a block in protein synthesis, so that the amino-acids collect in the body fluids; these are excreted in excess in the urine, and cystine, owing to its insolubility, is deposited intracellularly.

Clinical Picture.—It is only possible for me to outline briefly the wide variations in clinical signs which may be produced. They have received detailed attention from McCune *et al.* (1943) and Bickel *et al.* (1952). The first evidence of the disease may appear in infancy, usually after the first six months of life, as an acute disorder with acidosis, dehydration, thirst, and polyuria, anorexia, vomiting, constipation, pyrexial bouts, and failure to thrive. In fact, it may not be clinically distinguishable from hyperchloraemic acidosis or hypercalcaemia, although in these diseases there is no amino-aciduria or glycosuria. In older children there will be dwarfism, and often bone deformities, vitamin-D refractory rickets, or pathological fractures. A quite characteristic but not constant sign is photophobia, which is caused by deposits of cystine crystals in the cornea, iris, and conjunctiva. This form of the disease must be clearly separated from the so-called "renal rickets" of chronic glomerular insufficiency, in which amino-aciduria, glycosuria, and cystine storage do not occur.

Chemical Picture.—Bickel *et al.* (1952) point out that no single chemical change is constantly found in cases of this disease. The typical findings in the urine, which is alkaline when passed, are albuminuria, excess amino-aciduria, glycosuria, and hyperphosphaturia. Several specimens may have to be tested by sensitive methods such as paper chromatography (Dent, 1946) before these features are revealed. Up to twenty amino-acids may be excreted in excess, especially proline, leucine, valine, lysine, serine, cystine, threonine, glutamine, and alanine. The typical blood changes are lowered plasma bicarbonate due to metabolic acidosis, low plasma phosphorus, and low serum potassium levels. The blood urea may rise in the course of the disease. As renal failure supervenes there may develop hyperphosphataemia and hypocalcaemia, when the blood chemistry comes to resemble that seen in "renal rickets" due to glomerular inadequacy.

Diagnosis.—The demonstration of cystine storage should be regarded as the final proof of Lignac-Fanconi disease. This may be achieved in various ways: (1) Crystalline deposits may be seen in the eye with the slit-lamp. They may be identified as cystine by x-ray diffraction photography of a conjunctival biopsy specimen. (2) Thick bone-marrow smears may be examined for cystine crystals after fixation in absolute alcohol and staining with a solution of 0.5 g. basic fuchsin in 100 ml. of 50% alcohol. Cystine is dissolved out of tissues by routine fixatives and stains. (3) Microscopical examination of a lymph node.

Prognosis.—In the acute infantile form of the disease death occurs from acidosis and hypopotaemia, often aggravated by infection. The older children die ultimately of chronic progressive renal failure.

Treatment.—Healing of the rickets can be achieved by massive doses of calciferol (50,000 to 600,000 units daily). Acidosis should be corrected by Shohl's solution. If there is a lowered serum potassium, some of the sodium citrate may be replaced by the potassium salt. Strict blood chemical control is necessary. We cannot yet talk in terms of cure, but life can be prolonged along these lines.

Conclusion

It has been possible for me to outline only a few of the new diseases which have been defined within recent years. There are quite a few others, such as galactosuria (Holzel *et al.*, 1952), neonatal diabetes mellitus (Wylie 1953), sucrosuria (Moncrieff and Wilkinson, 1954), toxoplasmosis (Hutchison, 1949), and agammaglobulinaemia (Hayles *et al.*, 1954), most of which have been less fully studied up to the present. They may serve to refute the suggestion, made at times, that there is little left for the astute investigator in the field of curative paediatrics.

REFERENCES

- Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., and Roos, A. (1946). *Medicine*, 25, 399.
 Andersen, D. H. (1938). *Amer. J. Dis. Child.*, 56, 344.
 — and Early, M. V. (1942). *Ibid.*, 63, 891.
 — and Hodges, R. G. (1946). *Ibid.*, 72, 62.
 Anderson, J., Dent, C. E., Harper, C., and Philpott, G. R. (1954). *Lancet*, 2, 720.
 Baines, G. H., Barclay, J. A., and Cooke, W. T. (1945). *Quart. J. Med.*, 14, 113.
 Bickel, H., Baar, H. S., Astley, R., Douglas, A. A., Finch, E., Harris, H., Harvey, C. C., Hickmans, E. M., Philpott, M. G., Smallwood, W. C., Smellie, J. M., and Teall, C. G. (1952). *Acta paediat. (Uppsala)*, 42, Suppl. 90.
 Bodian, M., Carter, C. O., and Norman, A. P. (1952). *Fibrocystic Disease of the Pancreas*. Heinemann, London.
 Butler, A. M., Wilson, J. L., and Farber, S. (1936). *J. Pediat.*, 8, 489.
 Creery, R. D. G. (1953). *Lancet*, 2, 17.
 — and Neill, D. W. (1954). *Ibid.*, 2, 110.
 Darling, R. C., di Sant' Agnese, P. A., Perera, G. A., and Andersen, D. H. (1953). *Amer. J. med. Sci.*, 225, 67.
 Dawson, I. M. P., Craig, W. S., and Perera, F. J. C. (1954). *Arch. Dis. Child.*, 29, 475.
 Dent, C. E. (1946). *Lancet*, 2, 637.
 Doxiadis, S. A. (1952). *Arch. Dis. Child.*, 27, 409.
 Ehrenpreis, Th. (1955). *Ibid.*, 30, 8.
 Emery, J. L. (1952). *Ibid.*, 27, 67.
 Fanconi, G. (1931). *Jb. Kinderheilk.*, 133, 257.
 — Girardet, P., Schlesinger, B., Butler, N., and Black, J. (1952). *Helv. paediat. Acta*, 7, 314.
 Farber, S. (1944). *Arch. Path. (Chicago)*, 37, 238.
 Ferguson, A. W., and McGowan, G. K. (1954). *Lancet*, 1, 1272.
 Hartmann, A. F. (1939). *Ann. intern. Med.*, 13, 940.
 Hayles, A. B., Stickler, G. B., and McKenzie, B. F. (1954). *Pediatrics*, 14, 449.
 Holzel, A., Komrower, G. H., and Wilson, V. K. (1952). *British Medical Journal*, 1, 194.
 Hutchison, J. H. (1949). *Arch. Dis. Child.*, 24, 303.
 — and MacDonald, A. M. (1951). *Acta paediat. (Uppsala)*, 40, 371.
 Latner, A. L., and Burnard, E. D. (1950). *Quart. J. Med.*, 19, 285.
 Lightwood, R. (1952). *Proc. roy. Soc. Med.*, 45, 401.
 — Payne, W. W., and Black, J. A. (1953). *Pediatrics*, 12, 628.
 Lignac, G. O. E. (1924). *Dtsch. Arch. klin. Med.*, 145, 139.
 Lowe, K. G., Henderson, J. L., Park, W. W., and McGreal, D. A. (1954). *Lancet*, 2, 101.
 McCune, D. J., Mason, H. H., and Clarke, H. T. (1943). *Amer. J. Dis. Child.*, 65, 81.
 Moncrieff, A., and Wilkinson, R. H. (1954). *Acta paediat. (Uppsala)*, 43, Suppl. 100, p. 495.
 Norman, A. P. (1954). In *Recent Advances in Paediatrics*, edited by D. Gairdner, p. 247. Churchill, London.
 Wylie, M. E. S. (1953). *Arch. Dis. Child.*, 28, 297.

ORDER AND DISORDER IN PULMONARY FUNCTION*

BY

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PULMONARY CIRCULATION

The fact that the pulmonary circulation and its regulation is vital to efficient respiration needs no emphasis. There are various avenues of approach to this circulation. It can be considered from the purely structural angle as a system of branching vessels discharging into a capillary network which drains into a converging venous system, or it can be regarded as a limbo into which blood vanishes from the right ventricle and from which it emerges purified in the left auricle, without any great interest being taken in the vicissitudes of its journey through the lungs. Up till comparatively recently such was the conventional attitude of many who devoted themselves to cardiology, an outlook which in its restriction was matched only by that of the chest physician, whose only reminder of the pulmonary (or bronchial) circulation was the not infrequent occurrence of haemoptyses. Another approach is to conceive of the pulmonary circulation as a series of dimensions and energy levels related to one another by physical laws. This is essentially the physiological approach, and one which is in the closest harmony with current attitudes in internal medicine. I make no apology for basing my

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analysis on Poiseuille's equation, knowing that almost every other modern reviewer of this or any other functional aspect of the circulatory system has performed likewise.

The Poiseuille Equation

Poiseuille's law is fundamental to flow in tubes, and expressed symbolically is:

$$\Delta P = \frac{8nF}{\pi r^4}$$

where P = the pressure differential; F = flow; r = the cross-sectional radius of the tube; and n = the viscosity of the fluid.

It is important always to remember, however, that this law is precisely applicable only to a rigid, non-branching tube of uniform bore under conditions of axial or laminar flow. Therefore the only thing that is certain about its use in haemodynamics is that it does not describe exactly what is happening. Nevertheless it provides a very convenient expression of the important factors governing pulmonary flow.

I think the first thing to note about this formula is that, whereas all other factors operate in their first power, the diameter of the cross-section operates in the *fourth* power. That is to say, if that diameter were to undergo a twofold change, then the other factors, either individually or by integration among them, would have to make a sixteenfold adaptation to maintain the original pressure level.

Before considering these factors in detail there are several broad structural and functional features of the pulmonary circulation which must be emphasized. The flow through this circuit is the output of the right ventricle and the input of the left auricle and therefore the output of the left ventricle. The only qualification to this is in respect of the blood which goes to the lungs through the bronchial arteries and drains into the pulmonary capillary bed and that portion of the coronary flow which drains into those Thebesian veins terminating in the left ventricle. Of course, in cardiac defects involving shunts which by-pass the lungs in either direction this generalization is quite invalid. The balance between systemic and pulmonary flow must clearly be extremely accurate. A discrepancy of 1 ml. per beat (an error of only about 1.5%) in the same direction maintained for only a quarter of an hour would result in something like one litre increase of blood volume in one circuit at the expense of the other—a general trend which would be incompatible with life.

Another limiting circumstance is that, unlike systemic capillaries, there is no call for any considerable transudation from the pulmonary capillaries. So long as there is a thin film of water on the alveolar walls no fluid need escape. Even that film of water represents only a trifling amount, evaporating little, as the air is probably saturated by the time it reaches the alveoli as the result of the ample secretion of water from the walls of the bronchial and bronchiolar mucosa. Therefore pulmonary capillary pressure must not, for any substantial interval, exceed the osmotic pressure of the plasma proteins—that is, about 25 mm. Hg. In fact, the normal lungs have a marked capacity to absorb water, hypotonic and normal saline, and other electrolyte solutions if they be introduced in a fine spray, often called loosely an "aerosol." An anatomical feature of importance is that the pulmonary capillaries constitute a virtually unsupported network in the alveolar walls.

This is quite unlike the systemic capillaries, which are surrounded by a connective-tissue network the intercellular interstices of which are filled with water, the whole providing the support of several mm. Hg of tissue tension.

It will at once become clear, when we examine the factors in the Poiseuille equation, that the greatest obstacle to its precise use is that it is virtually impossible to measure simultaneously a sufficient number of the factors in relation to the same part of the circulation to reach the sort of solution which would satisfy the physicist. For instance, the infinite variety of combinations of ΔP , r , and F which is to be found in the passage of water from Lake Erie to Lake Ontario is, I am sure, relatively no greater than the range of these variables found between pulmonary valve and left auricle.

Adaptations of the Fick Principle

It is now necessary to examine in some detail the various factors which comprise Poiseuille's equation. Although much patient work by Daly and his colleagues (1938) had amply demonstrated the value of such a physical analysis in the study of the pulmonary circulation in acute experiment in the dog, application of these principles to man was almost exclusively a matter of inference and analogy until it became possible to measure pulmonary blood flow and pressures in the pulmonary circuit in man. The key which has unlocked the door to a treasure-house of information has been the cardiac catheter, and all honour is due to Forssman (1929), who introduced through a cubital vein in his own arm a ureteric catheter and advanced it into the right auricle, then walked to the x-ray room to have its position verified. This fact received very little attention at the time, and its emulation and application to circulatory haemodynamics was delayed for more than 10 years, until the reports of cardiac output in man by Cournand and Ranges (1941) and McMichael and Sharpey-Schafer (1944). I well remember, on several occasions during the war, beguiling idle moments in remote places by discussing various problems of cardiac function and pulmonary blood flow. These always seemed to conclude with the refrain, "If we could only measure the pulmonary artery pressure." What a joy it was, late in 1943, to visit Professor McMichael at Hammersmith and to see a cardiac catheterization enabling withdrawal of samples of mixed venous blood and the measurement of mean pressures in the right auricle.

While to Forssman goes the credit of taking the decisive technical step, the fundamental concept was announced to the Würzburg Medical Society by Fick (1870), when he pointed out that if one could find out the amount of oxygen in the mixed venous blood entering, and, in the arterial blood, leaving, the lungs, then the difference was the amount taken up by the blood. This value, divided into the amount of oxygen absorbed by the lungs, would yield a measure of the pulmonary blood flow. Incidentally this communication was made to the same society which twenty-six years later was to hear Röntgen announce and demonstrate his first x-ray pictures.

It would make a fascinating study to trace all the ramifications of the Fick principle in its application by many ingenious adaptations not only to cardiac and pulmonary blood flow but to renal blood flow, hepatic blood flow, cerebral and coronary blood flow, etc. Many applications of the Fick principle had been made to measuring pulmonary blood flow prior to cardiac catheterization, notably the CO_2 method (Haldane) and the use of foreign gases of high solubility in blood, such as acetylene, nitrous oxide, and ethyl iodide, but none of these were entirely satisfactory. However, this is no place to review in detail the development of methods of measuring cardiac output. That has been done many times by those competent to do it.

The last few years have seen a steady improvement in the technique of cardiac catheterization, with a consequent

increase in the accuracy of results and widening scope of the information obtained. Like all scientific procedures, full value is obtainable only by close attention to detail in the perfection of the measuring devices, the control of extraneous variables, and the statistical analysis of results so as to define their limits of variability and their separation into those due to the inherent errors of the technical measurements and those due to the biological variations. It is only against such a background that the changes due to different levels of healthy activity and the changes caused by disease can be adequately studied.

Donald and his colleagues have done much to enable pulmonary blood flow to be measured at frequent intervals, both at rest and during exercise. This they (Wade *et al.*, 1953) have achieved by the frequent collection of small samples of mixed venous blood and expired air and by the development of the Gatman (1952) rapid spectrophotometric method of estimating blood oxygen. This latter development enables as many as 50 duplicate analyses to be made in about three hours. To make these measurements by the Haldane or the Van Slyke method would occupy a skilled operator 15 minutes for each estimation. Another important condition of success is frequent sampling of arterial blood and expired air throughout each investigation.

Advances in Pressure Recording

The whole subject of pressure recording has made great strides in the last few years. There are now available a variety of devices (or transducers as they are termed) which will convert the very small range over which a relatively rigid diaphragm moves rectilinearly in relation to pressure into an electrical current varying in the same simple relationship. Furthermore, these devices can be made of such a small size and such materials as to have so high a frequency response that they react without distortion to all the wave motions accessible to the cardiac catheter. Amplifying and recording devices have made similar advances, enabling direct writing recorders to draw curves of pressure waves in the heart and great vessels. In fact, the present level of technical achievement in measuring the pressure-volume characteristics of the heart and pulmonary circulation, and the attendant laboratory organization, illustrates well the application to clinical science of principles of industrial efficiency. It is not enough to be able to make certain measurements. Simultaneous measurements of several variables must be made in sufficiently large number to gain insight into the sort of changes that occur in the pulmonary circuit. This is particularly true when it is realized that clinical physiology and clinical medicine in general are gaining emancipation from the stultifying effect of the "basal state" concept. The principle of "testing under load" has invaded almost every field, in particular the cardio-respiratory; this, naturally, has posed many technical problems. As we shall see, the measurement of pulmonary haemodynamics during exercise is a highly illuminating procedure.

Knowledge of the pressures in the pulmonary artery of normal people is not as yet based on any large series. Cournand (1950) and Dexter *et al.* (1950), in a very limited number of normals, have found them of the order of 22 systolic, 8 diastolic, and 14 mean in mm. Hg above a zero level of 10 cm. above the dorsal plane in the horizontal patient.

In considering such data care must be taken to note the zero level. The sternal angle, a plane 5 cm. dorsal to the sternal angle and 10 cm. above the dorsal plane are all used by different observers and even by the same observers at different times. Fortunately, the practice is growing of giving not only the zero references but the antero-posterior diameter of the chest, so that accurate conversions can readily be affected. The Tower of Babel has many subsidiary departments dealing with such variables as this, as well as screw pitches, electrical voltages and frequencies, electric plug dimensions, units of measurement, etc.

Recent Exercise Tests

A recent study by Donald *et al.* (1955) of 16 adult volunteers revealed a mean pulmonary artery pressure of 16.5 mm. Hg at rest. Their 16 subjects were exercised on a horizontal bicycle ergometer in groups of four, each doing work resulting, during the last three of five minutes' exercise, in an oxygen uptake of 295, 397, 564, and 1,047 ml./min./square m. of body surface respectively. They found that the mean PPA rose slightly from 3 to 9 mm. Hg in those performing the first three grades of work, while those doing the heaviest work had rises in pressure of from 5 to 33 mm. Hg; the greatest figure was seen in the oldest subject (49), in whom no abnormality could be elicited. This isolated observation, however, does indicate how desirable it would be to know the pulmonary artery pressure reaction to exercise in relation to age, especially in the light of the already known diminution of the maximum diffusion capacity in later life. At the same time it must be noted that another subject aged 28 performed the same work with a cardiac output of only 1 litre/min./square m. less than the older man (11 and 10 respectively), and yet his pulmonary artery mean pressure rose from only 19 to 24 mm. Hg. Much exploration in this field is obviously desirable. One of the most remarkable features of the pulmonary circulation is this facility with which flow can be increased without pronounced elevation of pressure.

In Group I (O_2 uptake at 295 ml./min./square m.) the A.-V. O_2 difference had increased from the resting level of 3.10 to 5.69 vols.%, and the cardiac output from 4.32 to 5.26 litres/min./square m. At the next grade of work (Group II with O_2 uptake at 397 ml./min./square m.) the A.-V. difference rose from 3.45 to 6.62 vols.%, and the cardiac output from 4.2 to 6.0 litres/min./square m. At the exercise level involving an O_2 uptake of 564 ml./min. the mean A.-V. O_2 difference more than doubled (from 3.23 to 8.41 vols.%) and the cardiac output rose from 4.64 to 6.70 litres/min./square m. At the arduous exercise of Group IV, entailing an oxygen uptake of 1,047 ml./min./square m. (a sixfold to eightfold increase), the A.-V. difference increased fourfold, from 3.07 to 11.32 vols.%. The cardiac output at this level was approximately doubled from 4.51 to 9.19 litres/min./square m. It will be seen that the main weight of the adaptation at these four levels of activity was taken by increasing the coefficient of oxygen utilization, thereby enabling the magnitude of increase in cardiac output to be restricted to about a twofold increase.

Donald *et al.* (1955) further analysed the relative contributions of increased pulse rate and increased stroke volume to the alteration in cardiac output. They found a wide range of adaptation, but in general the main adjustment was in rate. One could hardly find better illustrations than those just cited of the famous dictum of Joseph Barcroft, "Every adaptation is an integration."

In a patient with severe mitral stenosis the increased oxygen uptake of exercise cannot be met by a great increase in pulmonary blood flow, but has to be secured by a disproportionately great increase in A.-V. difference. In some patients mixed venous blood oxygen content has been found to fall as low as 2 vols.%. This means that the oxygen tension in the capillaries is of the same order as that in a climber on the North Col of Mount Everest. Small wonder that gross clinical features of anoxaemia dominate severe congestive cardiac failure. This illustrates the distorting effect of disease on the integrations of an adaptation.

Cournand *et al.* (1950) studied patients after pneumonectomy to try to determine the point at which further augmentation of blood flow was associated with substantial elevation of pulmonary artery pressure. They found that increases in flow above 5 litres/min./square m. through one lung resulted in increasing pulmonary hypertension. If this value is applied to a normal person it means that the pulmonary pressure might be expected to rise when the cardiac index exceeds about 10 litres/min. This value

accords well with the data of Dexter *et al.* and Donald *et al.*, except that they found that the elevation was already considerable at that level. It seems quite likely that in Cournand's one-lung patients a certain amount of adjustment in the form of a permanent vasodilatation had already taken place in the single lung. In that respect their observation is not altogether comparable with the acute exercise state in a person with two lungs. The numerous studies that have been made in patients with left-to-right shunts through septal defect and patent ductus arteriosus indicate that adaptation without hypertension to elevations of pulmonary blood flow of at least fourfold can occur.

It must be emphasized that in the Poiseuille equation the factor ΔP is a gradient to determine which it is necessary to know the pressure at both ends of the tube in question. Whereas the pulmonary artery pressure can be readily measured, the downstream recording is not so easy. Hellemis *et al.* (1949) found that if a cardiac catheter is pushed as far as it will go into the peripheral lung field it is possible to withdraw blood that is almost 100% saturated with oxygen, and a pressure can be recorded which is identical with that obtained by inserting the catheter through a defective atrial septum in a retrograde direction into a pulmonary vein. Epps and Adler (1953) and Allison and Linden (1953) have measured left auricular pressure directly in cases of mitral stenosis by inserting through the bronchial wall into the left auricle, via a bronchoscope, a needle attached to a bronchoscopic suction tube. A cardiac catheter was at the same time wedged in the peripheral lung field. It was possible, by using a three-way tap, to transfer the pressures in these two sites in quick succession to a transducer-recorder system. In every instance the mean pressures in the left atrium and blocked peripheral pulmonary artery were found to be equal, and these workers regarded this as confirming the view that the pulmonary capillary venous pressure measured by cardiac catheterization is an accurate measure of the left atrial pressure in mitral valve disease.

Björk (1954) has obtained similar confirmatory evidence by tapping left atrial pressure directly through a long needle inserted through the skin of the back into the left auricle in mitral stenosis. So far as I know, however, this critical direct demonstration of the validity of the transpulmonary "wedge" or P.C. pressure as an indicator of left atrial pressure has been made only in cases of mitral stenosis.

BRONCHIAL CIRCULATION

We now come to a consideration of the contribution of the bronchial circulation to haemodynamic adjustments in the pulmonary circulation. Until about twenty years ago this circulation was thought to have no other role than that of providing oxygen for the lung as a living tissue.

It has become clear, however, that the bronchial circulation reacts vigorously to a number of disease processes in the lung. Some doubt exists about the presence of broncho-pulmonary anastomoses in normal lungs. Lilienthal and Riley (1954), in an admirable review, concluded that the weight of evidence pointed to the existence of precapillary anastomoses between the two circulations. Miller (1947) had come to the conclusion that in dogs no such anastomoses could be found, and he thought that vasa vasorum to the pulmonary vessels were being mistaken for true anastomoses; but other workers, notably Marchand *et al.* (1950), by a variety of injection and histological techniques on anatomical specimens, were satisfied that such anastomoses existed. Marchand *et al.* also studied the vascular pattern in lung abscess and bronchiectasis, and found evidence of extensive and large broncho-pulmonary junctions. They pointed out that these appeared to be due to the opening of latent anastomoses, as they occurred at some distance from the site of the lesion, and bore no evidence of originating in vascular granulation tissue. Furthermore, they found them in emphysema in the absence of inflammation and necrosis. They further concluded that the calibre of these channels indicate a large volume of flow from bronchial to pulmonary arteries.

Broncho-Pulmonary Anastomoses

It is well established that in pulmonary stenosis, and particularly in pulmonary atresia, the predominant or sole source of access (in the absence of a patent ductus arteriosus) of blood to the pulmonary capillary bed is via broncho-pulmonary shunts. East and Barnard (1938) described four patients with Fallot's tetralogy who had complete and presumably lifelong atresia of the pulmonary artery and yet had survived for 33, 30, 20, and 6 years. Gross dilatation of the bronchial arteries was noted in two of these cases. Liebow *et al.* (1949) and Cockett and Vass (1951) have also shown in bronchiectasis that the bronchial vascular system is grossly enlarged and that numerous broncho-pulmonary channels are present in and around the diseased portions of the lungs. A number of studies of the vascular patterns of chronic pulmonary tuberculous lesions has shown that the blood supply of such areas comes to be almost exclusively bronchial, while the pulmonary vessels are frequently obliterated.

In primary lung tumours, bronchial arteries have been found to provide a rich blood supply (Wood and Miller, 1938). Primary bronchial carcinomata, but, curiously enough, no secondary lung carcinomata, were found by Cudkowicz and Armstrong (1953) to be associated with prominent broncho-pulmonary anastomoses. Gilroy *et al.* (1951) found that the blood obtained at operation from pulmonary arteries leading to lobes rendered atelectatic by bronchial obstruction was almost completely oxygenated. Injection studies of the excised areas showed that this was due to the presence of wide communications with the bronchial system. I have seen at operation the large high-pressure vessels containing arterialized blood that surround chronic bronchiectatic lobes, and have often been assured by thoracic surgeons that these are usually found in such cases.

Turn now to the more experimental approach to this problem. Daly and his colleagues have long insisted, on the basis of their studies on heart-lung preparations, that the bronchial circulation is capable of exerting profound influence on pressure-flow relationships in the pulmonary circuit. Bloomer *et al.* (1949) ligated the pulmonary artery in dogs and found that oxygenated blood reached the pulmonary artery distal to the ligature in large amounts from bronchial artery communications. Their studies had a sound functional basis, and showed that in the course of a few weeks the blood flow in the lung when the pulmonary artery was ligated rose from a value of 30 ml./min. to values of around 1 litre/min., and even, in one instance, as high as 2 litres/min. They calculated that in such a case the output of the left ventricle could be as much as one-third greater than that of the right ventricle. Subsequent anatomical studies of such lungs revealed precapillary anastomoses exceeding 50 μ in diameter.

The conclusion to be drawn from these varied observations is that in diseased states involving such processes as chronic inflammation, collapse, emphysema, pulmonary artery thromboses, the evaluation of pulmonary circulatory haemodynamics becomes exceedingly complex. Certainly the evaluation of pressure-flow relationships in such conditions by the methods which are adequate for the healthy state is likely to yield results which are anomalous, and even grossly misleading if accepted uncritically.

Arterio-venous Shunts

Closely analogous to this question of broncho-pulmonary anastomoses is that of shunts between pulmonary arteries and veins. As already mentioned in discussing ventilation-perfusion relationships, there is definite physiological evidence in the form of the "venous admixture factor" that blood can pass from artery to vein without adequate exposure to alveolar gas. These methods, however, cannot yet differentiate clearly between blood which may have passed through such A.-V. shunts and that which has passed

through capillaries in ill-perfused alveoli. Prinzmetal *et al.* (1948) developed the elegant technique of estimating the size of minute vascular beds by releasing into the circulation glass spheres of different diameter. The maximum size of sphere and the proportion of them passing through to the venous side of a capillary territory obviously provides a good indication of the size and number of the available channels. Tobin and Zariquiey (1950) applied this technique to fresh human lungs and found (1) shunts up to $500\ \mu$ in diameter at the apices of the lobular subdivisions of the broncho-pulmonary segments; (2) smaller shunts of $50\text{--}100\ \mu$ diameter at the level of the smaller bronchi and respiratory bronchioles; and (3) $20\text{--}25\ \mu$ shunts near the alveolar sacs and the alveoli. In this connexion it must be emphasized that it is unlikely that the normal alveolar capillary greatly exceeds in diameter that of an erythrocyte. However, one must remember that the maximum size of particle which can pass through a muscular tube may be many times greater than its normal calibre, as peristaltic action seems to be a widespread characteristic of such structures.

Vessel Diameter

The third important factor in the Poiseuille equation (pressure and flow being the other two) is the radius of the tube, or in this case the mean radius of that portion of the pulmonary vascular system in which the largest pressure difference (ΔP) exists. Now, in normal function we are entitled to believe, because flow increases threefold to fourfold with only a slight elevation of pressure, that the value of r adjusts so as to allow F to increase without change in P . This capacity of the pulmonary circulation to dilate, with increasing flow until a point is reached after which pressure increases quite rapidly, stimulates speculation about the nature of the peripheral resistance. May I remind you that what we are considering is "resistance to flow," which may be defined as the ratio of the pressure gradient to flow?

One of the simplest possible relationships is that in which equal increments of ΔP cause equal increments of F , a state in which the ratio of ΔP to F is a constant and r does not change.

The work of Donald *et al.* (1955) indicated a moderate increase in pulmonary artery pressure in the lower ranges while at high ranges of flow there may be rectilinear portions of the ΔP - F curve. What physical change, however, can bring about the marked inflexion of the curve that occurs? The inference is that up to that point there is some mechanism which keeps down resistance so as to allow a progressive fall in the ratio ΔP - F . Clearly that could be achieved in two ways: (a) by the opening of vessels which at low rates of flow are closed, and (b) by the increase in cross-sectional area of vessels already open. It is reasonable to resume that both mechanisms operate, each in its appropriate part of the lung. The increase in mean diameter of vessels required to accommodate a fourfold increase in flow is in the ratio of $1/\sqrt[4]{4}$ or $1/1.4$. Although there is, so far as I know, no direct proof of it, I think that is the sort of mean adjustment that takes places in the larger branches of the larger vessels; while in the smallest vessels—that is, the alveolar capillaries—the mechanism is probably that of the opening of capillaries normally closed. Whether, however, the transition from one mechanism to the other is abrupt at some particular order of size of vessel is at present imponderable. At any rate, it is clear that, whereas there is no known functional disadvantage in some increase in diameter of the precapillary vessels, the whole function of capillaries, pulmonary or elsewhere in diffusion zones, requires them to retain in all circumstances a high ratio of surface area to radius. If this assumption be correct in regard to the increase in the capillary bed then such a fourfold increase should be associated with an increase in open alveolar capillaries of the order of 50%. Roughton (1945), in his admirable study of the mean time spent by blood in a lung capillary, reached an approximate solution of the increase of capillary volume during exercise when the blood flow increased from 4.7 to 16 litres/min.; this amounted to a ratio

of 60/95—that is, around a 50% increase. There were no pulmonary artery or capillary pressure studies in his work, which was done before these became possible in intact man, but it is evident that the ratios and data obtained were of the same order as those which now emerge from the knowledge that increases of flow of this order are achieved without much elevation of pressure.

Work by Burton (1951) and Nichol *et al.* (1951) has shed light on the mechanisms of opening and closing of small blood vessels. He applied to small vessels the physical law enunciated by Laplace which governs the equilibrium of the wall of a cylindrical vessel. This states that the circumferential tension of the wall is the product of the pressure exerted on the inner surface and the radius of the vessel—that is, $T = P \times R$. Where the wall is not passive but can actively contract as can the muscular coat of a vessel, then there can arise a state in which the tension is so high in relation to the radius that the vessel closes—in fact, this law predicts that a small blood vessel must possess an intrinsic instability in which there is this "critical closing pressure" at which it is occluded. Some such mechanism provides a satisfactory explanation of many of the phenomena of capillary opening and closing, not only in the lung but elsewhere.

CONTROL OF PULMONARY CIRCULATION

Turning now to the control of the pulmonary circulation. There are naturally three groups of mechanisms to be considered: (a) those mediated by neurogenic means, (b) those induced by circulating substances, and (c) those due to alterations in the environment of the blood vessels mediated by local influence.

Nervous Control

The controversy on this question has been long and hotly debated. Many believe that the pulmonary circulation reflects passively the cardiac activity and systemic influences altering the distribution of blood between the two circuits. Time does not permit of any real review of the pros and cons of this weighty problem, only of the mention of some evidence in favour of the existence of nervous control. The other mechanisms are not in dispute, because the pulmonary system must inevitably adapt to the dynamics of the heart and major circulation. Many years ago Churchill and Cope (1929) demonstrated that alteration in pressure within the pulmonary vascular bed lowered systemic blood pressure and caused bradycardia, reactions which were abolished by vagal section. It has long been known that among the effects produced by multiple embolization of the arterial tree are action currents suggestive of a barrage of nerve impulses possibly originating in the plugged vessels.

Pearce and Whitteridge (1951) have studied the action currents in single fibres of the vagus and have identified impulses in phase with pulsation in the pulmonary artery and asynchronous with the aortic pressure wave. This pointed to the arterial side of the lesser circuit as containing the baroreceptors. Further evidence by Aviado *et al.* (1952) indicates that these are probably in the first part of the pulmonary artery. This is a readily acceptable hypothesis in view of the known location of such end organs in the embryologically analogous arch of the aorta (nerves of Cyon). The observations of Daly *et al.* (1938) suggesting the presence of pressure reflex zones in the pulmonary veins have also been supported. It hardly needs a critical application of another of Joseph Barcroft's famous principles—"The chance that a phenomenon has a significance"—to conclude that these nervous mechanisms are functionally important. Physiology has not led us to believe in the detecting, central transmission, and presumably recording of changes of state purely with a view to pigeon-holing without action. Such a purposeless phenomenon seems to be the prerogative of the bureaucratic machine.

We come now to possible effective mechanisms in pulmonary vascular innervation. Lillenthal and Riley (1954) state that the earliest observations which they can trace are those of Brown-Séquard in 1871, that mechanical stimuli

applied to certain neural structures elicited reactions which he concluded were transmitted peripherally along the dorsal sympathetic chain. In 1894 our illustrious former president John Rose Bradford, along with H. P. Dean, carried out an extensive investigation of the innervation of the pulmonary circulation in dogs. They observed simultaneously pressure in the pulmonary artery, a pulmonary vein, and a systemic artery during stimulation of various parts of nerves going to the lungs. They concluded that, while the vaso-motor control of the lung vasculature was poorly developed and feeble as compared with the highly developed neuro-genic control of the systemic circulation, its effects were functionally demonstrable as independent of changes in the systemic circuit. The outstanding work in this field during the last twenty-five years has been the systematic and progressive experimental analysis of this problem by Daly and his collaborators. They have studied the interplay of the parameters of the Poiseuille equation in the pulmonary vascular bed, initially in a simple canine heart-lung preparation, progressing step by step to the almost intact animal. Their accumulated evidence leaves virtually no doubt that substantial changes in these factors can be mediated both by vasoconstrictor and, to a less extent, by vasodilator impulses produced by stimulation of both adrenergic and cholinergic nerve supply.

The part played by neural control in the regulation of pulmonary haemodynamics in *human* health and disease is obscure. Certainly any of the operations that divide, in various ways, the cutaneous fibres of the upper sympathetic chain, the stellate ganglion, or the cardiac branches have not been associated with any gross alteration in pulmonary vascular function. The pulmonary hypertension which occurs in cerebral damage involving in particular the brain stem involves pulmonary veins, capillaries, and artery, and is often productive of pulmonary oedema. There seems little doubt that it is secondary to an abrupt and massive rise in systemic vasoconstriction resulting in acute left ventricular insufficiency, a state in all respects comparable to the left ventricular failure and passive pulmonary hypertension and oedema which may occur in acute glomerulonephritis, eclampsia, or extensive damage to the left ventricular myocardium as in infarction.

Effect of Circulating Substances

Space does not permit me to attempt any sort of critical evaluation of the influence of hormones, drugs, and "toxins" (used in the loosest sense). In this field it is very difficult to draw conclusions from observations in man because of the extreme difficulty in observing and recording simultaneously a sufficient number of variables to disentangle the effects on the systemic circuit, ventilation, etc., from those on the plain muscle in the walls of pulmonary arteries, capillaries, and veins. At the same time tests made in animals can be more comprehensive, but there is always the factor of species specificity to be reckoned with in any attempt to interpret human phenomena in their light. It can be said, however, that the following features characterize the extensive body of information available: (1) a capacity on the part of the pulmonary circulation to respond to a variety of biological agents and their antagonists. These responses tend to be comparatively slight in healthy states but may be large in diseased states; (2) a variability in response to such agents determined by the immediate environment and recent experience of the pulmonary circulation; and (3) a clear trend of evidence which indicates that the pulmonary circuit can respond in itself and that the reactions are not secondary to the systemic circuit changes.

Influence of Alveolar Gas Tensions

The discovery of the effect of gas tension on the pulmonary circulation is one of the most exciting developments of the last ten years. It starts with the observations of von Euler and Liljestrand (1946) that in the cat under chloralose anaesthesia and closed chest, anoxia or raised inspired CO_2 tension produced an increase of pulmonary arterial pressure

which was independent of respiration or alterations in left auricular pressure and persisted after vagotomy or stellate ganglionectomy. They also noted the converse reaction that breathing a high concentration of oxygen lowered the P_{PA} below the normal room air level. Since then there has accumulated a mass of evidence that depression of alveolar O_2 raises pulmonary artery pressure. In man this effect was noted by Motley *et al.* (1947), and since then there has been a great weight of confirmatory evidence.

At first some uncertainty arose whether the elevation in P_{PA} was due simply to the elevation of flow that anoxia stimulated; however, later studies in which resistance was measured, using the pulmonary capillary or wedge pressure as the lower limit of the pressure gradient, have demonstrated clearly that the pressure required to drive unit blood flow is raised. This indicates conclusively that the cross-sectional area of the pulmonary bed (or πr^4 of the Poiseuille equation) is reduced. In these conclusions, of course, there is implicit the assumption that total or near total flow is measured by this particular application of the Fick principle. If a substantial amount of blood were introduced at high pressure into the pulmonary circuit, as for instance by the opening of shunts with the bronchial circuit, the conclusions would be invalid. I think this possibility can be disregarded, as there is no reason to believe that the bronchial circulation is capable of doing this at short notice. In disease states, however, as we have already seen, such a possibility cannot be lightly disregarded.

The practice of direct pressure measurement in the pulmonary circuit of cases of cardio-pulmonary disease has revealed some extremely interesting relationships. It seems clear that in mitral stenosis there is elevation of pulmonary venous and capillary pressures inversely proportional to the reduction in area of the mitral orifice. This is the inevitable result of maintained flow through a reduced bore. The elevation of capillary pressure dare not exceed for any length of time the oncotic pressure of the blood, as death then occurs from pulmonary oedema. However there also occurs in the evolution of mitral stenosis a disproportionately great elevation of pulmonary artery pressure, which may increase fourfold the pulmonary artery/pulmonary capillary gradient (Wood, 1954). This indicates that the vessels lying between the pulmonary artery and the capillaries offer an abnormally small lumen, or, put differently, they fail to relax so as to allow flow without this gross hypertension. Much speculation has arisen about the nature of this loss of distensibility of the pre-capillary vessels.

The morbid anatomical observations of Brenner (1935), Parker and Weiss (1936), and others seem to me to provide a reasonable explanation. These workers have demonstrated in mitral stenosis a thickening of the pulmonary vessel walls particularly marked in the subintimal zone. This thickening may well be due to the "back pressure." Its inevitable result is to reduce the lumen and to greatly impair distensibility, or, put more dynamically, to alter the volume-elasticity characteristics of the pulmonary vascular bed. The effect of this is to require a greater pressure to maintain flow. I fully realize that the validity of this hypothesis requires proof that these structural changes develop hand in hand with increase in the artery/capillary gradient. It is quite possible that they are the result and not the cause of the elevation of pressure, as seems to be the case in systemic hypertension.

Conclusion

In conclusion I would emphasize that I have reviewed, of necessity superficially, much that is old and a little that is comparatively new concerning the three vital zones in the lung—that is, the alveolar gas, the alveolar capillary, and the intervening tissue septum. I have attempted to demonstrate that pulmonary disease can be portrayed in terms of quantitative dynamic relationships providing concepts complementary to and at least as useful as those

based on the necropsy, the microscopical preparation, and the radiograph. The task has given me many hours of happy toil. I hope that I have in a small way discharged the obligation of Dr. George Oliver to "encourage the application of physiological knowledge to the prevention and cure of disease."

REFERENCES

- Aitken, R. S., and Clark-Kennedy, A. E. (1927). *J. Physiol. (Lond.)*, **64**, 17P.
- Allison, P. R., and Linden, R. J. (1953). *Circulation*, **7**, 669.
- Armitage, G. H., and Arnott, W. M. (1949a). *J. Physiol. (Lond.)*, **109**, 64.
- (1949b). *Ibid.*, **109**, 70.
- and Pincoc, A. C. (1949). *Ibid.*, **108**, 27P.
- Austrian, R., McClement, J. H., Renzetti, A. D., Donald, K. W., Riley, R. L., and Courmand, A. (1951). *Amer. J. Med.*, **11**, 667.
- Aviado, D. M., Cerletti, A., Alanis, J., Bulle, P. H., and Schmidt, C. F. (1952). *Amer. J. Physiol.*, **169**, 460.
- Barcroft, J. (1934). *Features in the Architecture of Physiological Function*. Cambridge Univ. Press, Cambridge.
- Björk, V. O. (1954). *Acta chir. scand.*, **107**, 466.
- Bloomer, W. E., Harrison, W., Lindsog, G. F., and Liebow, A. A. (1949). *Amer. J. Physiol.*, **157**, 317.
- Bohr, C. (1909). *Skand. Arch. Physiol.*, **22**, 221.
- Bradford, J. R., and Dean, H. P. (1894). *J. Physiol. (Lond.)*, **16**, 34.
- Brenner, O. (1935). *Arch. intern. Med.*, **56**, 211, 457, 724, 976, 1189.
- Briscoe, W. A., Becklade, M. R., and Rose, T. F. (1951). *Clin. Sci.*, **10**, 37.
- Burton, A. C. (1951). *Amer. J. Physiol.*, **164**, 319.
- Churchill, E. D., and Cope, O. (1929). *J. exp. Med.*, **49**, 531.
- Cockett, F. B., and Vass, C. C. N. (1951). *Thorax*, **6**, 268.
- Cohn, J. E., Carroll, D. G., Armstrong, B. W., Shepard, R. H., and Riley, R. L. (1954). *J. appl. Physiol.*, **6**, 588.
- Comroe, J. H., and Fowler, W. S. (1951). *Amer. J. Med.*, **10**, 408.
- Courmand, A. (1950). *Circulation*, **2**, 641.
- and Ranges, H. A. (1951). *Proc. Soc. exp. Biol. (N.Y.)*, **46**, 462.
- Riley, R. L., Himmelstein, A., and Austrian, R. (1950). *J. thorac. Surg.*, **19**, 80.
- Cudkowicz, L., and Armstrong, J. B. (1953). *Thorax*, **8**, 152.
- Daly, I. de B., Ludány, G., Todd, A., and Verney, E. B. (1938). *Quart. J. exp. Physiol.*, **27**, 123.
- Darling, R. C., Courmand, A., and Richards, D. W. (1944). *J. clin. Invest.*, **23**, 55.
- Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T., and Helles, H. K. (1950). *Ibid.*, **29**, 602.
- Donald, K. W., Bishop, J. M., Cumming, G., and Wade, O. L. (1955). *Clin. Sci.*, **14**, 37.
- Renzetti, A., Riley, R. L., and Courmand, A. (1952). *J. appl. Physiol.*, **4**, 497.
- East, T., and Barnard, W. G. (1938). *Lancet*, **1**, 834.
- Epps, R. G., and Adler, R. H. (1953). *Brit. Heart J.*, **15**, 298.
- von Euler, E. S., and Liljestrand, G. (1946). *Acta physiol. scand.*, **12**, 301.
- Fick, A. (1870). *S.B. phys.-med. Ges. Würzburg*, p. 16.
- Filley, G. F., Gregoire, F., and Wright, G. W. (1954). *J. clin. Invest.*, **33**, 517.
- Forssman, W. (1929). *Klin. Wschr.*, **8**, 2085.
- Forster, R. E., Fowler, W. S., Bates, D. V., and Van Lingen, B. (1954). *J. clin. Invest.*, **33**, 1135.
- Fowler, W. S. (1949). *J. appl. Physiol.*, **2**, 283.
- Gasman, H. W. A. (1952). Unpublished communication.
- Gilroy, J. C., Wilson, V. H., and Marchand, P. (1951). *Thorax*, **6**, 137.
- Gréhant, N. (1864). *J. Anat. (Paris)*, **1**, 523.
- Haldane, J. (1895). *J. Physiol. (Lond.)*, **18**, 201.
- Hamman, L., and Rich, A. R. (1944). *Bull. Johns Hopk. Hosp.*, **74**, 177.
- Helles, H. K., Haynes, F. W., and Dexter, L. (1949). *J. appl. Physiol.*, **2**, 24.
- Krogh, M. (1915). *J. Physiol. (Lond.)*, **49**, 271.
- and Lindhard, J. (1917). *Ibid.*, **51**, 59.
- Liebow, A. A., Hales, M. R., and Lindsog, G. E. (1949). *Amer. J. Path.*, **25**, 211.
- Lilienthal, J. L., and Riley, R. L. (1954). In *Annual Review of Medicine*, **5**, 237.
- Proemmel, D. D., and Franke, R. E. (1946). *Amer. J. Physiol.*, **147**, 199.
- Lilly, J. C. (1946). *Fed. Proc.*, **5**, 64.
- and Hervey, J. B. (1948). *Science in World War II*, **1**, 314. Little Brown and Co., Boston.
- McMichael, J., and Sharpey-Schafer, E. P. (1944). *Brit. Heart J.*, **6**, 33.
- Marchand, P., Gilroy, J. C., and Wilson, V. H. (1950). *Thorax*, **5**, 207.
- Miller, W. S. (1947). *The Lung*. Thomas, Springfield, Ill.
- Motley, H. L., Courmand, A., Werckö, L., Himmelstein, A., and Dresdale, D. (1947). *Amer. J. Physiol.*, **150**, 315.
- Nichol, J., Girling, F., Jerrard, W., Claxton, E. B., and Burton, A. C. (1951). *Ibid.*, **164**, 330.
- Parker, F., and Weiss, S. (1936). *Amer. J. Path.*, **12**, 573.
- Pearce, J. W., and Whitteridge, D. (1951). *Quart. J. exp. Physiol.*, **36**, 177.
- Prinzmetal, M., Ornitz, E. M., Simkin, B., and Bergman, H. C. (1948). *Amer. J. Physiol.*, **152**, 48.
- Riley, R. (1951). *Amer. J. Med.*, **10**, 210.
- Riley, R. L., and Courmand, A. (1951). *J. appl. Physiol.*, **4**, 77.
- Donald, K. W., and Courmand, A. (1951). *Ibid.*, **4**, 102.
- Lilienthal, J. L., Proemmel, D. D., and Franke, R. E. (1946). *Amer. J. Physiol.*, **147**, 191.
- Shepard, R. H., Cohn, J. E., Carroll, D. G., and Armstrong, B. W. (1954). *J. appl. Physiol.*, **6**, 573.
- Robertson, J. S., Siri, W. E., and Jones, H. B. (1950). *J. clin. Invest.*, **29**, 577.
- Roelsen, E. (1938). *Acta med. scand.*, **95**, 452.
- (1939). *Ibid.*, **98**, 141.
- Roughton, F. J. W. (1945). *Amer. J. Physiol.*, **143**, 621.
- Siebeck, R. (1910). *Z. Biol.*, **55**, 267.
- Sonne, C. (1934). *Z. ges. exp. Med.*, **94**, 13.
- Tobin, C. E., and Zariwsky, M. O. (1950). *Proc. Soc. exp. Biol. (N.Y.)*, **75**, 827.
- Wade, O. L., Bishop, J. M., Cumming, G., and Donald, K. W. (1953). *British Medical Journal*, **2**, 902.
- Wood, D. A., and Miller, M. (1938). *J. thorac. Surg.*, **7**, 649.
- Wood, P. (1954). *British Medical Journal*, **1**, 1051, 1113.

CLINICAL OBSERVATIONS ON VENO-OCCLUSIVE DISEASE OF THE LIVER IN JAMAICAN ADULTS

BY

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Veno-occlusive disease of the liver (V.O.D.) is a term given on histological grounds to a form of liver disease occurring frequently in Jamaican children and occasionally in adults (Bras *et al.*, 1954a, 1954b). The clinical features in children have been fully described by Rhodes (1954) and Jelliffe *et al.* (1954). Sometimes two or more members of the same family are affected. The disease is divided into three often ill-defined and overlapping stages. The acute stage is characterized by the sudden development of abdominal pain, hepatomegaly, often gross, and usually considerable ascites. Vomiting is common. Slight splenomegaly and ankle oedema sometimes occur. Children between the ages of 18 months and 3 years are primarily affected. Rhodes (1954) drew attention to the fact that the condition is often precipitated by other illnesses such as whooping-cough, respiratory infections, etc. Repeated paracenteses may be required in the acute stage; but subsidence of the hepatomegaly and ascites may occur with remarkable rapidity, sometimes disappearing completely in seven to fourteen days. The majority of patients appear to recover completely; but some die in the acute stage of liver failure (Bras *et al.*, 1954a, 1954b). The acute stage may pass, often imperceptibly, into the subacute stage of the disease; or it may be subacute apparently from the onset (Jelliffe *et al.*, 1954).

The subacute stage is characterized by a firm persistent hepatomegaly, and sometimes recurring ascites. It is often symptom-free, with the patient maintaining apparently normal health, and it is discovered only on routine examination or on examination for an unassociated complaint. The spleen is usually enlarged at this stage. Jaundice is rare in any stage of the disease except terminally. It would appear that complete resolution may occur even in the subacute stage of the condition. Alternatively, this stage may pass into the chronic stage of the disease. Acute episodes may occur in both the subacute and chronic stages.

The clinical features in the chronic stage are similar to those of any other form of cirrhosis, and often indistinguishable from them. It would appear, however, to progress more rapidly than cirrhosis from other causes. Death in this stage is often due to haematemesis from ruptured oesophageal varices. Hepatic failure and cholaemia are also frequent causes of death.

Theories of aetiology of this syndrome have been discussed in previous papers (Bras *et al.*, 1954a, 1954b; Rhodes, 1954). While it is possible that there is no uniform aetiology, there are certain common factors that appear to underlie this syndrome in Jamaica. All the cases seen here occur in the poorer economic groups, and, although the clinical stigmata of malnutrition are often minimal or absent, malnutrition or subnutrition, as judged from available dietary histories, forms the unvarying background to this disease (Rhodes, 1954).