were essentially normal in all cases. In contrast to the findings with the Coxsackie B viruses, glucose levels and glucose tolerance tests were clearly abnormal after infection of mice with the M variant of encephalomyocarditis virus, a known beta-cell pathogen.<sup>7,8</sup>

Previous studies<sup>5,6</sup> of Coxsackie virus infections in mice have utilized prototype viral strains with many passages since their original isolation; our results indicate that fresh isolates also do not significantly damage beta-cells or cause glucose intolerance. Though the prototype Coxsackie B2 virus does not damage the pancreas,<sup>6</sup> the present data clearly demonstrate that fresh isolates of Coxsackie B2 may infect and damage acinar cells.

Dr. T. J. Coleman and his colleagues kindly provided a sample of the Coxsackie B4 virus used in their study<sup>5</sup>; we have examined approximately 70 CD-1 mice infected with this virus. The pathological changes of acinar pancreatitis were supported by the finding of hyperamylasaemia during the acute infection. Non-fasting glucose level (1, 2, 3, 4, 5, and 10 weeks after infection) and glucose tolerance tests (1, 2, and 3 weeks after infection) all failed to reveal evidence of glucose intolerance. Histological sections showed no evidence of beta-cell damage. Though we cannot explain the discrepancies between our studies and those of Coleman *et al.*,<sup>5</sup> other work has shown that male CD-1 mice spontaneously develop a diabetic syndrome in response to a high-fat diet.<sup>9</sup> Conceivably, Coxsackie B virus infection of CD-1 mice on a high-fat diet might accelerate the known diabetic tendency of these mice.

Though there may be unusual Coxsackie virus variants, our experiments failed to find any evidence that Coxsackie B viruses can cause a diabetes-like syndrome in mice.—We are, etc.,

MICHAEL E. ROSS  
ABNER LOUIS NOTRINS

Laboratory of Oral Medicine,  
National Institute of Dental Research,  
Bethesda, Maryland

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### Guitar Nipple

SIR,—I have recently seen three patients with traumatic mastitis of one breast. These were all girls aged between 8 and 10 and the mastitis consisted of a slightly inflamed cystic swelling about the base of the nipple. Questioning revealed that all three were learning to play the classical guitar, which requires close attention to the position of the instrument in relation to the body. In

each case a full-sized guitar was used and the edge of the soundbox pressed against the nipple. Two of the patients were right-handed and consequently had a right-sided mastitis while the third was left-handed with a left-sided mastitis. When the guitar-playing was stopped the mastitis subsided spontaneously.

I would be interested to know whether any other doctors have come across this condition.—I am, etc.,

P. CURTIS

Winchester.

### Compensation for Dust Disease

SIR,—After consideration of various relevant matters, the report<sup>1</sup> referred to in your leading article (9 March, p. 404) concludes that bronchitis and emphysema cannot, on the evidence available, be prescribed at present as industrial diseases in their own right. Many workers with disabling bronchitis have been exposed for many years to mineral dust arising from their respective occupations. These bronchitics, unless they show radiological evidence of pneumoconiosis, are denied industrial disablement benefit under the present regulations.

One proposal, mooted over the years, is that bronchitis should be accepted as liable to aggravation but not caused by long exposure to occupational mineral dust. (Incidentally, for the purpose of war pensions in certain cases it is accepted that war service is capable of aggravating bronchitis.) Has aggravation of bronchitis by exposure to occupational mineral dust duly received knowledgeable consideration? If not, does it merit any future consideration?

"Whatsoever things are just . . . think on these things."—I am, etc.,

G. B. MURRAY

Sale, Cheshire

- Pneumoconiosis and Byssinosis*, London. H.M.S.O., 1973.

### New Endotracheal Intubation Trainer

SIR,—The intubation trainer described here is a readily portable simulator moulded on a human head, with anatomical positions of the structures of the upper respiratory tract located correctly by radiological techniques. Thus, combined with life-like mobility, texture, and colouring of components, the essential anatomy requiring recognition by the trainee is rendered representative of the human adult subject. Its lips are sufficiently supple for manipulation and the mobile lower jaw can be moved forward by up to 2 cm, but only if laryngoscope traction is exerted in the correct direction. If backward leverage is employed the top of the laryngoscope automatically dislodges forward from its correct position, thus reminding the trainee to retract the laryngoscope in line with the handle at all times.

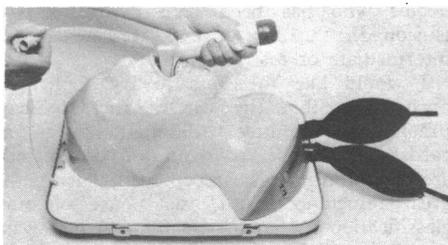
A natural tongue-epiglottis-vocal cords configuration provides effective simulation of the laryngoscope blade action. Depressing the tongue reveals the tip of the epiglottis; flexing the epiglottis towards the tongue reveals the vocal cords and entrance to the trachea. The energy required to lift the mandible correctly (and safely) is similar to that needed in the average human subject.

Inadvertent intubation of the oesophagus can be demonstrated via the retro-laryngeal pathway. Intubation of the right bronchus is possible owing

to the tracheal bifurcation following a natural anatomical angle. Thus the importance of not pushing the tube down too far, which can be avoided by choosing a correct length of tube, can be demonstrated.

Two detachable "lungs" provide demonstration facilities for mouth-to-tube resuscitation, self-inflating bag resuscitation, endotracheal suctioning, or visualizing intubation of the right bronchus. A warning buzzer will sound if the laryngoscope is levered against the upper teeth. Pressure on the larynx can be simulated, permitting the demonstration of this useful manoeuvre often needed to facilitate a difficult laryngeal view, such as when the larynx is lying in anterior position.

A unique feature of the intubation trainer is that it allows the simulation of varying degrees of difficulty for the trainee. Anterior or posterior positional movement of the larynx assembly in relation to the spine is adjustable, thereby permitting repeatable settings of degrees of difficulty from "very easy" to "difficult." Supplementing the apparatus is a set of teaching cards which supply, with teaching notes, the necessary information to perform the manoeuvre in the correct manner.



Though primarily designed for teaching by experts to small classes, the nature of the presentation is readily amenable to self-teaching, the student following the description booklet and the teaching cards and practising on the intubation trainer until he understands the manipulation and achieves repeated intubation success.

While it cannot be claimed that the ability to intubate the "trachea" of a stimulator satisfactorily means proficiency in the human situation, nevertheless the dexterity required and the understanding of the principles involved for intubation permit a highly informed approach to the "live" event. Medical students who had been trained by the teaching scheme using the Laerdal model (the only alternative commercial apparatus) displayed a ready expertise when faced with endotracheal intubation on the anaesthetized patient. On the normal adult patient most students were able to perform intubation satisfactorily and without tissue damage or undue delay on their first attempt.<sup>1</sup>

The scheme, known as the Royal Free Hospital Endotracheal Intubation Training Scheme, complete with intubation simulator, instruction manual, and display teaching cards, is being commercially prepared and distributed by Vitalograph Limited of Buckingham.

—I am, etc.,

T. HILARY HOWELLS

Royal Free Hospital,  
London N.W.3

<sup>1</sup> Howells, T. H., Emery, F. M., and Twentyman, J. E. C., *British Journal of Anaesthesia*, 1973, 45, 400.

#### Psychiatric Referral in the General Hospital

SIR,—Dr. G. P. Maguire and his colleagues (16 February, p. 268) have described an interesting investigation of psychiatric morbidity and referral in the medical ward. However, in discussing factors affecting referral there is some confusion between those likely to be related to recognition of psychiatric illness and others

which may then influence the decision to refer. A record of past psychiatric illness would seem to fall into the first category while severity of psychiatric disturbance is probably related not only to recognition of illness but also to the choice of which ill patients to refer. The only evidence specifically related to the second category concerns the 26% referral of patients whose notes indicated an awareness of psychiatric disturbance. Referral was "very strongly determined by how far their behaviour had obtruded or created problems for the medical staff"—a disappointing reflexion on the relative emphasis of management problems over clinical factors in the decision to refer.

A more optimistic picture, however, was revealed by study<sup>1</sup> by M. J. Pritchard of factors related to psychiatric referral in this general hospital. Here the comparison was between referred and non-referred patients, all of whom were diagnosed (that is, recognized) as psychiatrically ill. Referral occurred in about a third of the 252 cases and was found to be related to such factors as age, type of psychiatric illness, and the extent to which it was due to organic disease, as well as the existence of a suicidal attempt. Previous psychiatric contact within this group was inversely related to referral—a possible interpretation being that information from the earlier psychiatric assessment was often considered to be sufficient for the present admission.

From these results it appeared that referral was not a matter of chance but was being influenced by identifiable and valid clinical factors. At the same time, however, considerable differences were found between physicians in their use of psychiatric referral. This correlated with other variables thought to reflect the psychiatric awareness of the physician and/or his relationship with the psychiatric department, pointing again to the value of liaison work for the psychiatrist in the general hospital.—I am, etc.,

M. J. PRITCHARD

Department of Psychiatry,  
The London Hospital,  
London E.1

<sup>1</sup> Pritchard, M. J., *Postgraduate Medical Journal*, 1972, 48, 645.

#### Co-trimoxazole Resistance

SIR,—In the recent correspondence about co-trimoxazole resistance Dr. R. W. Lacey and Mrs. Evelyn L. Lewis (20 October, p. 164) referred to our report of thymine-requiring mutants isolated from infected urine and Drs. R. Then and P. Angehrn (12 January, p. 78) quoted our findings in support of their view that "the selection of thy mutants in vivo which are able to survive and are due to the use of co-trimoxazole is obviously a rare event of little importance for clinical therapy." Perhaps our experience may help to clarify some of the points raised in these letters.

The three strains of thy mutants of *Proteus mirabilis* which we isolated from infected urine in 1971 and 1972 alerted us to the existence of the phenomenon, but despite a very careful watch since 1972 only one *Escherichia coli* thy mutant has been isolated from over 75,000 urines examined. The patient had renal calculi with gross pyuria, as did the other three patients pre-

viously reported,<sup>1</sup> and had been given co-trimoxazole for long-term suppressive therapy. The thy mutants isolated from these patients were all stable in vitro and have not reverted to normal wild type organisms in up to three years of preservation by subcultures on Dorsett egg medium. In all our patients the thy mutants disappeared from the urine and were replaced by normal organisms after cessation of co-trimoxazole therapy. These findings suggest to us that the thy mutants are rare and can be associated with certain clinical situations, particularly infected renal calculi treated with long-term co-trimoxazole.

It is possible that the urine of these patients may have contained a quantity of thymine sufficient to maintain the growth of the mutants, and this could be related to the pyuria. However, we have treated over 100 patients with infection and pyuria, but no stones, with long-term co-trimoxazole in similar dosage and have not encountered thy mutants. It is well recognized that live organisms persist in the matrix of infected calculi,<sup>2</sup> and therefore they could be exposed to co-trimoxazole for very much longer than is the case in infection without stones. A similar situation could obtain in other clinical conditions, and it is interesting that Dr. Lacey and Mrs. Lewis have recently isolated a thymidine-requiring strain of *Staphylococcus aureus* from the sputum of a child with fibrocystic lung disease who had been treated with co-trimoxazole. Live organisms could have persisted in the scar tissue allowing the mutation to occur.

We have also observed in vitro that *E. coli* NCTC 10418 and other strains of *E. coli* and *P. mirabilis* can produce a growth factor which enables these organisms to grow on minimal agar without thymine. If this were the case in vivo, one would not need to postulate pus cells as the source of thymine or thymidine. Persistence of live organisms in the stone might suffice.

Finally we think that the emergence of thy mutants in the urine of these patients represents failure to co-trimoxazole therapy, and it is important therefore to be aware of their existence.—We are, etc.,

O. A. OKUBADJO  
R. M. MASKELL

Public Health Laboratory,  
St. Mary's General Hospital,  
Portsmouth

<sup>1</sup> Okubadjo, O. A., and Maskell, R. M., *Journal of General Microbiology*, 1973, 77, 533.

<sup>2</sup> Nemoy, N. J., and Stamey, T. A., *Journal of the American Medical Association*, 1971, 215, 1470.

#### The Solitary Thyroid Nodule

SIR,—Your leading article on this subject (10 November, p. 310) was the second in as many years (25 September 1971, p. 720) and indicates continuing interest in this problem. The more recent article rightly points out the different incidence of malignancy in various parts of the world. However, neither mentions the significance of sex in relation to the incidence of malignancy. There appears to be such a relationship in South India, where the overall incidence of malignancy in solitary nodules is comparatively high.

In our institution analysis<sup>1</sup> of 178 thyroid nodules considered to be "solitary" at operation disclosed 62 carcinomas (25 in