

infected with either *P. falciparum* or *P. vivax* reacted more strongly than those from the controls. The reaction of a few of the 55 parasitologically negative Iranian samples was also stronger than that of the controls. The mean value for the parasitologically negative Iranian samples was below that for the malaria-positive ones.

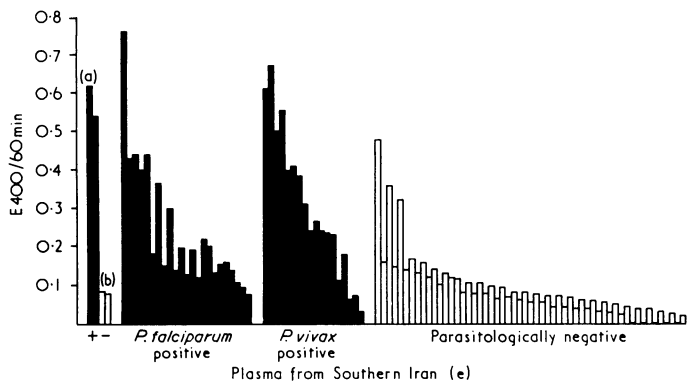


FIG. 3—Results of second trial with sera tested against *P. knowlesi* antigen.

## Discussion

These results show that the enzyme-linked immunosorbent assay detects and measures antibodies to malarial infections. Even when the antigen is derived from *P. knowlesi*, as in this study, the test seems to be sensitive in detecting antibodies to *P. falciparum* and *P. vivax*. When simian parasites have been used to provide the antigen for other malaria serological tests they have generally proved to be less sensitive than those derived from the human parasites. We used *P. knowlesi* antigen, however, because the large quantities of heavily parasitized blood needed for the development of the test could be obtained from infected *Macaca mulatta* monkeys, which are readily available. Soon we hope to test antigens prepared from *P. falciparum* and *P. vivax*. The antigen used here was a crude extract, and a purified antigen may be expected to have higher specific activity.

Our samples from malaria-infected patients and malaria-endemic areas reacted much more strongly than those from the European controls. Almost certainly the reaction is a malaria-specific antigen-antibody one, but we realize the dangers of possible false-positive reactions due to heterophiles, agglutinins, and "autoimmune" antibodies commonly found in the sera of people living in the tropics. The fact that absorption

of the sera with sheep erythrocytes did not reduce their reactivity suggests that heterophiles were not playing an important part. Only extensive tests on many control antisera can rule out all non-specific factors.

The fact that the test gave a positive result in all except one of the Tanzanian samples and yet only half showed parasitaemia shows that it can complement parasitological data by indicating recent as well as current infections.

The tests on the Iranian samples show that good results may be obtained when a time is set for the final enzyme reaction. Used in this way the test is more suitable for routine application. The results in the Iranian samples also show that *P. vivax* is as readily detected as *P. falciparum*. The preponderance of serological negatives among the parasitologically negative samples contrasts with the findings in the Tanzanian samples, virtually all of which were positive. This reflects the much lower malaria endemicity in Iran.

The tests can be carried out on blood samples collected by finger-prick. This and the fact that the samples tested are highly diluted means that the procedure is suitable for large-scale epidemiological programmes using tubes coated with different antigens. Ruitenber *et al.*<sup>6</sup> reported that, fully automated, several-thousand tests can be done daily. Our studies, however, were done with simple, inexpensive equipment well within the reach of most laboratories.

Preliminary trials with the wells of microhaemagglutination plates as the antigen-carrying surface gave promising results. These were read visually. This may lead to a simple field test yielding positive or negative results of possible value for screening.

We thank Dr. G. Heden for his constant encouragement, Dr. G. Edrissian for the Iranian samples, and Mr. Y. G. Matola for the Tanzanian ones. Financial help from the Salen Foundation and the World Health Organization made this work possible.

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# MEDICAL MEMORANDA

## Cardiac Arrhythmia and Imipramine Therapy

K. B. RAMANATHAN, C. DAVIDSON

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Cardiac arrhythmias are a common problem in patients who attempt suicide with tricyclic antidepressants, but it is less well recognized that arrhythmias may occur with these drugs in the standard therapeutic range. We report here a patient who de-

veloped recurrent supraventricular arrhythmias and heart failure during treatment with imipramine. Since stopping this drug all her symptoms resolved, and she subsequently had no evidence of cardiac disease.

### Case Report

A 61-year-old housewife was admitted on 29 December 1972 with a 24-hour history of palpitations and acute dyspnoea. She had previously been in good health, but four months earlier she had become depressed and was treated with imipramine 25 mg three times a day. During this period she had experienced occasional short-lived attacks of palpitations but had no other cardiac or systemic symptoms. In 1960 she had been found to be hypothyroid and had since taken thyroxine 0.3 mg/day.

On admission she had the clinical and radiological features of acute pulmonary oedema. An E.C.G. showed rapid atrial fibrillation and left bundle-branch block, and in the absence of any other specific features a provisional diagnosis of acute myocarditis was made. She

Cardiac Department, Leeds General Infirmary, Leeds LS1 3EX  
K. B. RAMANATHAN, M.D., M.R.C.P., Registrar  
C. DAVIDSON, M.B., M.R.C.P., Senior Registrar

responded promptly to treatment with digoxin and diuretics and reverted to sinus rhythm though left bundle-branch block persisted. Both thyroxine and imipramine were discontinued as possible aggravating factors, and she was discharged on digoxin 0.25 mg/day.

She remained well for several months but then developed the signs and symptoms of hypothyroidism, which was confirmed by thyroid function tests. Thyroxine 0.3 mg/day was restarted and the digoxin stopped. Despite a good clinical response to thyroxine she remained depressed and was again treated with imipramine 25 mg three times a day. Soon afterwards her episodes of palpitation recurred and on 1 August 1973 she was readmitted with acute heart failure. The E.C.G. showed supraventricular tachycardia (rate 150/min) with left bundle-branch block. After treatment with digoxin and diuretics the pulmonary oedema cleared and sinus rhythm was restored. She was discharged taking quinidine as a prophylactic measure in addition to digoxin and thyroxine, but soon after going home imipramine was added by her practitioner. When seen a month later she continued to complain of palpitations and an E.C.G. showed frequent ectopics and a short run of supraventricular tachycardia. The relationship between treatment with imipramine and her arrhythmia finally became apparent and the drug was discontinued. Since then she remained well and an E.C.G. taken three months later showed that the left bundle-branch block had resolved, the only residual abnormality being lateral S-T changes related to her digoxin treatment. There was no radiological or clinical evidence of cardiac disease.

### Comment

Though the potential hazards of the tricyclic antidepressants have been recognized for over 10 years (Kristiansen, 1961) the results of two recent retrospective surveys have conflicted (Coull *et al.*, 1970; Boston Collaborative Drug Surveillance Program, 1972). The Boston Collaborative Drug Surveillance Survey (1972) found no higher incidence of arrhythmias in patients on these drugs than in the rest of the hospital population. Nevertheless, there are enough reports of patients with supraventricular tachycardia (Alexander and Nino, 1969), atrial fibrillation (Rosen, 1960; Moorhead and Knox, 1965), bundle-

branch block (Alexander and Nino, 1969), and ventricular tachycardia (Scollins *et al.*, 1972) to suggest that arrhythmias can be caused by tricyclic therapy, particularly when, as in our case, the arrhythmias resolves on stopping treatment.

The relationship between the tricyclic drugs and heart failure is less clear. In previous case reports (Cossa *et al.*, 1960; Alexander and Nino, 1969; Luke, 1971) there has been evidence of underlying heart disease or patients have been receiving large doses of phenothiazines at the same time. In our patient underlying heart disease could not be excluded with certainty but the complete resolution of both the heart failure and the E.C.G. abnormality strongly support the causative role of imipramine. In theory some interaction between imipramine and thyroxine may have occurred, as suggested with guanethidine in another case (Williams, 1971). Thyroxine is known to sensitize tissues to the effects of circulating catecholamines (Harrison, 1964), which may be increased during treatment with psychotropic drugs (Carlsson *et al.*, 1966). Tricyclic antidepressants should therefore be prescribed with caution to patients already taking thyroxine.

We thank Dr. W. Whitaker for permission to report the details of this patient under his care.

Requests for reprints should be sent to Dr. C. Davidson.

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## Transvenous Biopsy of Carcinoma of Bronchus Causing Superior Vena Caval Obstruction

P. ARMSTRONG, D. F. HAYES, P. J. RICHARDSON

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A histological diagnosis in patients presenting with superior mediastinal obstruction of suspected neoplastic origin may be difficult to establish. We recently encountered just such a patient from whom we obtained tissue with a transvenous endomyocardial biptome introduced percutaneously.

### Case Report

A 66-year-old white woman presented in September 1969 complaining of backache, breathlessness, flatulence, and swelling of the face.

#### King's College Hospital, London SE5 9RS

P. ARMSTRONG, M.B., F.F.R., Consultant Radiologist  
 D. F. HAYES, M.B., M.R.C.P., Research Assistant, Chest Unit  
 P. J. RICHARDSON, M.B., M.R.C.P., Research Fellow, Department of Cardiology

She had previously had a hysterectomy for a benign lesion and had suffered for some years from depression. She smoked 15 cigarettes a day. She was on prednisone 2 mg on alternate days for late onset asthma.

The chest x-ray film showed slight elevation of the right hemidiaphragm and enlargement of the superior mediastinum in the right paratracheal region compatible with lymph node enlargement. She developed obvious superior vena caval obstruction and became very distressed. Bronchoscopy was carried out and no intraluminal lesion was seen but the roof of the right upper lobe bronchus bulged inwards due to an external mass. A biopsy of this area was performed. While awaiting the results of histological analysis, in view of the rapidly progressive obstruction which was almost certainly due to malignant disease, radiotherapy with <sup>60</sup>Co was started on 2 November 1969. She was given a mid-point dose of 3600 rads over 27 days to the mediastinum with great relief of symptoms. Histological analysis proved unhelpful and a definite diagnosis was never arrived at.

The patient was seen several times over the next few years and in 1972 was investigated for a peripheral neuropathy, which was thought to be related to the mediastinal malignancy. On 24 July 1974 she was again admitted with a recurrence of the superior vena caval obstruction. She also had profound bilateral posterior column impairment.

The chest x-ray film showed a raised right hemidiaphragm which on fluoroscopy was shown to be paralysed. Apart from bullae in the right upper lobe no other abnormality was present. There was no evidence of a superior mediastinal mass.

A superior venacavagram on 2 August 1974 showed an obstruction of the superior vena cava due to a spherical intraluminal filling defect which was apparently attached to its left wall at the level of