The failure of indices of glucose tolerance to contribute to this regression might be explained on two counts. First, while glucose tolerance improved a lot between the first and second tests, there was little further improvement at the third test. Second, consideration of the Reaven "horseshoe" relationship between O.G.T.T. sugar and insulin areas suggests that the O.G.T.T.-insulin area is likely to change only slightly in patients showing minor changes of glucose tolerance in the mildly diabetic range. The remarkable recovery of insulin response to an oral glucose load in some newly diagnosed diabetic patients after dietary treatment emphasises the observation that the initial O.G.T.T.-insulin area does not contribute to the prediction of the response to diet. This conclusion, however, only applies to the early response to treatment and does not preclude the possibility that the initial O.G.T.T. plasma-insulin curve may be of value in predicting the need for oral antidiabetic drugs or insulin at a later stage.

It seems that prolonged overstimulation of impaired islet-cell tissue by high blood-glucose levels causes progressive failure of insulin secretion, but that, in part, this may be reversed. In some ways, this endocrine disturbance resembles the relation described by Starling [15] in which the left-ventricular output of the heart initially increases as the filling pressure rises. Beyond a certain point, however, a further rise causes the ventricular output to fall. The diabetic state is aggravated by obesity in that higher plasma-insulin levels are required to produce a given degree of glucose tolerance. As with the failing left ventricle, considerable improvement in function can be obtained by reducing the load. Restricted calorie diets presumably improve glucose tolerance in two ways. First, weight reduction will allow relatively better glucose tolerance for a given level of insulin secretion after a glucose load. Second, reduction of $\beta$-cytotrophic overstimulation may permit some recovery of islet-cell function. The observation that nearly all our patients improved their glucose tolerance with dietary treatment and that most of them achieved satisfactory diabetic control implies that diet should remain the first line of management in newly diagnosed non-ketotic diabetic patients.

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# MORBIDITY AND MORTALITY IN PSEUDOPOLYCYTHÆMIA

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***Summary*** A follow-up of 35 patients with pseudopolycythæmia showed that symptoms, high packed-cell volumes, and low plasma volumes persisted in most patients. The death-rate in these patients was six times greater than expected. Patients with pseudopolycythæmia are often regarded as having a good prognosis; however, this view should be revised in the light of these findings.

## Introduction

PATIENTS with a high packed-cell volume (P.C.V.), low plasma volume, and normal red-blood-cell volume (R.C.V.) have been variously described as having pseudopolycythæmia,[1] Geisböck's syndrome,[2] relative polycythæmia,[3,4] polycythæmia of stress,[5] and benign polycythæmia.[6] Others maintain that these patients fall at the end of a normal distribution curve and have no disease.[7,8] Geisböck described patients with hypertension and a raised hæmoglobin and red-blood-cell count as having polycythæmia hypertonica,[9] but this was before plasma volume and R.C.V. could be measured.

So far there is little information on the natural history of this disease. Some have suggested that it is a benign condition [6] and others that it is often associated with vascular disease.[2,4,5] We report the first attempt to follow-up a group of patients with pseudopolycythæmia.

## Patients

Thirty-five patients presenting between 1962 and 1974 at University College Hospital, London, were investigated. All these patients were referred for estimation of R.C.V. and plasma volumes because a raised P.C.V. had been found, and it was necessary to confirm or exclude the diagnosis of primary polycythæmia. This service was available to all clinicians, the patients coming from many different clinics. Only two were referred from the hypertension clinic. The patients were selected by examining the records of blood-volume estimations. Criteria for inclusion were: a stable P.C.V. of 50% or more; an R.C.V. of 36 ml. per kg. or below; a plasma volume of 36 ml. per kg. or below; and no evidence of hypoxia arteriovenous shunting or myeloproliferative disorder.

All patients fulfilling these criteria were included and a follow-up of all those presenting before June, 1973, (twenty-seven patients) was attempted. Repeat estimates of blood and plasma volumes were obtained in most of these.

## Methods

P.C.V. was measured manually by the microhæmatocrit method at the time of study. Blood-volume was estimated essentially as described by the International Committee for Standardisation in Hæmatology.[10]

R.C.V. was estimated using $^{51}$Cr-labelled autologous red blood-cells. Samples were taken from the opposite arm 10, 20, and 30 minutes after injection of the radioisotope,

and the mean of these results was calculated. The plasma volume was measured simultaneously using $^{131}$I-labelled human albumin. Apparent plasma volumes were plotted against time and the line extrapolated to zero time to give the true plasma volume. Patients received 60 mg. potassium iodide before the study to prevent damage to the thyroid. Normal values for our laboratory are: R.C.V. 24·7–35·9 ml. per kg. (mean 30·3 ml. per kg. body-weight); plasma volume 35·5–46·7 ml. per kg. (mean 41·4 ml. per kg. body-weight); blood-volume 63·5–79·3 ml. per kg. (mean 71·7 ml. per kg. body-weight); and whole-body hæmatocrit/venous hæmatocrit 0·91–0·93. Plasma-uric-acid was measured (Technicon Methodology N. 13b). Normal values in our laboratory for men aged 40–60 are 2·9–8·3 ml. per 100 ml.

## Results

There were thirty-two men (mean age 49·8 years at presentation, range 29–68). The three women were aged 45, 46, and 67. The main presenting symptoms are shown in table I. At presentation twenty-four

TABLE I—MAIN SYMPTOMS IN 35 PATIENTS AT PRESENTATION

| Symptom | No.* |
|---|---|
| Tiredness, lethargy | 11 |
| Headache | 9 |
| Epigastric pain | 6 |
| Sweating | 5 |
| Breathlessness | 5 |
| Gout | 5 |
| Anxiety | 5 |
| Transient cerebral ischæmia attacks | 5 |
| Dizziness | 4 |
| Cerebrovascular accidents | 3 |
| Palpitations | 2 |
| Claudication | 2 |
| Angina | 2 |
| Non-specific chest pain | 2 |
| Deep-vein thrombosis | 2 |
| Paræsthesiæ | 2 |
| Epistaxis | 1 |
| Depression | 1 |
| Impotence | 1 |
| Vasculitis | 1 |

* Many patients had more than one symptom.

patients smoked, most heavily, six patients did not smoke, and for five there are no records. Seven patients were heavy drinkers. None were regarded as alcoholics. Twenty-three patients were believed to be anxious or under undue stress. A drug history was taken from all patients; nine patients were receiving thiazides when studied—eight for hypertension and one for no clear reason. Associated diseases at presentation are shown in table II. The spleen was initially just palpable in one patient, but was impalpable at follow-up; none of the other patients had palpable splenomegaly. Plethora was observed in twenty-one patients. A casual blood-pressure of 140/90 mm. Hg or below was recorded in twenty-two patients. There was systolic hypertension alone in

TABLE II—ASSOCIATED DISEASES AT PRESENTATION

| Disease | No. |
|---|---|
| Hypertension | 9 |
| Gout | 5 |
| Duodenal ulcer | 3 |
| Diabetes mellitus | 1 |
| Chronic pyelonephritis | 1 |
| Dupuytren's contracture | 1 |

TABLE III—HÆMATOLOGICAL DATA ON 37 PATIENTS AT PRESENTATION

| — | Hæmoglobin (g./100 ml.) | P.C.V. % | W.B.C. per c.mm. | E.S.R. (mm./hr.) | Platelets/ c.mm. |
|---|---|---|---|---|---|
| Mean | 17·8 | 53·6 | 9400 | 6·3 | 240,000 |
| Range | 16·7–20·3 | 50–60 | 5100–18,100 | 1–41 | 51,000–580,000 |

W.B.C. = white-blood-cell count.
E.S.R. = erythrocyte sedimentation-rate.

TABLE IV—BLOOD-VOLUME DATA OF 37 PATIENTS AT PRESENTATION

| — | Plasma volume (ml./kg.) | R.C.V. (ml./kg.*) | Whole-blood volume (ml./kg.*) | Whole-body hæmatocrit/ venous hæmatocrit |
|---|---|---|---|---|
| Mean | 31·7 | 28·8 | 60·5 | 0·92 |
| Range | 19·8–36·0 | 24·9–34·0 | 46·9–74·0 | 0·82–1·07 |

* Body-weight.

five patients; five patients had a diastolic blood-pressure of 90–100 mm. Hg, one of 110, and one of 140. Two of the normotensive group were on hypotensive treatment at the time. Several of the patients were overweight. The average weight for the men was 79·3 kg. and for the women 63·2 kg. The results of initial hæmatology are shown in table III and of volume studies in table IV. Eleven patients had a white-blood-cell count of over 10,000 per c.mm. and four of over 12,000 per c.mm. The erythrocyte sedimentation-rate was 3 or below in nineteen out of thirty patients. The platelet-count was over 400,000 per c.mm. in three patients and under 150,000 per c.mm. in four patients. The leucocyte-alkaline-phosphatase score was measured in ten patients (normal 15–120%). It was below 15 in three patients and never above 120.

Plasma-uric-acid was measured in seventeen patients. The average value was 7·1 mg. per 100 ml. It was over 8·3 mg. per 100 ml. in one patient only, apart from the five with clinical gout (three of whom were on allopurinol).

### *Follow-up*

We attempted to follow-up all twenty-seven patients who presented before June, 1973. The period of follow-up varied from 6 months to 12 years (mean 4 years). Three patients were lost to follow-up and one private patient was not recalled. Thus twenty-three patients were studied. Of these, one had developed polycythæmia rubra vera (R.C.V. 45·5 ml. per kg.) and had been treated with venesections at another hospital. Five patients no longer had a P.C.V. above 50%. Of these, two had experienced no change in symptoms; one had improved on diazepam, one was well, and one had had a myocardial infarction and pulmonary embolus and had retired because of disability. The plasma volume was measured in three of these patients; it had decreased in two and remained the same in one. Six patients were known to have died (mean survival 15 months after study) from the following causes: sudden death (2); myocardial infarction (1); cerebral thrombosis (1); glioma (parietal) (1); unknown cause (1). Only one of these had previously been hypertensive.

At follow-up the remaining eleven patients still

TABLE V—HÆMATOLOGICAL RESULTS ON 16 SURVIVING PATIENTS AT FOLLOW-UP*

| — | Hæmoglobin (g. per 100 ml.) | P.C.V.% | Plasma volume (ml./kg.†) | R.C.V. (ml./kg.)† | Whole-blood volume (ml./kg.†) |
|---|---|---|---|---|---|
| Mean | 17·4 | 52·1 | 30·8 | 31 | 59·8 |
| Range | 13·5–19·5 | 42·4–57·5 | 26–37·5 | 24·4–38·2 | 52·4–70·4 |

* Mean 4 years after initial study.
† Body-weight.

fulfilled the initial criteria. Mild hypertension had developed in two. One patient had had two myocardial infarctions and one had survived occlusion of the superior mesenteric artery, which had been treated by bowel resection. Only one described himself as well. One patient had a slightly raised R.C.V. at first follow-up (38·2 ml. per kg. body-weight). However, two subsequent measurements were normal. The follow-up results for these patients are summarised in table V.

The patient in whom true polycythæmia developed was omitted from table V. She was the only patient who received specific treatment.

The expected number of deaths was calculated for the twenty-three patients followed up. A man-years table was constructed (on the age, sex, and year of follow-up, corrected to the nearest month) and multiplied by the expected death-rates as published by the Registrar General. The expected number of deaths in the total follow-up period for males was 0·89 and for the females 0·19. Therefore, only 1·08 deaths would have been expected, and 6 were observed. This is a highly significant excess of deaths in our group of patients with pseudopolycythæmia ($P=0·015$).

## Discussion

The presenting features of our patients agree well with those described by others. Headache, dizziness, angina, and a thrombotic tendency are all manifestations of hyperviscosity.[11] Many of these symptoms are commonly found in anxious patients and this makes diagnosis difficult. In nine of our thirty-five patients diastolic blood-pressure was above 90 mm. Hg—this is a lower frequency of hypertension than that found by others in similar patients.

Previous attempts at follow-up have been incomplete. Russell and Conley[6] suggested that the disease was benign. They followed up ten out of twenty-five patients; eight were well after 10 years and two were well after 5 years. Their hæmatological status remained the same. Lawrence and Berlin[5] followed five out of eighteen patients for a short time and reported no hæmatological changes. Hall,[2] describing a slightly different group of patients, some with normal plasma volumes, followed twelve out of twenty patients. In five, repeat volume estimations showed no change in status. He found that the P.C.V. sometimes fell temporarily during hospital admission. Four of his patients were known to have died, and several of his patients were treated with venesection. Kaung and Peterson[3] found that one patient remained hæmatologically unchanged after 3½ years, but two out of ten died of myocardial infarction and a further three had thromboembolic complications.

Our series is the first aimed at determining the natural history of pseudopolycythæmia. Many of our patients had only a slightly increased P.C.V. and the mean value (53·58%) is below that of many other series. Despite this, morbidity was high, and the death-rate was six times greater than expected. True polycythæmia rubra vera developed in 1 of our patients who had initially fulfilled our criteria. Whether this represents an error in volume measurements or the concurrence of two conditions is not clear. Hæmatological remission had occurred in five out of twenty-three at the time of follow-up. However, three still had their initial symptoms and reduced plasma volume, and may well have had only a temporary reduction in their P.C.V.

Nine of our patients were taking thiazide diuretics when initially studied. These are well known to reduce the plasma volume for about a week, but several studies[12–14] demonstrated that the plasma volume returns to normal after about a month. The hypotensive effect is retained. In our series one patient was started on bendrofluazide between his initial and final studies; his plasma volume increased slightly after starting the diuretic. Another patient was receiving cyclopenthiazide when first studied; this had been stopped well before his final measurements. His plasma volume was lower on his final measurement than on his first measurement. The thiazides, therefore, seem unlikely to have influenced the initial results. Blood-viscosity increases exponentially as P.C.V. rises above 50% (at high shear-rates and without red blood-cell aggregations blood-viscosity is a direct function of the hæmatocrit).[15] Our patients who have raised P.C.V.s are likely therefore to have the same viscosity-related symptoms and complications as patients with true polycythæmia. This seems to be the case in our study, and the mortality seems to be of the same order. We found no evidence of leukæmia or marrow aplasia, which are myeloproliferative features of true polycythæmia.

Prankerd[16] suggested that the low plasma volume was due to a low setting of the volume receptors, and that this might be due to an inadequate aldosterone response. He found that after temporary expansion of the plasma volume it soon returned to its pre-existing level. All but one of his patients demonstrated a significant reduction in aldosterone excretion, and in two a low-salt diet failed to increase their aldosterone excretion. Aldosterone infusion in one patient returned the plasma volume temporarily to normal.

Marrow kinetic studies[2,5] have been normal, as expected. Brown et al.[8] did not demonstrate any difference between a group of patients with "spurious" polycythæmia and a control group. However, morbidity and cardiovascular disease were common in their control group, which was selected within a polycythæmia clinic!

Other possible ætiological factors in this condition include smoking, alcohol, and stress. Smoking may be a factor and most of our patients were heavy smokers. There seems little correlation with alcohol consumption and stress is too widespread to be evaluated in this series.

The argument whether pseudopolycythæmia is a single disease or just one end of a normal spectrum is academic, since patients have symptoms which often produce disability and increased mortality. They would therefore be a suitable group for a prospective trial of treatment. Several patients have been treated randomly by venesection in other studies without obvious benefit. A trial of fludrocortisone would be the most logical step.

We thank Lynn Aston for starting to collect the data, Ian Robertson for working out the mortality statistics, and the patients for their cooperation.

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# MEASUREMENT OF LIVER-CADMIUM CONCENTRATIONS IN PATIENTS AND INDUSTRIAL WORKERS BY NEUTRON-ACTIVATION ANALYSIS

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***Summary*** A new, rapid, non-invasive technique for measuring tissue-cadmium concentrations in patients and industrial workers has been designed and developed with a view to studying the cadmium content of the liver. The method utilises the principle of neutron-activation analysis whereby the specific changes produced by the interaction of nuclei and neutrons are analysed. Liver-cadmium content has been studied in cadavers and in four men with known or suspected cadmium poisoning. The patients all showed very high liver-cadmium levels of between 35 and 200 p.p.m. compared with under 1·0 p.p.m. in non-exposed subjects. The dose of radiation used in clinical studies was 0·4–1·0 rem and the detection limit of cadmium was 1·0 p.p.m.

## Introduction

CADMIUM is an important metal with widespread applications in industry, notably in metallurgy, nuclear and electrical engineering, and the paint and pigment industry. Cadmium is toxic and represents a health hazard to man of as yet undefined proportions. As the industrial applications of cadmium have been extended, so too has contamination of the environment, and traces of cadmium are found in food, water, and air.[1–4]

When absorbed through the lungs or gastrointestinal tract, cadmium becomes very strongly bound to a carrier protein, metallothionine, and is selectively concentrated in the liver and kidneys.[5] The biological half-life of cadmium is measured in decades, so that even intermittent low-level exposure to the element leads to a continuous accumulation of the metal in the body tissues throughout life.[6] Toxicological interest in this metal[7–10] has been hampered by difficulties in measuring cadmium in low concentrations. Moreover, blood and urine levels seem to bear little relationship to toxic effects.[11,12] Studies of tissue levels seem more promising, but so far only post-mortem data have been published and human tissue levels have never been studied in vivo.

In 1972 we suggested that neutron-activation analysis (N.A.A.) might be used to study cadmium concentration in vivo,[13] and we have since developed a system for clinical use.[14]

## Methods

*N.A.A.*

Any material irradiated with neutrons undergoes a series of complex nuclear interactions which lead to emission of gamma-rays specific for the elements of the material. Certain elements lend themselves to detection by this method because of their unique nuclear properties. Since 1964 various centres have been measuring selected elements in living man in this way.[15–20]

One of the stable isotopes of cadmium ($^{113}Cd$) has a high affinity for neutron capture (which is why the metal is used to make control rods and shields for nuclear reactors). This affinity is several orders of magnitude greater than that of the common body elements. When $^{113}Cd$ captures a neutron, the stable isotope $^{114}Cd$ is formed, and the excess energy that results from "binding" the extra neutron is discharged as gamma-rays, the most intense of which is a photon with an energy of 559 keV. The whole reaction takes place in $10^{-16}$ seconds (known as "prompt"), and "activation" and "analysis" must be done together.

We have developed a system to deliver a beam of neutrons with on-line analysis of the gamma-radiation produced in the region of the specific cadmium photopeak. The operation sounds formidable but the technique is little more complex and much less alarming to patients than most investigations in nuclear medicine or radiology.

*Method*

Studies are done in a special laboratory adjacent to the Nuffield cyclotron in the university physics department. The method is a greatly modified version of the prompt-gamma analysis system used to measure whole-body nitrogen in man.[21,22] Protons are accelerated in the 152 cm. cyclotron to an energy of 10 MeV to impinge on a beryllium target thereby producing "fast" (average energy=2·6 MeV) neutrons. The neutron fluence is collimated to produce a narrow vertical beam 14 cm. in diameter.

The subject lies on a canvas bed (fig. 1) in a semi-prone position so that the anatomical position of the liver (as determined by surface markings) is directly over the centre of the neutron beam. We decided to study liver