would be perfectly satisfactory. But in actual practice the larger the "sample" the less probable is it that the conditions will be fulfilled, and the possibility of controlling a sample of the order of 10 per cent. of the whole annual births is virtually an impossibility. Take a less ambitious scheme, and suppose that in some town of moderate size, a town of some sixty or seventy thousand inhabitants, with an annual quota of, say, 1,000 births, the children could be treated randomly—for example, every second child whose birth was registered from January 1st in some year to be treated. We should expect on the average less than one registered death from tuberculosis in the control 500, and no strong presumption of advantage would be raised by a *nil* return from the treated series, taking only a year's experience.

Evidently it was a sound instinct to seek for a decision amongst the class of material where a higher rate of mortality was to be expected. That is the significance of Kjer-Petersen and Ostenfeld's work. What can we conclude from their investigation as to the probable range of mortality in the first year of life of in-contacts? We can, of course, at once dismiss the preposterous suggestions of rates of mortality of the order of 25 per cent., even from all causes. Had such a rate really prevailed in the population sampled by Kjer-Petersen and Ostenfeld, their "expectation" would have been 61 deaths with a standard deviation of 6.77. Actually they observed 19, and the odds against such a deviation as 42 are of the order of a thousand millions to one. If, however, one might postulate a rate of mortality from tuberculosis in the first year of life even of the order of 5 to 10 per cent., the comparison of samples of order 500 would not be waste of time. We should expect

in our control 500 from 25 to 50 deaths, and if the treated sample returned, say, only some 15 to 30 or fewer deaths, a case would have been made out which would be rather strong. Whether it would be practically possible to use this method, here or in America, it is hard to say. The number of instances of births in families with one or more cases of open tuberculosis which come to the notice of the public health authorities within any one area and within a limited period of time is small, and the difficulty of strict random sampling is great. We are concerned, not with guinea-pigs, but with human beings, and it is not easy to induce those who have the medical charge of human beings to administer to any of them a treatment which they regard as worthless, or to abstain from administering to any of them a treatment which they regard as valuable. None of us can dramatize this conflict with the art of Mr. Sinclair Lewis in *Martin Arrowsmith*, but all of us have, to a greater or less degree, participated in it. I do not expect that the value of B.C.G. will be determined on these lines. Like most methods of treatment, its use or neglect will be determined by psychological considerations. But to the still small, but increasing, number of medical men who attach importance to statistical accuracy it is of some moment that methodological errors having the sanction of the name of a distinguished investigator should at once be pointed out. That is my reason for writing this article.

REFERENCES.

- ¹ *Ann. de l'Institut Pasteur*, xlii, 1928, 1. ² *Ibid.*, xli, 1927, 201. ³ *British Medical Journal*, 1927, i, 815. ⁴ *Ibid.*, 1928, i, 754. ⁵ *Ibid.*, 1927, i, 856. ⁶ *Ibid.*, 1927, i, 1082. ⁷ *Ibid.*, 1928, i, 520. ⁸ *Ugeskrift for Læger*, March 31st, 1927 (No. 13), pp. 257-261. ⁹ *Deut. Med. Woch.*, 41st 2., 1915, 1310. ¹⁰ *Beitr. z. Klin. d. Tuberk.*, xx, 1911, 20.

VITAL CAPACITY IN HEART DISEASE.*

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It has been the aim of investigators for many years to devise some simple test to estimate the functional capacity of the heart, apart from the subjective sensations of the patient. Many tests have been introduced from time to time for this purpose, based as a rule on the response of the heart to some form of exercise—the simplest consisting of taking the pulse rate before a fixed amount of exercise, immediately after the exercise has ended, and after an interval of a few minutes. An exercise tolerance test of this type has largely been made use of by the Ministry of Pensions for purposes of assessment of cardiac disabilities.

A test like this one, based on changes in the pulse rate, however, is open to the objection that it is more a measure of the excitability of the sino-auricular node than an indication of the capacity of the heart, and depends on many other factors quite independent of the cardiac reserve power. After vital capacity had been introduced as a measure of the extent and progress of certain lung conditions this test was applied to patients suffering from cardiac disabilities by several observers (see references 1 to 4), who found that the vital capacity was very much below normal standard when any serious cardiac condition was present; while Peabody and Wentworth⁵ also drew attention to the fact that there was a definite relationship between diminution in the vital capacity and a tendency to dyspnoea on exertion.

Before considering the changes which occur in cardiac patients it is advisable to consider what is meant by vital capacity. Hutchinson⁶ many years ago divided the volume of air in the lungs into the following divisions:

1. *Residual air*—air which cannot be expelled and is left in the lungs.
2. *Reserve air*—air which can be expelled by effort at the end of normal expiration.
3. *Tidal air*—air which is inspired or expired during normal respiration.
4. *Complementary air*—air which can be inspired after normal inspiration.

* Based on a paper read before the Liverpool Medical Institution.

5. *Vital capacity*—the sum of the reserve air, tidal air, and complementary air—that is, the greatest amount of air which can be expelled after the deepest possible inspiration.

In this investigation a simple water spirometer (Fig. 1) has been used, graduated in cubic centimetres and balanced so that no effort is required to raise the cylinder. A large number of glass mouthpieces were provided, so that they could be readily disinfected between each patient without loss of time.

It is always advisable to explain fully the working of the machine before actually taking the measurement, as it is necessary to get the patient's whole-hearted co-operation to obtain an accurate result. Each patient was given three attempts, the highest being taken as the vital capacity. In taking the reading, if there is any tendency to expire through the nose this should be closed by pinching during expiration. When patients were not confined to bed the record was always taken standing, and generally in their ordinary clothes. With regard to the patients who were confined to bed they were all able to sit up in bed when taking

FIG. 1.—Water spirometer.

the reading, so that it was not necessary to correct the reading for the 5 per cent. diminution in the vital capacity which has been shown by Christie and Beams⁶ and Rabnowitch⁷ to occur when the reading is taken in the recumbent position. Owing to the variability of the vital capacity according to the height, sex, age, and race of the individual concerned, the simple reading of the number of cubic centimetres expired gives little indication of the deviation from the normal, unless the reading is expressed in percentages of the standard vital capacity for that individual.

In this investigation the vital capacity is expressed as percentages of the standard vital capacity for that particular patient. It would be out of the scope of this paper to enter into all the different methods for calculating the

standard vital capacity; probably the most accurate is that calculated on the surface area of the body as estimated by the method of Du Bois,⁸ where the vital capacity is two and a half times the surface area in men and twice the surface area in women. This is, however, a somewhat lengthy proceeding, and West⁹ has shown that for all practical purposes the standard vital capacity in cubic centimetres can be determined by multiplying the standing height of the patient in centimetres by twenty-five in men and twenty in women. Age also modifies the reading considerably, but it has been shown by the work of Bowen and Platt¹⁰ that this alteration with age only takes place during youth and after 50 years of age. As the cases in this series, with one or two exceptions in the high tension group, fell between the ages of 20 and 50, it was felt that the variation due to this factor would not materially alter the results.

Before investigating cardiac cases it was thought desirable to take a series of normal men and women and see what variations took place between the actual vital capacity as tested by the spirometer and the calculated standard vital capacity of the individual by means of West's formula. Fifty men, mostly medical students, and fifty women, chiefly nurses with a few students, were tested in this way.

Vital Capacity of Fifty Normal Males.

An examination of Fig. 2 shows that there are considerable variations among healthy individuals, and readings of 20 to 30 per

FIG. 2.—Showing the vital capacity of fifty normal males. The vertical line indicates the vital capacity in cubic centimetres, the horizontal line the heights, and the oblique line the standard vital capacity for each height as calculated by means of the formula. Each individual reading is shown as a dot.

cent. above or below normal are quite common without any apparent evidence in the health of the individual. In spite of these individual variations, however, the average of the group works out at 102 per cent., which is very near the normal figure of 100 per cent.

Vital Capacity of Fifty Normal Females. (Fig. 3.)

The variations in this group are if anything greater than in the male group, and the number of cases in which the actual

FIG. 3.—Showing the vital capacity of fifty normal females.

vital capacity was much below the calculated normal are more numerous. The average for the whole group is 95 per cent.—slightly below normal.

The Effect of Organic Cardiac Disease on Vital Capacity. (Fig. 4.)

The percentage incidence of organic cardiac disease is shown on the vertical line and the percentage of the normal vital capacity on the horizontal line. The normal curve is taken from 100

FIG. 4.—Curve to show the effect of organic cardiac disease on vital capacity.

normal individuals and is shown by the broken line. The curve of the organic cardiac cases is taken from 50 cases and is indicated by the continuous line.

Readings obtained in the Various Groups of Organic Cardiac Cases.

GROUP I: The Average Vital Capacity of all Organic Cardiac Cases.—Most of the cases in this group were able to attend the heart department, and only in comparatively few cases were the patients confined to bed. The cases examined numbered 54; the average vital capacity was 53 per cent.

GROUP II: The Vital Capacity of High Blood Pressure Cases.—All over 160 mm. systolic pressure, most of them over 200 mm. Number of cases 13; average vital capacity 55 per cent.

GROUP III: The Vital Capacity of Mitral Stenosis Cases.—These cases are subdivided into two groups—those with normal rhythm and those with auricular fibrillation. The average vital capacity for the whole group was 47 per cent. (25 cases); for the normal rhythm group 56 per cent. (12 cases); for the auricular fibrillation group 40 per cent. (13 cases).

GROUP IV: The Vital Capacity of Cases of Aortic Regurgitation.—The number of cases in this group was 10; the average vital capacity 59 per cent.

GROUP V: The Vital Capacity of Cases of Auricular Fibrillation of All Kinds.—There were 16 cases in this group, with an average vital capacity of 45 per cent.

GROUP VI: The Vital Capacity of Cases showing Abnormalities in their Electro-cardiographic Record.—(1) Left ventricle preponderating—average vital capacity 50 per cent. (13 cases). (2) Right ventricle preponderating—average vital capacity 51 per cent. (5 cases). (3) Inverted "T" (ex. Lead III only)—average vital capacity 51 per cent. (7 cases). (4) Q R S abnormal—average vital capacity 58 per cent. (3 cases). (5) Auricular fibrillation—average vital capacity 42 per cent. (14 cases).

These figures show that the vital capacity is markedly diminished when any organic cardiac condition is present. In certain conditions, especially in the mitral stenosis group with auricular fibrillation, this diminution is very marked, while in the high tension cases and in aortic disease it is not relatively so marked. In the cases showing changes in the electro-cardiographic record, apart from the low reading in the fibrillation group which has already been noted there is no special change in the average reading of any of these particular groups. A series of cases were kept under observation for a considerable time to see if any change took place in the vital capacity with varying states of compensation in the same patient. In two of these cases auricular fibrillation supervened during the period of observation, and we had the good fortune to obtain records of the cases while the heart was beating with its normal rhythm and subsequently records of the same patient when auricular fibrillation was present.

The first of these cases was a man, aged 44, suffering from mitral stenosis with a slight mitral leak. Fig. 5 shows the heart rate and vital capacity of this patient for a period of two months. The

FIG. 5.—Chart showing the heart rate and vital capacity for a period of two months of a man suffering from mitral stenosis.

chart shows clearly the drop in the vital capacity which occurred with the onset of auricular fibrillation and the subsequent improvement which took place on full doses of digitalis. (I am indebted to Dr. Ince for this chart and that shown in Fig. 6.)

The second case was that of a woman aged 26, also with mitral stenosis. Fig. 6 shows the effect of rest and digitalis on the heart rate and vital capacity when the heart was beating with a normal rhythm, the pulse rate falling steadily, and the vital capacity rising. The second part of the chart shows the record obtained

FIG. 6.—Chart showing the effect of rest and digitalis on the heart rate and vital capacity of a young woman with mitral stenosis.

from the same patient when she was readmitted two months later with auricular flutter, which soon became auricular fibrillation. She was extremely distressed on admission, and the vital capacity was not taken until she had improved considerably, but even then it was very much below the lowest figure when normal rhythm was present, and though improvement took place under digitalis it never subsequently reached its previous figure.

Another interesting case of this series was that of a healthy man in whom auricular fibrillation had been accidentally induced by means of an electric shock. His heart was turned back to its normal rhythm by quinidine, but relapsed into fibrillation and again had to be turned back by quinidine. We took records of his vital capacity during the whole of the period of transition from one rhythm to the other, and at no time did the change in the vital capacity between the period of normal rhythm and the periods of fibrillation exceed 100 c.cm.—a relatively very slight change.

A series of cases of disorderly action of the heart, or the "effort syndrome," were also investigated. This group

is of special interest in view of the marked dyspnoea on exertion which, as a rule, is one of the characteristic features of this disease.

All the cases investigated were very well marked examples of this condition, and were mostly of men in receipt of a pension for this disability as a result of service in the war. The cases investigated numbered 9, the average vital capacity being 85 per cent.; the lowest individual reading was 75 per cent.

These results in cases with disorderly action of the heart are in agreement with those published by Levine and Wilson¹¹ in this country and by White¹² and Adams and Sturgis¹³ in America. The very slight diminution in the vital capacity of this group is very curious in view of the marked dyspnoea which all these patients had, and shows that the dyspnoea which is associated with functional disease of the heart is very different in origin from that due to organic cardiac disease. Leaving out this group, which is in a class by itself and depends on so many factors outside the cardiac condition, it is apparent that the vital capacity is an indication of the amount of dyspnoea in cardiac disease, and though many² question that it pictures the cardiac condition more clearly than records of the blood pressure and pulse rate, and in support emphasize those cases where the reading does not change rapidly with varying states of compensation, yet there is no doubt that it is a valuable numerical expression of the amount of dyspnoea.

If one takes all the cases together they can, broadly speaking, be divided roughly into the following four classes, according to the amount of dyspnoea:

1. V.C. above 60 per cent.—dyspnoea not very marked.
2. V.C. between 60 and 40 per cent.—moderate amount of dyspnoea.
3. V.C. below 40 per cent.—considerable amount of dyspnoea.
4. V.C. below 30 per cent.—patient usually confined to bed with orthopnoea.

As in normal persons, however, a considerable amount of individual variation takes place.

Many views have been expressed as to how this diminution in the vital capacity in cardiac conditions is brought about. Siebeck¹⁴ believes that it is due to engorgement of the capillaries of the lung alveoli causing distension of the alveolar walls with increase in the fibrous tissue. Drinker, Peabody, and Blumgart¹⁵ have investigated the effect of pulmonary congestion on the ventilation of the lungs in cats, and have shown that pulmonary congestion produced by compressing the pulmonary veins at their entrance into the left auricle caused a marked diminution in the air passing through the lungs, and that recovery soon occurred when the pressure was released; but that if this compression was maintained for sufficient time to cause exudate into the lungs a more or less permanent diminution in the air passing through occurred. They believe that vascular congestion can act in two ways: (1) by encroaching upon the alveolar spaces by the congestion limiting their size; (2) by diminishing the elasticity of the lungs owing to the congestion, like erectile tissue.

Meakins and Davies,¹⁶ in summing up the evidence, express the opinion that the decrease in cases of organic cardiac disease is probably due to some structural change in the lungs. In favour of such a change taking place is the slow alteration in the reading with changes in the degree of compensation, and also the fact that the diminution is greatest in cases of mitral stenosis, especially when associated with auricular fibrillation, a lesion which is extremely likely to produce permanent changes in the lungs.

In conclusion, I should like to emphasize the following points:

1. The vital capacity is a valuable numerical expression of the amount of dyspnoea in organic cardiac cases.
2. It is a useful indication as to the general progress of treatment, though the changes in the reading only follow slowly the varying degrees of compensation of the heart.
3. The vital capacity is most diminished in cases of mitral stenosis, especially when associated with auricular fibrillation.

4. The reading is no indication of the amount of dyspnoea in disorderly action of the heart or functional disease.

5. It is of little value in the early diagnosis of cardiac conditions, owing to the variability of normal standards.

REFERENCES.

- ¹ Pratt, J. H.: *Amer. Journ. Med. Sci.*, 1922, clxiv, 819. ² Opitz, R. B.: *Journ. Amer. Med. Assoc.*, 1922, lxxviii, 1686. ³ Peabody, F. W., and Wentworth, J. A.: *Arch. Intern. Med.*, 1917, xv, 648. ⁴ Ziskin, T. A.: *Ibid.*, 1925, xxv, 259. ⁵ Hutchinson, John: *Med.-Chir. Trans.* (Lond.), 1846, xxix, 137. ⁶ Christie, C. D., and Beams, A. J.: *Arch. Intern. Med.*, 1922, xxx, 34. ⁷ Rabnowitch, I. M.: *Ibid.*, 1923, xxxi, 910. ⁸ Du Bois, D., and E. F.: *Ibid.*, 1916, xvii, 863. ⁹ West, H. F.: *Ibid.*, 1920, xxv, 206. ¹⁰ Bowen, B. D., and Platt, D. L.: *Ibid.*, 1923, xxxi, 579. ¹¹ Levine, S. A., and Wilson, F. N.: *Heart*, 1919, vii, 53. ¹² White, P. D.: *Amer. Journ. Med. Sci.*, 1920, clxiv, 856. ¹³ Adams, F. D., and Sturgis, C. C.: *Ibid.*, 1919, clviii, 816. ¹⁴ Siebeck, R.: *Deut. Arch. f. Klin. Med.*, 1910, C, 204. ¹⁵ Drinker, C. K., Peabody, F. W., and Blumgart, H. L.: *Arch. Intern. Med.*, 1922, xxxv, 77. ¹⁶ Meakins, J. C., and Davies, H. W.: *Respiratory Function in Disease*.

ORAL ADMINISTRATION OF PANCREATIC AND OTHER PREPARATIONS IN THE TREATMENT OF DIABETES.

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THE discovery of insulin entirely changed the former more or less hopeless outlook in cases of diabetes mellitus. It has enabled diabetic patients, who under previous conditions would have been dead before now, to lead active and useful lives in comparative good health. Such emergencies as operations and coma arising in the diabetic patient are no longer regarded with the same dread as formerly, for, in the majority of cases, both can now be dealt with successfully.

The mode of action of insulin is still a matter of conjecture, but it apparently helps to store carbohydrate in the liver and other tissues; at the same time it plays a part in the combustion of sugar. In the normal individual there is found an almost constant difference between the arterial and venous blood sugar content, the latter being less by approximately 0.04 per cent. In cases of diabetes this difference is reduced or disappears, showing an inability on the part of the tissues to deal adequately with supplies of glucose. Similarly in diabetes the lengthening of the normal blood sugar curve after the ingestion of carbohydrate shows that the liver is unable to store glycogen from the portal circulation as in the normal individual. After adequate treatment with insulin and suitable diet both these abnormalities show a return towards the normal.

It has been proved definitely that insulin is destroyed both by the gastric and the intestinal juice; whether given in acid or alkaline media, or in alcohol or glycerin, it exerts no appreciable effect on the blood sugar or carbohydrate metabolism. Oral administration on a full or empty stomach appears to make no difference; no absorption of active substance takes place. It was hoped at first that some way could be found of giving insulin by the mouth to obviate the unpleasantness of frequent hypodermic injections, but so far these attempts have not been attended with success.

In this respect insulin seems to bear a close resemblance to the extract of the posterior lobe of the pituitary gland, which on hypodermic injection has a definite effect in raising blood pressure and causing all unstriated muscle in the body to contract, whereas after oral administration it has no demonstrable effect.

Thyroid extract, when its value was first discovered in the treatment of myxoedema, was given by injection, but later it was found that it could equally well be given orally, as it was absorbed and exerted its effect in the same manner. For this reason after the discovery of insulin a fresh impetus was given to the use of various

pancreatic and other extracts for oral administration in the cases of diabetes mellitus.

The continued hypodermic injections in the case of patients on insulin treatment soon become irksome and may give rise to considerable trouble through sepsis if the patient be not careful with his cleansing of skin and syringe. In the case of the hospital class of patient the expense of the insulin very often gives rise to difficulty, though now, since the considerable decrease in price, this is not of so much importance as formerly.

These points have made it seem worth while to investigate some of the many oral preparations which are at present on the market for use in the treatment of diabetes mellitus. The claims made for these preparations are many and varied. In some cases the pamphlets even go so far as to claim cures on an ordinary mixed diet. For example, the synthetic insulin tablets A and B were said to produce a cure in a fortnight whilst the patient was on an ordinary diet. A similar claim was made for the diatana mixture.

Parke Davis's pancreatic extract (Mackenzie Wallis) is claimed to be of value in some cases of diabetes; in from two to three weeks on a suitable diet the extract is said to cause a reduction in blood and urine sugar and an improvement in the patient's clinical condition. Messrs. Parke Davis state that if no improvement is found in from two to three weeks the treatment should be discontinued. The improvement alleged in some cases might quite well be due to the strict dieting, and not to the pancreatic extract at all. They state that they do not aim at reducing the blood sugar to the region of 0.1 per cent., but they endeavour to reduce the blood sugar to the region of 0.15 to 0.20 per cent., and to decrease the sugar in the urine. No reference is made to the effect on the ketone bodies, which are in many respects of more importance in estimating the patient's condition than the amount of glycosuria.

Messrs. Carnrick, in their literature relating to the pancreatic extract put on the market by them, give a graph showing the blood sugar and urine sugar in a case treated on their preparation. In this case the sugar disappeared from the urine and the blood sugar fell to normal in a few days. They state, however, that the patient was placed on a restricted diet, presumably at the same time as he started taking the pancreatic extract, so that the fall in blood and urine sugar may have been due to the restricted diet. Indeed, in the light of my observations (recorded later) there is little doubt that the diet was the only effective factor.

Another point which must be considered is the fact that diabetes is well known to vary from time to time, and that temporary improvement may occur apparently spontaneously.

Various claims as to the exact method of action of pancreatic preparations for oral administration are made by the vendors. In most cases these claims are rather vague, and generally state or infer that the active component is insulin. These assertions must obviously be wrong, as insulin is destroyed rapidly in the stomach and intestine. It is, however, possible that there may be some other substance, not insulin, present in these preparations which, when administered orally, may be absorbed and stimulate some mechanism which controls carbohydrate metabolism in the body.

It has been found experimentally in dogs that if the pancreas be completely removed, injections of insulin will only keep the dog alive for a short period. If, however, a very small portion of the pancreas be left, insulin injections will keep the dog alive for an indefinite period. This rather points to the fact that the pancreas may secrete some other internal hormone besides insulin, and it is conceivable that this substance, whatever it may be, might be present in the oral preparations and might be absorbed from the alimentary tract when administered by the mouth. If this were so it might benefit cases of diabetes to be treated with these preparations, even though, of course, they were not absorbing any of the insulin contained in the preparations. All kinds of theories could be formed as to the type and mode of action of this pancreatic secretion, but as its presence is a pure hypothesis, conjectures as to its