It is certain that similar changes have been taking place in other countries during the period under examination. For instance, in Toronto, Canada, typical 6-year-old elementary-school children were 2 in. taller in 1939 than in 1892, 9-year-old children were 3 in. taller, and 13-year-old girls and 14-year-old boys were about 3.2 in. taller. Half of the observed differences have taken place since 1923 (Meredith and Meredith, 1944).

It is clear that the remarkable changes which have occurred in the mean statures and weights of children over the last seventy years are part of a long-term trend in the growth of children. The changes defined not only imply the need of up-to-date height and weight standards for paediatric practice, and the making of corresponding adjustments in the size and relative dimensions of children's clothing and school equipment, but they make it apparent that anthropometric measurements can yield information of great interest.

Summary

Anthropometric measurements of children aged from 5 to 13 years, made between 1880 and 1947, have been standardized and examined.

The average stature and weight have increased by from 2.5 to 3.5 in. and from 4 to 11 lb. respectively over this period, the increases being greatest in the older children.

The increases found are greater than can be accounted for by systematic and random sampling errors, and indicate that, on the average, there has been an acceleration of 18 months' growth. Thus an average 6-year-old child is now of much the same size as one of 7.5 years in 1880.

The rate of increase in mean stature and weight is not constant over the years. It begins slowly, and is first evident in the lower-income group and in the 5- to 7-year-old children in the upper- and middle-income groups. The rate of increase was greatest in the inter-war years, when it was shown by all groups. The upward trend was interrupted during both the first and the second world wars. The increase in the mean measurements has been greatest in the lower-income group, so that the difference which existed in 1880 between the average measurements of children in this group and the middle-income group no longer exists. The differences in stature and weight between average children in the upper- and lower-income groups were 4 in. and 7 lb. in the late nineteenth century and 2 in. and 2 lb. in 1947.

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A METHOD FOR THE RAPID ESTIMATION OF THE PERCENTAGE OXYGEN SATURATION AND OXYGEN CONTENT OF BLOOD

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The manometric method of Van Slyke and Neill (1924) is the standard procedure for the estimation of blood oxygen content and capacity. This manometric analysis is time-consuming and makes heavy demands on laboratory workers. Further, since the reliability of results diminishes with fatigue, the number of blood samples that can be accurately analysed on any single occasion is limited. In this paper a spectrophotometric method of estimating the percentage oxygen saturation, the oxygen capacity, and the oxygen content of blood is described. It employs relatively simple apparatus, allows the rapid analysis of a large number of blood samples, and has been found most valuable in the study of the cardiac output and the investigation of abnormal shunts in the heart and great vessels.

Photometric methods of estimating the haemoglobin content and oxygen saturation of blood have been in use in laboratories for some 20 years; Hall (1934) and various German workers, notably Kramer (1934), described methods which were not, however, suitable for routine use in clinical investigations.

In 1936 Drabkin and Austin described a new type of spectroscopic cell or cuvette of 0.007 cm. depth which enabled them to study haemolysed undiluted blood under anaerobic conditions. Valuable fundamental information was obtained, but the method was not suited to routine estimations on multiple samples. Most of the subsequent methods are based on the data obtained by these workers, who showed that Beer's law (see below) was valid for haemoglobin solutions. These workers (Drabkin and Austin, 1936; Hickham and Frayser, 1949; Nahas, 1951) employ cuvettes and precision spectrophotometers of the Beckman type, and readings are taken at two wave-lengths to increase accuracy.

The method here described is a modification of that devised by Gatman (1952).

Principle of the Method

The method is based on the measurement of the optical density of haemoglobin solutions. The optical density D of any medium is defined by Lambert's law as follows:

$$D = \log_{10} \frac{I_0}{I}$$

where I_0 is the intensity of the incident light and I the intensity after transmission by the medium considered.

The optical density of any medium depends on the length of the light pathway through that medium and upon its absorption characteristics—i.e. :

$$D = E \cdot d$$

where d is the path-length and E is the extinction coefficient, which is constant for a given medium, wave-length, and wave-band width.

Beer studied the optical properties of solutions, and showed that the optical density of a light-absorbing solution was directly proportional to its concentration. In dealing with solutions, therefore, Lambert's law is modified as follows :

$$D = E \cdot c \cdot d$$

where c is the concentration of the solution. Thus the concentration of a single pigment can be easily measured by determination of the optical density of the solution.

The determination of percentage saturation of haemoglobin, however, involves the measurement of the relative concentration of two separate pigments (haemoglobin and oxyhaemoglobin) each with its own characteristic extinction coefficient. The optical density of a solution of blood will be a function of the relative amounts of the two pigments present. If the optical density of aliquots of the same solution in the same tube is determined, in which all pigment has been respectively reduced and oxygenated, then the percentage saturation is easily obtained from the following proportionality equation,

$$\text{Percentage saturation} = \frac{D_{Hb} - D_{mixed}}{D_{Hb} - D_{HbO_2}}$$

Thus the three measurements necessary for the determination are as follows : (1) the optical density of the original anaerobic blood solution, D_{mixed} ; (2) the optical density of the blood solution reduced, D_{Hb} ; (3) the optical density of the blood solution oxygenated, D_{HbO_2} .

It will be noted that, under the constant conditions specified, the optical properties of the tube need not be considered in the determination of percentage saturation.

The optical densities are measured with light of a wave-length of $630 \text{ m}\mu$. The absorption curves for haemoglobin and reduced haemoglobin show that the rate of change of optical density with wave-length is small in this region. This minimizes any error caused by slight changes in the calibration of the spectrophotometer.

Measurements of total haemoglobin content, and thus of the oxygen capacity of blood, are made at a wave-length of $540 \text{ m}\mu$; for here, with a wave-band of about $30 \text{ m}\mu$ as used in this method, the optical densities of haemoglobin and reduced haemoglobin are equal. If a known constant dilution of blood is made and the optical density is measured, the haemoglobin content may be found from the linear relationship obtained by previous direct calibration against estimations of oxygen capacity made by the Van Slyke and Neill method.

Most of the optical methods to determine the percentage saturation of blood *in vitro* described previously require the Beckman spectrophotometer, a precision instrument which is not often available in clinical laboratories. In the method here described an instrument which is found in most biochemical laboratories is used, and satisfactory results are obtained with considerably diluted blood solutions. This allows the use of sample tubes made of inexpensive glass tubing with a relatively long light path, and obviates the need for special cuvettes, which are in any case unsuited for rapid estimations on large numbers of blood samples.

Details of the Method

The following apparatus and solutions are required :

1. A unicam spectrophotometer (model S.P. 350), which is modified by inserting a half-inch-square mask on the light condenser and by narrowing the collimator slit. This reduces the wave-band width to about $30\text{--}40 \text{ m}\mu$, but there is some sacrifice of light intensity. It is thought probable

that satisfactory results would be obtained on the unmodified instrument, but this has not yet been demonstrated. A holder for tubes of 8 mm. diameter, on which an alignment mark is engraved, replaces the usual holder. The spectrophotometer is switched on half an hour before readings are taken. It is advisable to check the wave-length calibration on each occasion with a carefully cleaned didymium glass filter.

2. Sample tubes for the spectrophotometer. These are made from heat-resisting glass tubing of 6 mm. bore and 8 mm. external diameter. The use of special optical glass or precision tubing is unnecessary. Each tube is 11 cm. long, is numbered, and has a longitudinal line inscribed on its upper end with a diamond. Alignment of the line with the mark on the spectrophotometer holder ensures that an identical optical pathway is used each time a reading is taken with a given tube. After each experiment the tubes are washed with tap water, rinsed with distilled water, and dried by heat.

3. Boiling-tubes $\frac{1}{2}$ in. (1.25 cm.) diameter by $4\frac{1}{2}$ in. (11.4 cm.). These are numbered and provided with lips to facilitate pouring.

4. Numbered racks to hold 30 sample tubes and 15 boiling-tubes.

5. Angled needles used for diluting and handling the blood. These are made from steel tubing 1 mm. bore and 13 cm. long soldered to a needle hub. In each needle there is a right-angle bend 1 cm. from the needle hub. It is important that the needle tip should reach the bottom both of the sample tubes and the flask containing the diluting solution.

6. Gas-free solution of sodium carbonate and saponin, which is prepared freshly for each experiment. Two hundred ml. of 0.1% sodium carbonate solution is boiled for 15–20 minutes in a conical flask, allowance for evaporation being made by the previous addition of distilled water to the solution. Immediately after boiling, a few millilitres of the solution are decanted to dissolve 1 g. of pure white saponin. When the saponin* has dissolved, the resulting solution is poured back down the side of the conical flask into the boiled solution. A layer of liquid paraffin is poured over the surface of the solution, which is then allowed to cool. It must not be shaken, and can be used during the next 24 hours. It is convenient to keep the flask tilted in a small wooden holder.

7. Cold saturated sodium hydrosulphite solution, which is made up freshly for each day's work.

8. Sample tubes, 1 cm. by 9 cm., as supplied with the spectrophotometer, for the estimation of blood oxygen capacity.

Estimation of Percentage Oxygen Saturation of Blood

Blood samples of 4 ml. are drawn into lightly oiled 10-ml. all-glass syringes, the dead space of which is filled with heparin or dextran sulphate (5,000 units per ml.). At the earliest possible moment after sampling, $\frac{1}{4}\text{--}\frac{1}{2}$ ml. of mercury is drawn into the syringe, which is sealed with a hub cap and vigorously shaken to ensure even distribution of the anticoagulant. While awaiting analysis the syringe is placed on a rotating cone so that sedimentation of red cells does not occur. For analysis the syringe hub is removed and an angled needle is fitted firmly to the syringe. Blood is expelled through the needle until the appropriate amount is left in the syringe, allowance being made for the mercury present. The carbonate-saponin solution is

*Pure white saponin is difficult to obtain, and the usual pigmented commercial material has not proved satisfactory. Preliminary experiments show that 0.5 ml. of a concentrated solution of the synthetic detergent "lissapol" can be used as a satisfactory substitute for the saponin. When lissapol is added to boiled distilled water the mixture becomes turbid, but the turbidity disappears on cooling.

then drawn into the syringe, care being taken to avoid drawing up globules of paraffin. The extent of dilution, which need not be of great accuracy, is as follows :

Haemoglobin Content of Blood, g. 100 ml. (Approx.)	Oxygen Capacity of Blood, Vols. % Oxygen (Approx.)	Ml. of Blood Diluted with Carbonate-Saponin Solution to 10 ml.
7.5	10	3
11	15	2.5
15	20	2
19	25	1.5
22.5	30	1

After dilution and shaking, the angled needle is detached and the syringe laid on the bench for at least five minutes to allow haemolysis of the blood, fifteen syringes of blood being treated in this manner at a time. When haemolysis is complete a clean angled needle is attached to each syringe. A few drops of the clear haemolysed solution are expelled through the needle and discarded, the tip of the needle is inserted to the bottom of a sampling tube, and 2.5 ml. of the solution is slowly injected, the needle tip being withdrawn as this is done so that it lies always just below the surface, undue turbulence being thereby avoided. The upper fluid acts as an efficient barrier, preventing oxygenation of the solution in the lower half of the tube, through which light is transmitted. It is not necessary to cover the surface with paraffin. Two tubes are filled from each syringe, and the remaining solution is transferred to a lipped boiling-tube to await oxygenation by the passage of a stream of oxygen bubbles for a period of half a minute.

When a rack of tubes has been filled the optical density of the "mixed solutions" is determined with reasonable dispatch. Before any series of readings the galvanometer is adjusted to indicate zero transmission with no light incident on the photocell, and then the intensity of light is adjusted to give 100% transmission (zero optical density) when there is no tube in the holder. The latter reading is adjusted, if necessary, each time a tube is withdrawn from the holder. Each sample tube is polished with a dry cloth and is placed in the holder and rotated until its engraved line is in alignment with the mark on the holder before the reading is taken on the logarithmic scale. It is convenient to take the "mixed" readings of all the tubes in the rack and then to reduce all the solutions. The contents of each tube are drawn into a Pasteur pipette which already contains about 0.1 ml. of the saturated solution of sodium hydrosulphite. The mixture is drawn up and down several times to effect complete mixing and to allow complete reduction of the haemoglobin, the most efficient method being to suck solution from the bottom of the tube and then pour it back on to the top of any remaining solution. Although care must be taken not to carry solution from one tube to another, there is no need to clean the pipette between each reduction. Each sample tube is again polished and placed in the holder in correct alignment and the optical density of the reduced solution is then read on the logarithmic scale. The reduced solution is now sucked out and discarded and the tubes are cleaned and dried with pledgets of cotton-wool on a burred metal rod. A small rat-tail file is useful. When the tubes are clean the oxygenated haemolysed solution is transferred to them from the corresponding boiling-tubes.

Most of these procedures are carried out with the tubes in the rack, as this reduces the amount of handling and the need for polishing. The optical densities of the oxygenated solutions are then read on the logarithmic scale.

From these three readings the percentage oxygen saturation is estimated and the mean of the results from each pair of tubes is taken, these results seldom differing by more than 1%. Two observers can, by this method, make duplicate estimations of the percentage oxygen saturation of 15 specimens of blood in one hour.

Occasionally small blood clots appear in the syringes despite the presence of the anticoagulants. This is often

due to failure or delay in shaking the syringe after the addition of the mercury. If the syringe is held with the nozzle elevated for a short time the clots fall to the bottom and the tubes can be filled with solution which is free from clots. In this way accurate results can be obtained despite considerable clotting.

If good results are to be obtained cleanliness of apparatus and careful handling of the blood and the haemolysed solutions are essential. The commonest error is for air bubbles to be drawn into the syringe either when the blood is sampled or when the blood is diluted with the carbonate-saponin solution, the latter causing more serious errors.

The method used by Gatman (1952) differs in two respects from the method described here. In his method readings are taken with the reduced and oxygenated specimens of each blood sample in a pair of tubes that have to be optically matched. In the present method all readings are taken in the same tube. Secondly, reduction of the solution is effected by the addition of powdered sodium hydrosulphite, which in our hands occasionally causes precipitation and coagulation of blood proteins.

Determination of the Oxygen Capacity of Blood

This determination is necessary in order to convert percentage saturation into oxygen content. The capacity can be determined by any of the recognized methods; the one we have used is as follows. Light of wave-length 540 m μ is used. Four ml. of 0.1% sodium carbonate is pipetted into a standard tube of 1 cm. diameter, which is placed in its holder in the spectrophotometer. Twenty c.mm. of blood is next drawn up into a pipette and, with the tube in place, the light intensity is adjusted to give a reading of zero optical density so that the tube containing carbonate solution acts as its own blank. The tube is now withdrawn and the blood is added, the micropipette being rinsed in the usual manner to ensure complete delivery. After mixing, the tube is returned to the holder and the optical density is determined on the logarithmic scale. If the previously prepared haemoglobin solution is transferred to a 1-cm. cell for the reading to be taken, a second cell containing sodium carbonate solution may act as a blank. This method is just as convenient, and probably

FIG. 1.—Relation between optical density and oxygen capacity.

gives more accurate results. It has been customary to take the mean of the readings of optical density of three dilutions provided the scatter between the greatest and smallest does not exceed 0.010. The haemoglobin content or oxygen capacity is then obtained from the calibration chart.

TABLE I.—*Relation Between Optical Density and Oxygen Capacity*

Optical Density (log I ₀)	Blood Oxygen Capacity vols. % (Manometric Method)
0.313	12.32
0.499	19.64
0.483	18.66
0.409	16.10
0.398	15.75
0.238	9.47
0.444	17.94
0.418	16.51
0.453	17.86
0.537	20.63
0.383	14.87
0.506	20.10
0.398	15.49
0.421	16.28
0.602	23.17
0.523	20.13
0.466	17.93
0.111	4.50
0.446	17.33
0.383	14.80
0.452	17.32
0.412	16.21
0.451	17.80
0.390	15.01
0.500	19.23

Table I and Fig. 1 show the data with which the spectrophotometer was calibrated. Measurements of oxygen capacity were determined by the standard Van Slyke manometric method. The blood specimens had been rotated in a tonometer for twenty minutes in equilibrium with air. Although the coefficient of linear correlation between the spectrophotometer readings and the Van Slyke determinations is very high (0.99), it became apparent during the work which is here reported that a spectrophotometer in which the wave-length of light is adjustable is not the ideal instrument for the determination of absolute optical density, as the calibration of the instrument tends to vary slightly from day to day. The fault is of little importance in measuring the percentage saturation of blood where the result depends on the relationship of three consecutive readings taken within a short time of each other, and where the slight changes in the wave-length of the light from day to day would in any case have an insignificant effect on the results.

Comparison of Results Obtained by Spectrophotometric and Standard Manometric Analyses

1. The Oxygen Content of Blood Samples

An experiment was planned in which three consecutive samples of blood were collected within a period of a minute and a half from either an arterial needle inserted in a brachial artery or from a cardiac catheter with its tip lying in the pulmonary artery. The percentage oxygen saturation of the first and third samples was determined by spectrophotometry. The total haemoglobin content and oxygen capacity of one of the specimens was also determined spectrophotometrically, and two measurements of the oxygen content of blood were thus obtained. The second blood sample was submitted to two analyses of oxygen content by the Van Slyke and Neill standard manometric method. On 48 occasions samples of blood were obtained in which the two spectrophotometric estimates checked to within 0.2 vol. % oxygen content and in which the two estimates made by the manometric method checked with each other to within 0.2 vol. %. As it was felt that for the purposes of comparison the estimation by each method should be reliable, the results were rejected in all instances when the duplicate oxygen content estimations by either method differed by more than 0.2 vol. %.

TABLE II.—*Comparison of Measurements of Blood Oxygen Content (48 Observations on 15 Subjects)*

Subject	No. of Blood Samples	Oxygen Content in vols. %	
		Spectrophotometric	Manometric
A.118	1	12.76	13.39
	2	18.20	18.50
A.119	1	18.33	18.27
	2	18.85	18.66
A.120	1	17.78	17.65
	2	13.72	13.19
	3	17.84	17.31
	4	13.61	12.63
A.121	3	11.90	11.03
	4	18.06	17.10
	5	12.03	11.19
A.122	2	14.59	14.73
	3	11.31	11.21
	4	14.69	14.77
	5	11.14	10.87
A.123	1	15.29	15.73
	2	15.34	15.57
	3	16.35	16.90
A.124	2	15.36	15.25
	4	15.58	15.28
A.125	1	13.50	12.01
	2	17.42	16.42
	3	13.27	12.23
	4	17.53	16.21
A.126	2	16.96	16.52
	3	13.44	12.88
A.127	3	11.17	11.23
	4	18.66	18.33
A.128	1	14.55	13.96
	2	22.01	20.95
	3	14.48	13.82
	4	22.08	20.84
A.130	1	13.04	12.98
	2	19.00	19.12
	3	12.94	12.51
	4	19.10	18.89
A.132	1	14.53	14.24
	2	20.15	19.64
	3	14.61	13.72
	4	19.98	19.11
A.133	1	9.59	9.37
	2	15.84	15.78
	3	9.55	9.25
	4	15.99	15.95
A.134	1	14.71	14.45
	2	19.28	19.34
	3	13.65	13.69
	4	19.44	19.66

In Table II the mean of the duplicate estimates of oxygen content made by spectrophotometry is compared with the mean of the duplicate estimates made by the manometric method on the blood samples obtained on these 48 occasions. The results are plotted in Fig. 2.

There is a close relationship between the results obtained by the two methods, and the coefficient of linear correlation is $r=0.99$. More detailed analysis, however, reveals signs of heterogeneity of the data. It is found that the two methods relate excellently in estimating the oxygen content of samples of blood from a single individual, but that the location of the regression line changes slightly from subject to subject. It is believed that for the most part this change in the location of the regression line is due to errors in the estimation of the blood oxygen capacity, which in part are due to the day-to-day variation in the calibration of wave-length of the spectrophotometer. Variable amounts of carboxyhaemoglobin and methaemoglobin in the blood may also cause errors (Roughton *et al.*, 1944). It is also possible that the small samples of blood taken for spectrophotometric analysis are not always representative of the larger sample which is taken for manometric determination of oxygen capacity.

2. Estimation of the Arteriovenous Oxygen Content Difference in the Measurements of Cardiac Output

An experiment was designed in which two determinations of the cardiac output were made in 14 subjects, the arteriovenous oxygen content difference being determined for each estimation of cardiac output by both the manometric and the spectrophotometric method. The two measurements

FIG. 2.—Comparison of measurements of blood oxygen content.

of cardiac output in each subject were not meant to be comparable with each other, as these subjects were not in the steady state. For each determination of cardiac output the expired air was collected for a three-minute period in a Tissot spirometer; while the gas was being collected three samples of arterial blood were collected and three samples of mixed venous blood were drawn from the pulmonary artery. The second arterial and venous samples were analysed in duplicate by the Van Slyke and Neill manometric method and the arteriovenous oxygen content difference was determined in vols. % of oxygen content. The percentage saturation of the first and third samples of arterial and venous blood was determined spectrophotometrically and the arteriovenous oxygen difference was obtained in terms of the percentage saturation. An estimate of the oxygen capacity was made by the spectrophotometer on one sample of the blood so that the arteriovenous difference of both samples could be expressed in terms of oxygen content in vols. %.

TABLE III.—Comparison of Measurements of Arteriovenous Oxygen Content Differences

Subject	Observation No.	Spectrophotometric Mean of two Measurements (vols. Oxygen %)	Manometric Mean of two Measurements (vols. Oxygen %)
A.118	{ I II	5.43 5.26	5.11 5.94
A.120	{ I II	4.06 4.22	4.46 4.68
A.121	{ I II	5.85 6.03	6.13 5.91
A.122	{ I II	3.28 3.55	3.52 3.90
A.124	{ I II	2.19 3.06	2.33 2.89
A.125	{ I II	3.91 4.26	4.41 3.98
A.126	{ I II	3.33 3.48	3.41 3.52
A.127	{ I II	7.80 7.49	7.80 7.10
A.128	{ I II	7.51 7.60	6.99 7.02
A.130	{ I II	5.96 6.16	6.14 6.38
A.132	{ I II	5.62 5.46	5.40 5.39
A.133	{ I II	6.25 6.44	6.41 6.70
A.134	{ I II	4.57 5.81	4.89 5.97

A.119 rejected, see text.

A.123, A.129, and A.131 were investigated for congenital heart disease: measurements of cardiac output were not made.

Fourteen subjects were catheterized in sequence, and blood and gas samples were obtained successfully in all cases. One subject (A.119) has been omitted from the series, as manometric determinations were not obtained owing to breakage of apparatus.

The measurements of arteriovenous oxygen content difference determined by the two methods in the thirteen remaining subjects are given in Table III and are plotted in Fig. 3. The relationship between the measurements made by the two methods is good and is consistent from subject to subject. The coefficient of linear correlation is $r=0.98$. The

FIG. 3.—Arteriovenous oxygen content difference measured by the two methods.

regression line is given by the formula: manometric reading = $0.527 + (0.912 \times \text{spectroscopic reading})$. The regression coefficient 0.912 has a standard error of 0.038 and therefore differs significantly from unity. In practice the slight modification of the result obtained by use of the regression equation is of no practical importance.

Discussion

The results reported in this paper were obtained in the first few weeks after the development of the spectroscopic technique of blood analysis in this laboratory. Comparison with manometric technique was essential at this early stage, as the reliability of the method had to be determined before it could be adopted routinely for more fundamental research. There is little doubt that if the work were to be repeated at present after the method has been in use for several months, the results would be even more satisfactory. The method has already proved itself invaluable for work that demands analysis of the oxygen content or percentage saturation of large numbers of blood samples. It is believed that further improvement in the determination of blood oxygen capacity will be obtained when a constant wave-length photometer using standard filters is employed.

Summary

A rapid spectrophotometric method of estimating percentage oxygen saturation of blood and blood oxygen content is described. The apparatus required

is simple and easily available. Two observers using the method can make duplicate estimations of the percentage oxygen saturation on 15 specimens of blood in one hour.

A comparison between results obtained by spectrophotometric analysis and by standard manometric blood-gas analysis is reported in detail.

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THROMBOPHLEBITIS MIGRANS AND CARCINOMA OF BODY AND TAIL OF PANCREAS

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The association between thrombophlebitis migrans and carcinoma has long been known. In 1877 Trousseau gave an excellent clinical description of the recurrent painful venous thromboses affecting the arms and legs which he regarded as an important sign of carcinoma. A remarkable feature has been the frequency with which thrombophlebitis migrans is associated with carcinoma of the pancreas, particularly of the body and tail. Thoenes (1932) noted this association in three cases, and further examples were recorded by Umlauf (1933), Thomson (1938), Kenney (1943), and Jennings and Russell (1948). Sproul (1938) made a careful analysis of 4,258 consecutive necropsies and found multiple venous thromboses in 5 out of 16 cases of carcinoma of the body or tail of the pancreas and in only 3 out of 31 cases of carcinoma of the head of that organ. In addition 2 out of 81 patients with carcinoma of the lung and 2 out of 147 with carcinoma of the stomach also had multiple venous thromboses. Sproul demonstrated that in these cases there was no invasion of the veins by neoplasm nor direct compression by tumour.

By 1949 Edwards was able to analyse 29 cases of thrombophlebitis migrans associated with carcinoma—

23 from the literature and 6 of his own. The site of the primary growth was in the pancreas in 16, the stomach in 4, the lung in 4, the gall-bladder in 2, and undetermined in 3. A further 8 cases were added to the literature by Smith and Albright (1952), who studied the necropsy records of 37 cases of carcinoma of the body and tail of the pancreas. The degree of preponderance of carcinoma of the body or tail of the pancreas compared with carcinoma in other sites cannot be determined from the figures available, because many workers have selected carcinoma of the pancreas for their reports. Only in Sproul's analysis has the relative infrequency of carcinoma of the body or tail of the pancreas, when compared, for instance, with carcinoma of the lung or stomach, been taken into account. The relatively frequent association of thrombophlebitis migrans with carcinoma of the body or tail of the pancreas thus becomes all the more significant.

We wish to report two further cases, drawing attention to the occurrence of arterial thrombi as well as venous thrombi and to the presence of thrombotic vegetations on the heart valves. One of our cases had a carcinoma of the tail of the pancreas, and in the other the primary growth was not found, but from the distribution of the secondary deposits it was probably also in the pancreas.

Case 1

A man aged 43 was admitted to the Manchester Royal Infirmary in December, 1951, with a six-months history of increasing weakness and recurrent attacks of thrombosis of the superficial veins of both legs and left arm. A course of anticoagulants had failed to prevent further attacks. More recently he had begun to lose weight, and shortly before admission he had some right-sided lower abdominal pain and vomiting.

On examination the patient was obviously seriously ill, with a normal temperature and a blood pressure of 170/100 mm. Hg. Thrombosed veins could be felt in both legs and the left arm. There was a persistent heavy albuminuria (10–20 g./litre). During his stay in hospital he developed a right femoral venous thrombosis and had two attacks of left-sided pleural pain. Four weeks after admission he suddenly developed a right hemiplegia and aphasia. He died three weeks later.

A blood count showed: red cells, 4,830,000 per c.mm.; haemoglobin, 14.2 g. per 100 ml.; white cells, 24,100 per c.mm., with 82% polymorphs. Microscopy and culture of the urine revealed some red cells, pus cells, cellular and granular casts, and a light growth of a coliform organism. Blood urea was 42 mg. per 100 ml., thymol turbidity 1.6 units per 100 ml., alkaline phosphatase (King-Armstrong) 28 units per 100 ml., serum albumin 3 g. per 100 ml., and serum globulin 2.9 g. per 100 ml. The blood sedimentation rate (Wintrobe) was 36 mm. in one hour. Sternal marrow examination showed slight myeloid hyperplasia with some increase of plasma cells. Intravenous and retrograde pyelograms showed no abnormality. X-ray examination of the lungs, skull, and pelvis was normal.

Necropsy

Naked-eye Examination.—The body was that of an emaciated man. *Venous system:* There were thrombi of varying ages in all the large and small veins of the right leg. The inferior vena cava was occluded by a thrombus to just below the entrance of the renal veins, but the latter were normal. *Heart:* On the lines of closure of the aortic cusps there were friable vegetations, the largest 1 cm. long, resembling those seen in subacute bacterial endocarditis. The underlying valve and the other valves appeared to be healthy. *Liver* (weight 1,570 g.): This contained many secondary carcinomatous deposits 2 to 15 mm. in diameter.

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