"The Metabolic and Respiratory Action of Aspirin"

by

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Contents.

Introduction.

The antipyretic-analgesic action of salicylate and the well-known stimulation of respiration resulting from large doses of the drug have generally been attributed to a central action on the nervous system. Doubts about the validity of this view were first aroused when it was found that the analgesic action of salicylate in the acute arthritis of rheumatic fever was invariably accompanied by diminution in joint swelling (Reid, Watson & Sproull, 1950). This observation was supported by the fact that no precise site of action in the brain is known where a drug may relieve pain without affecting consciousness. Furthermore, doubts about a central action were strengthened by the establishment of salicylate as a metabolic stimulant in man (Cochran 1952) and by appreciation of the specificity of salicylate in relieving rheumatic fever (Gaddum 1955). Finally the possibility of a central action was rejected by the discovery that the metabolic action was peripheral and could be demonstrated with tissue slices (Sproull 1954), which had no connections with the nervous system.

This metabolic stimulant effect of salicylate has been clearly demonstrated in plants, in animal tissues and in whole animals including man. In 1957 Reid showed that the oxygen consumption of wheat coleoptile segments was increased when grown in salicylate solution. Reports of animal tissue response were confused, including a negligible effect as well as ones of stimulation and depression according to the drug concentration used (Alwall 1939, Lutwak-Mann 1942 and Fishgold et al 1951). The matter was resolved however in 1954 when Sproull showed the true pattern of salicylate stimulation in mouse liver slices over the complete dose range. In rabbits (Reid 1952), dogs (Dodd et al 1937, Tenney & Miller 1955) and rats (Meade 1954), parenterally administered salicylate was shown to increase oxygen consumption. More recently, oral administration of the drug to man both in health (Cochran 1952) and in disease (Cochran 1952, Alexander & Johnson 1956) has proved that the metabolic stimulating effect could also be demonstrated in the human. The precise dose-response relations however have still to be determined.

The main purpose of this work was to determine

the dose- or concentration-response relations between oxygen consumption and serum salicylate level in man. The obvious difficulty of obtaining normal subjects for long-term salicylate administration in order to establish a control series had to be overcome by referring to a group of convalescent rheumatic patients who were being maintained on aspirin and were clinically and biochemically normal at the time of the investigations. When the concentration-response relation was established in these patients, observations were extended to a miscellaneous group of patients and the results compared. This group included an obese woman, a diabetic receiving aspirin in a trial of its hypoglycaemic activity, and several myxoedematous patients whose resting metabolic rates were characteristically subnormal and who were being treated with aspirin to study the effect on the metabolic rate and on the manifestations of myxoedema.

In addition to defining the concentration-response relationship in these patients, measurement of carbon dioxide production as well as oxygen consumption was made in a selected group of convalescent controls over a similar period of aspirin therapy

and the pattern of change in respiratory quotient was determined.

A quantitative investigation of the respiratory response to salicylate was also undertaken in convalescent and myxoedematous patients to clarify the relationship between metabolic stimulation and respiratory stimulation after salicylate. When this was completed a comparison between salicylate and 2:4-dinitrophenol was made to find out whether or not these two stimulants had a similar action regarding oxygen consumption and respiration, and the comparison was extended to observations of the glycogenolytic action of both salicylate and dinitrophenol in the rat.

Chapter 1.

The Metabolic Response to Salicylate.

The quantitative aspects of the relationship between salicylate administration and metabolic stimulation in man have been examined. Difficulty in obtaining normal individuals to take salicylate for prolonged periods has already been mentioned and made it necessary to confine the investigation to patients convalescent from rheumatic fever. Clinical signs of active rheumatic disease were absent, the erythrocyte sedimentation rate and plasma fibrinogen were normal and there was no evidence of metabolic or biochemical abnormality when the investigation was carried out. Thus, while the metabolism of these patients did not differ in any known respect from that of normal individuals it is emphasised that they were employed as controls or, rather, reference standards for the purposes of this investigation only.

The patients received 3 to 10 g. aspirin daily in divided doses. By adjusting the doses, a wide

scatter over the therapeutic dose-range was obtained in each case. Estimations of oxygen consumption were made with a Benedict-Roth apparatus three to four times each week over a period of two to four weeks at about 9 a.m. Patients were either fasting or were given one cup of tea and half a slice of buttered toast at least two hours previously. Duplicate tracings of oxygen consumption were obtained and the results were accepted only if they were within 10 ml. oxygen/min. of each other at standard temperature and pressure (s.t.p.). This is equivalent to a variation of $\pm 3\%$ oxygen consumption of a man's average rate, taken as 300 ml./min. at s.t.p. The untreated control oxygen consumption of each subject obtained after salicylate therapy had been discontinued was either the lowest of three or more consecutive daily runs, or was the same on two consecutive daily runs. This value provided the base-line from which the effect of salicylate administration on oxygen consumption was judged. Results have been expressed as a percentage of the normal basal metabolic rate (B.M.R.), determined by the standards of Robertson & Reid (1952) and adjusted for the surface area of the individual.

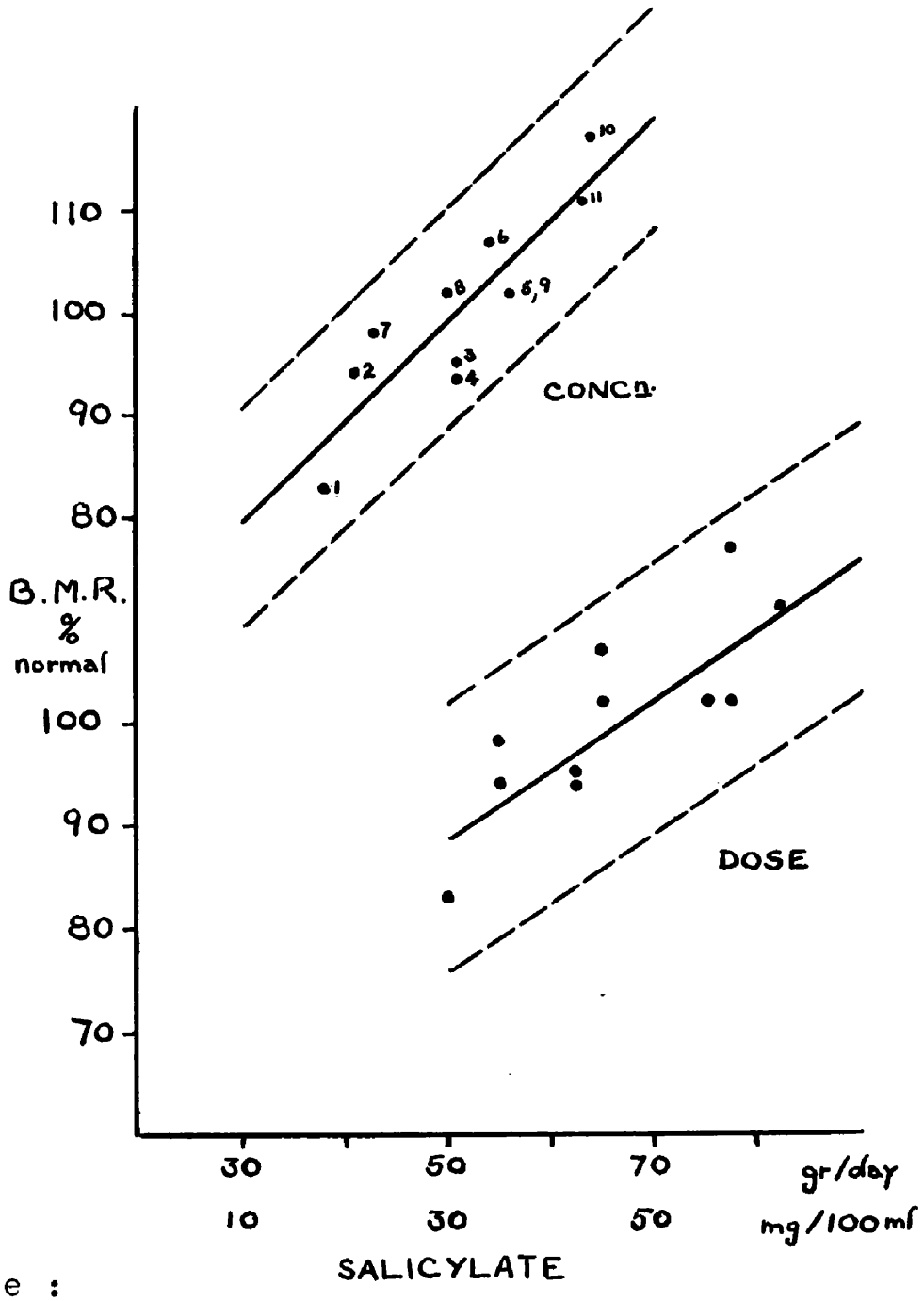
Venepunctures were carried out immediately after the B.M.R. for the estimation of the serum drug level by the Trinder (1954) method.

Before detailed investigation of the convalescent patients was carried out, it was necessary to decide by preliminary experiment whether oral dose or serum concentration of the drug would be the more practical and accurate index of reference for the metabolic response. Guidance on this point was obtained by determining dose-response and concentration-response curves in one patient. The results are shown in Table 1 (Appendix), where it will be observed that over a period of 15 days the dose was progressively increased every 2 days from 50 gr. to 82.5 gr. (3.2 to 5.3 g.)/day, the serum salicylate steadily rising from 18 to 44 mg./100 ml. and the oxygen consumption from 155 to 218 ml./min. at s.t.p. This represented an overall increase in B.M.R. of about 40%.

The relation between dose of aspirin and B.M.R., and serum concentration and B.M.R. were examined separately and details of the results are shown in Fig. 1. From inspection of the two scatter

Fig.1.

Comparison of dose-response and concentration-response curves.



Note :
As will be seen from the numbering of the observations in the concentration-response diagram in chronological order, no evidence of tolerance to the drug occurred during the period of investigation.

diagrams, it was noted that although each set of points approximated to a straight line, the scatter was greater in the case of the dose-response diagram. From the data shown, regression lines were drawn. The dose-response curve gave a correlation coefficient, $r = 0.79$ ($P < 0.01$) and the standard deviation of the scatter $\sigma = 5.95$. The equation of the regression was $y = 0.68x + 55.25$. The concentration-response curve gave a correlation coefficient, $r = 0.88$ ($P < 0.001$) and the standard deviation of the scatter $\sigma = 4.64$. The equation of the regression was $y = 0.98x + 69.5$. 95% confidence limits of the lines were drawn (± 13.27 for dose-response and ± 10.49 for concentration-response, Fig. 1).

The significance of the dose-response and concentration-response regression lines were each estimated by comparing the mean square and the residual mean square (Table 2). F ratio for dose-response = 13.1 ($0.1 > P < 1.0$) and for concentration-response = 28.2 ($P < 0.1$).

Thus preliminary investigation indicates that drug concentration is a suitable dose metameter. Neither is the choice of concentration rather than dose unexpected from pharmacological considerations

Table 2.

(a) Dose-response regression equation:

$y = 0.68x + 55.25.$ $n = 11.$

Source of variation	Sum of squares	Degrees of Freedom	Mean squares
Due to regression	528.1	1	528.1
Residual	321.0	8	40.1
Total	849	9	

Variance Ratio = 13.1

Therefore 0.01 $P < 0.001$.

(b) Concentration-response regression equation:

$y = 0.98x + 69.5.$ $n = 11.$

Source of variation	Sum of squares	Degrees of Freedom	Mean squares
Due to regression	669.4	1	669.4
Residual	189.6	8	23.7
Total	859.0	9	

Variance Ratio = 28.2

Therefore $P < 0.001$.

connected with oral therapy, such as variation in absorption and the comparatively long time required to attain a stable response for each particular dose. Serum concentration, on the other hand, is more closely related to its pharmacological site of action and it also furnishes an immediate measure of the drug circulating at the time of estimation of oxygen consumption.

For these reasons the serum concentration of salicylate was chosen as the reference index for all the investigations which follow.

Serum Salicylate Concentration and Metabolic Rate in Convalescents.

Concentration-response curves of seven convalescent patients, three males and four females, were determined. The ages of the patients ranged from 14 to 37 years. Particulars of the metabolic response of each patient to aspirin are given below, and a summary of the clinical data is given in Table 3 (Appendix).

Patient G.W. (Case 1) a young man 25 years

old, was studied for 20 days. During this time the serum salicylate ranged from 15 to 50 mg./100 ml. After aspirin administration was discontinued and no salicylate was detected in the blood, the normal resting B.M.R. was determined. The control B.M.R. after stopping aspirin was 101%: the maximum metabolic rate reached during treatment was 132%, and this coincided with the highest serum concentration of the drug. Eighteen observations were made and a closely correlated linear regression was derived: $r = 0.91$, ($P < 0.001$) and the 95% confidence limits of the line only ± 4.79. The equation of the regression was $y = 0.59x + 102.5$ (Fig. 2 Table 4 (Appendix).

Patient S.H.(Case 2), a young woman of 24 years was investigated over 18 days. Serum salicylate concentrations varied from 13 to 51 mg./100 ml. and the B.M.R. rose from 83% to 122%. Because of this unusually low post-treatment value, this patient was readmitted to hospital at a later date for investigation of thyroid function. ^{131}I uptakes of her thyroid gland, showed no abnormality and this, together with the complete absence of any clinical signs of myxoedema, ruled out the possibility

of hypothyroidism. It was concluded that she had a low but normal resting metabolic rate which was within the limits quoted for normal British men and women in a recent report (Booyens & McCance 1957).

Good linear correlation was again shown between serum salicylate and B.M.R.: $r = 0.92$, ($P < 0.001$) and the 95% confidence limits of the regression line were ± 12.24. The equation of the regression was $y = 0.94x + 71.8$, (Fig. 3 Table 5).

Patient R.C. (Case 3) was a young man of 23 years. Normal convalescence continued throughout the period of investigation. Eighteen observations were made during 28 days. Serum salicylate concentrations ranged from 6 to 49 mg./100 ml. and the B.M.R. rose from a post-treatment value of 117% to a maximum of 149% normal. The regression line drawn from these observations showed linearity, with a coefficient of correlation, $r = 0.76$ ($P < 0.001$) and the 95% confidence limits of the line ± 17.87. The equation of the regression was $y = 1.11x + 93.7$ (Fig. 4 Table 6).

Patient A.W. (Case 4) was a young man of

18 years who was studied during convalescence during a period of 32 days. Fifteen observations were made. The range in serum salicylate concentration was 8 to 52 mg./100 ml.; the B.M.R. rose to a maximum of 133% of normal from a non-treatment control value of 103%. A close linear correlation was established, $r = 0.93$, ($P < 0.001$), and the 95% confidence limits of the line were ± 10.07. The equation of the regression was $y = 0.85x + 86.2$ (Fig. 5 Table 7).

Patient C. McC. (Case 5), a young woman aged 37 years, was studied during a convalescent period of 27 days. Fifteen observations were made while receiving treatment with aspirin, after which the customary establishment of the untreated control B.M.R. was determined after discontinuing aspirin. The serum salicylate concentration varied from 10 to 49 mg./100 ml. This patient's post-treatment B.M.R. was 102% normal and the maximum achieved during therapy was 166%. Linear correlation between serum salicylate concentration and response was again shown, $r = 0.91$ ($P < 0.001$). The 95% confidence limits of the line were ± 15.94 and the equation of the regression was $y = 1.20x + 105.1$ (Fig. 6 Table 8).

Patient J.McW. (Case 6), was a girl of 16 years. Over a period of 32 days the serum salicylate concentration varied from 17 to 74 mg./100 ml., and her B.M.R. rose to a maximum of 168%. The control post-treatment value was 95% normal. The regression line constructed from 12 observations showed linearity, the correlation coefficient, $r = 0.88$, ($P < 0.001$). The scatter of points in this individual was fairly extensive, the 95% confidence limits of the line being ± 30.1. The equation of the regression was $y = 1.48x + 65.5$ (Fig. 7 Table 9).

Patient M.Gr. (Case 7), aged 14, was the last of the convalescent control patients to be studied over a period of 29 days. Fourteen observations were made while she was receiving salicylate therapy and her untreated control B.M.R. was then determined. Salicylate concentrations ranged from 10 to 50 mg./100 ml., and the B.M.R. rose from a control value of 96% normal to a maximum of 151%. The correlation coefficient of the linear regression so formed was $r = 0.95$, ($P < 0.001$). 95% confidence limits of the line were ± 15.2. The equation of the

regression was $y = 1.37x + 73.1$ (Fig. 8 Table 10).

In each of the seven convalescent patients a linear correlation was established between the serum salicylate concentration, expressed as mg./100 ml., and metabolic stimulation. In every case the significance of the probability of linearity was $< 0.001\%$. (Table 11).

Before examining the results of the individual patients to find out whether a composite regression line could be established for the group as a whole, the relation of the individual lines to the patients' ages was examined. Their ages and the slopes of the regression lines were as follows:-

Age in yrs.	Regression coefficient b	Patient's No.
14	1.37	7
16	1.48	6
18	0.85	4
23	1.11	3
24	0.94	2
25	0.59	1
37	1.20	5

Between the ages of 14 and 37 years no obvious trend in the values of the regression coefficients was noted when taken in ascending order of age of the patients.

The next step was to examine the seven regression lines on the same graph (Fig. 9) and it was observed that the difference of slopes and intercepts between the convalescents was not great and the obvious question that arose was whether these seven convalescents could be regarded as one, as far as their metabolic stimulation from aspirin was concerned. This led to the construction of a composite concentration-response curve using the 104 pairs of observations in the seven cases. The initial non-treatment values of the B.M.R. varied from patient to patient, so that a more accurate assessment of the degree of stimulation was obtained by expressing each observation as the increment of oxygen consumption (ΔO_2) in cals./m^2/hr. above the individual's untreated control value.

The composite regression curve so formed had a coefficient of correlation $r = 0.896$, ($P < 0.001$). The equation of the regression was $y = 0.46x - 7.6$, and the 95% confidence limits of the line were ± 5.94, which was a measure of the difference in response due to individual variation in this control group (Fig. 10, Table 12).

Fig. 9.

Summary of concentration-response curves

cases 1 to 7.

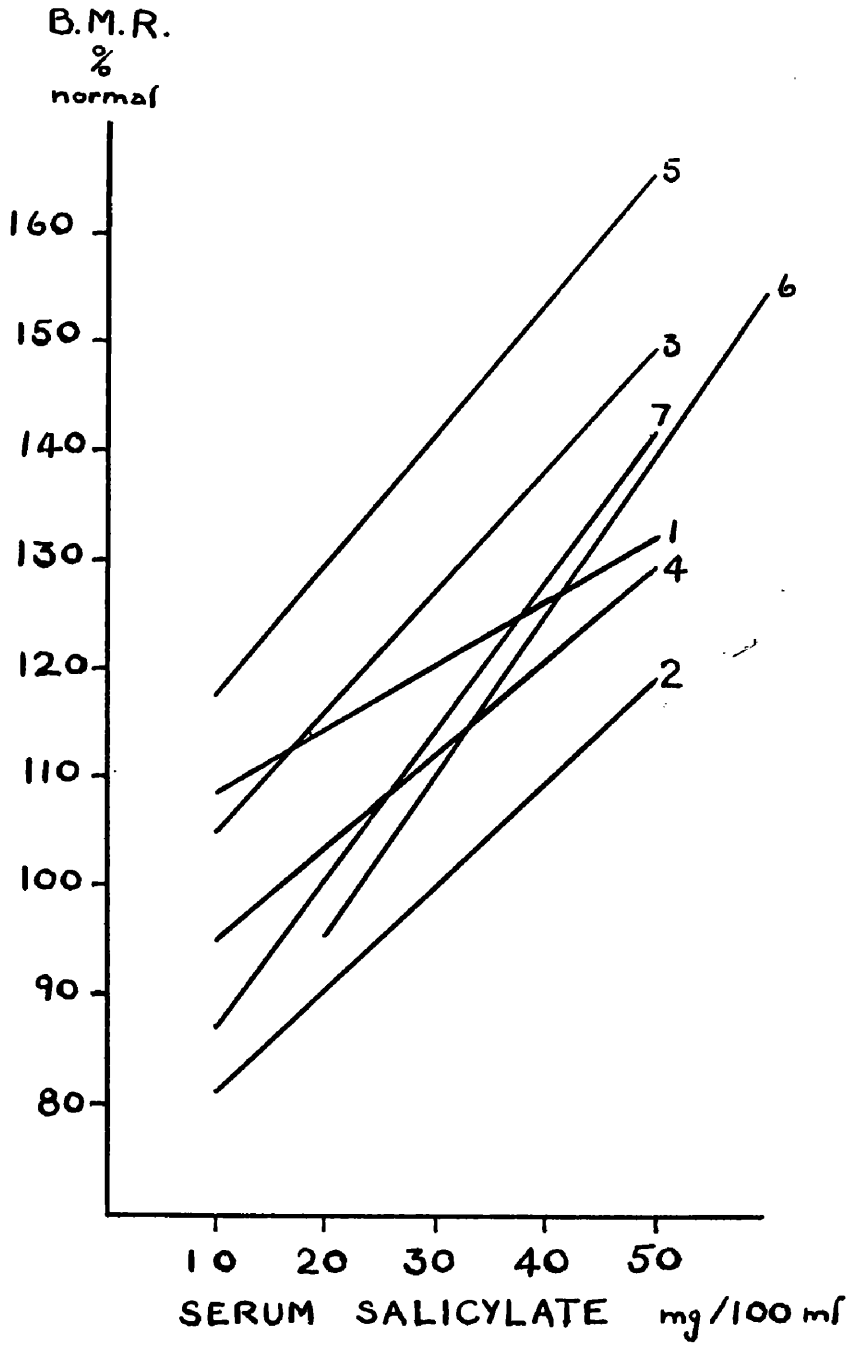
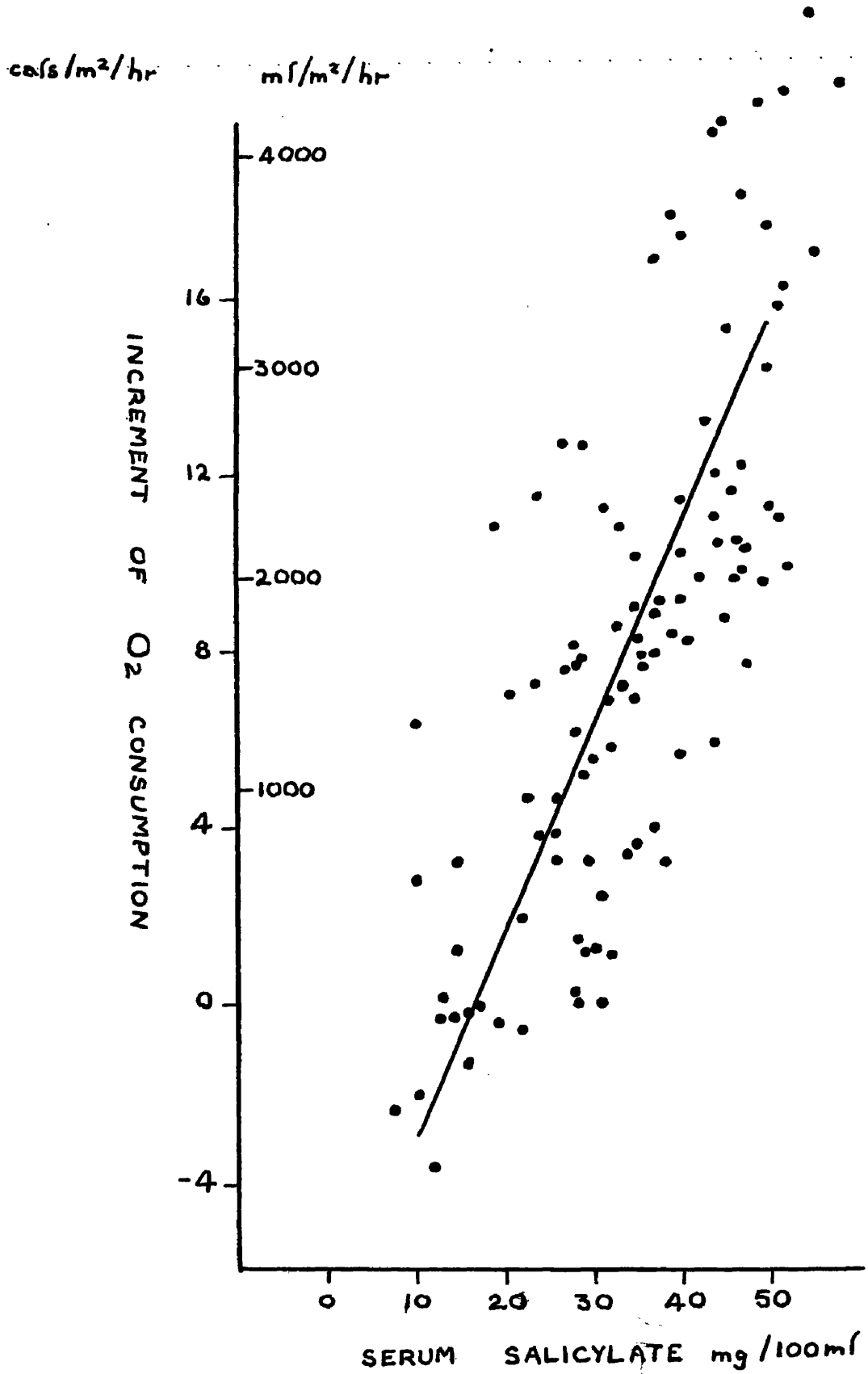


Fig. 10.

Composite regression line: convalescents.

cases 1 to 7.



The main purpose in establishing this concentration-response relationship in the convalescent rheumatic patients was to compare the metabolic response to aspirin in other diseases, particularly in myxoedema where the metabolic rate at the outset was below normal. Six patients with primary myxoedema were given a course of aspirin and observations of their oxygen consumption in relation to the serum concentration of salicylate were made.

Serum Salicylate Concentration and Metabolic Rate in Myxoedema.

Concentration-response curves of six myxoedematous patients were constructed in exactly the same manner as that of the convalescent rheumatics except that the untreated control value of the B.M.R. was determined before starting salicylate administration. Particulars of each patient and the metabolic responses to salicylate will be presented before proceeding to examination of the group concentration-response curve.

Patient M.McM. (Case 8), a man of 52 years was thought to have had myxoedema for three to four

years. He presented the classical stolid facies with scaly appearance of the skin, and had recently complained of incapacitating attacks of angina. He was well built but was not overweight. Radio-iodine studies confirmed the diagnosis of myxoedema (4-hourly uptake of ^{131}I by the thyroid gland was 7.4% of the dose administered, which was barely half of the minimal value accepted in cases of normal thyroid function). Oxygen consumption and serum salicylate were estimated on nine occasions over a period of 23 days including the basal control period for establishing a pre-treatment B.M.R.. The serum salicylate concentration varied from 16 to 46 mg./100 ml. and the B.M.R. rose from 76% to 108% normal. No deleterious effects were noted at any point during the trial and no increase in anginal symptoms was noted even at the height of metabolic stimulation. A very close linear correlation was established between drug concentration and response, the correlation coefficient, $r = 0.97$, ($P < 0.001$). 95% confidence limits of the line were ± 6.8 and the equation of the regression was $y = 1.08x + 59.1$ (Fig. 11, Table 13 (appendix).

Patient A.McL. (Case 9), a woman of 65 years had myxoedema which had been diagnosed some 10 years previously. For some time prior to this trial with salicylate she had been without adequate therapy and on admission complained of lethargy and angina of effort. Routine radio-iodine tests confirmed the diagnosis (uptake of ^{131}I by the thyroid four hours after administration of the dose was 8.1%). Fifteen observations during a period of 23 days were made while she was receiving aspirin. Variation in salicylate concentration from 9 to 49 mg./100 ml. was accompanied by an increase in metabolic stimulation of up to 117% normal. The pre-treatment B.M.R. was 85%. A linear regression was formed with a correlation coefficient, $r = 0.93$, ($P < 0.001$) and 95% confidence limits of the line ± 10.3. The equation of the regression was $y = 0.99x + 69.2$ (Fig. 12, Table 14).

Patient I.McG. (Case 10) was an obese woman of 72 years who presented as a case of long-established myxoedema with retarded mental processes, deafness, slurring of speech as well as the typical facies. ^{131}I tests confirmed the diagnosis of hypothyroidism by a 4-hour uptake of the thyroid gland of 7.1% of the

dose. Additional injection of TSH established the myxoedema as primary. Tests of metabolic stimulation were carried out during 25 days. Seventeen observations were made, while the salicylate concentrations varied from 20 to 56 mg./100 ml. The pre-treatment B.M.R. was as low as 61% and rose with treatment to 97% normal. Analysis showed a highly significant linear correlation, the coefficient $r = 0.96$, $(P < 0.001)$. Small variation due to the individual's response to a given dose was noted and the 95% confidence limits of the line were ± 6.4. The equation of the regression was $y = 0.88x + 50.6$ (Fig. 13, Table 15).

Patient F.F. (Case 11) was a 72 year old woman, overweight and anaemic, with dry opalescent skin and typical appearance of hypothyroidism. Radio-iodine studies again confirmed the diagnosis. She was investigated over a period of 29 days. The serum salicylate level varied from 14 to 52 mg./100 ml. during which 15 observations were made. Her pre-treatment B.M.R. was 80% and with aspirin a maximum of 114% was reached. Analysis of the points showed a linear regression with a coefficient of correlation,

$r = 0.94$, ($P < 0.001$) and 95% confidence limits of the line ± 7.7. The equation of the regression was $y = 0.83x + 69.4$ (Fig. 14, Table 16).

Patient M.B. (Case 12) was a woman of 43 years who was thought to have had myxoedema for about a year. She was not obese but had been aware of a change of countenance and unusual lassitude. Radio-iodine studies confirmed myxoedema (^{131}I uptake by the thyroid gland after 4 hours was 10.6% of the dose given) and injection of TSH showed that it was a primary type. B.M.R.'s were carried out over a period of 28 days. Thirteen observations were made during which the salicylate concentration ranged from 16 to 59 mg./100 ml. This patient's pre-treatment B.M.R. was 78% and the maximum reached during aspirin therapy was 115% normal. The linear regression formed by the points gave a correlation coefficient, $r = 0.95$ ($P < 0.001$). The 95% confidence limits of the line were ± 9.8 and the equation of the regression was $y = 0.93x + 62.3$ (Fig. 15, Table 17).

Patient F.A. (Case 13), aged 52, was a tall well-built woman with myxoedematous appearance and

complaining of anginal pain. Her B.M.R. was 80% normal and the diagnosis was confirmed as before by estimation of ^{131}I uptake of the thyroid (at 4 hours, 11.1%). She was investigated over 20 days, during which the serum salicylate concentration ranged from 9 to 50 mg./100 ml. and the B.M.R. rose as high as 106% normal. Thirteen observations were made and a linear regression was again established. The correlation coefficient, $r = 0.92$ ($P < 0.001$) and the 95% confidence limits of the line were ± 10.3. The equation of the regression was $y = 0.73x + 68.3$ (Fig. 16, Table 18).

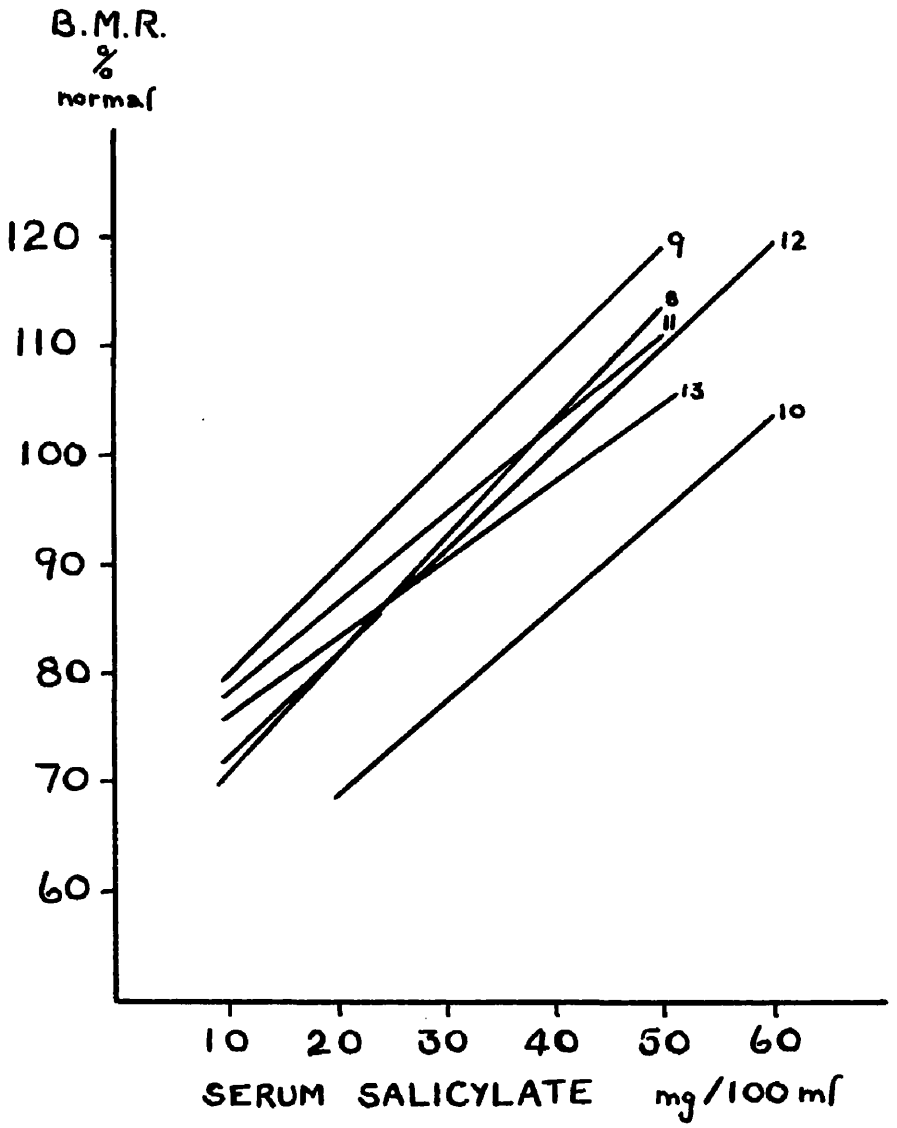
These results indicate that the metabolic stimulating effect of salicylate in patients with myxoedema is also closely correlated with the serum salicylate concentration. A graphical summary of the data from all the myxoedematous patients is presented in Fig. 17 and details of their clinical particulars are summarised in Table 3.

The regression data are summarised in Table 11. A composite regression line was constructed from the 82 points derived from all the observations on the myxoedemas, each one expressed as an increment of

Fig. 17.

Summary of concentration-response curves

cases 8 to 13.



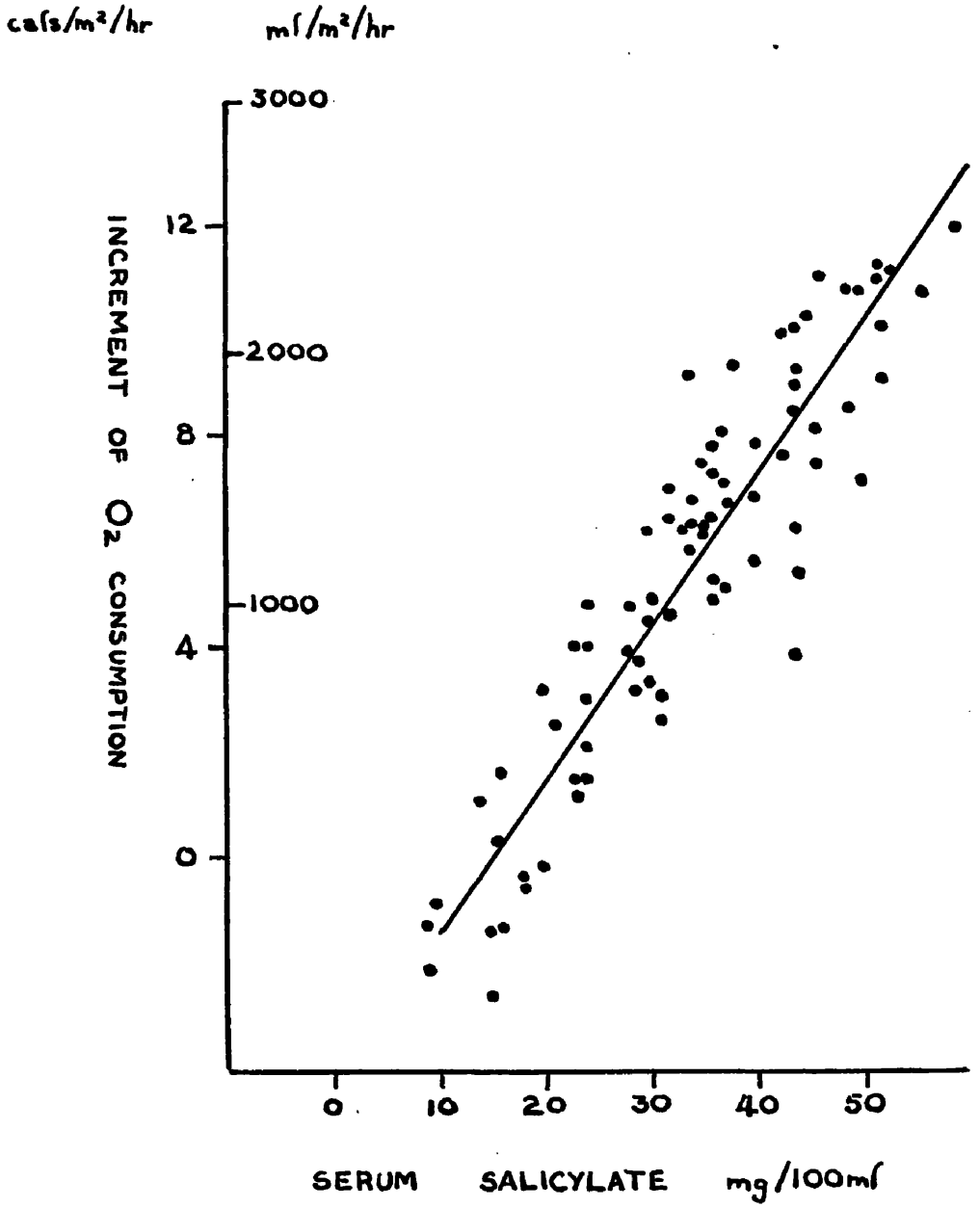
the individual's value before treatment. The coefficient of correlation for the group as a whole was r = 0.94 ($P<0.001$) and the 95% confidence limits of the line were ± 2.54. The equation of the regression was y = 0.29x - 4.26 (Fig. 18, Table 19).

Comparison of the Myxoedematous and the Convalescent Rheumatic Group.

From inspection of the composite lines of the convalescent rheumatics and the patients with myxoedema (Figs. 10, 18), it was noted that the myxoedematous group approximated more closely to a linear function than did the convalescent group. This may be due to the nature of the disease process in myxoedema. The mental state is one of lethargy, although the patients are usually eager to cooperate. Slow deliberation is characteristic of any physical movement. It is therefore understandable that determination of a response like B.M.R. which is, to a large extent, dependent on the patient's ability and willingness to achieve a basal unemotional condition should be technically superior in those people whose existence tends toward the vegetative.

Fig. 18.

Composite regression line : myxoedematous patients, cases 8 to 13.



This difference in individual variation in response was substantiated by the confidence limits of the two composite lines viz. ± 2.54 for the myxoedematous group and ± 5.94 for the reference group of convalescents (Tables 12 and 19).

It was also observed (Fig. 18) that the gradient of the myxoedematous group was considerably less steep than that of the convalescent rheumatic group (Fig. 10). The two lines were therefore examined for difference in slope and intercept:

Equation of regression line of myxoedematous group

$$y_1 = 0.29x_1 - 4.26$$

Equation of regression line of convalescent group

$$y_2 = 0.46x_2 - 7.6.$$

Analysis of variance of the regression coefficients $b_1 = 0.29$ (myxoedema) and $b_2 = 0.46$ (convalescent), gave

Weighted average residual variance = 2.18.

Variance of their difference = $0.00031 = \sigma_{12}^2$

calculated $t = (b_1 - b_2)/\sigma_{12} = 9.4$.

For $(n_1 + n_2) = 186$ degrees of freedom, $t_{0.05} = 1.96$.

Therefore calculated $T > t_{0.05}$.

It was therefore concluded that the slopes of the two groups were significantly different from one another.

The intercepts of the two lines were compared by using the formula:-

$$\frac{a_1 - a_2}{s\sqrt{\frac{1}{n_1} + \frac{1}{n_2} + \frac{\bar{x}_1^2}{\Sigma(x_1-\bar{x})^2} + \frac{\bar{x}_2^2}{\Sigma(x_2-\bar{x})^2}}} \qquad \text{(a)}$$

Expression (a) = 1.32, and is distributed as t. For (n - 3) degrees of freedom i.e. 183, this distribution of t gave a less than 10% degree of significance of difference.

It was concluded the lines showed no difference in intercept.

Summary of the Concentration-Response Data.

A series of seven clinically normal convalescent rheumatics receiving oral aspirin was chosen as a standard reference group and measurement of change in oxygen consumption was made with different amounts of the drug in order to assay quantitatively the metabolic response. Using serum salicylate concentration as the abscissa and basal metabolic rate as the ordinate, linear correlation was derived in each case over the therapeutic dose range. A

composite regression line was constructed and the responses of other individuals were compared with the response of the convalescents. A composite regression line formed from data of myxoedematous patients showed a difference in gradient, though not in intercept. It was noted too that one other patient (Case 14, Fig. 19, Table 20), with simple obesity, showed a response to salicylate which approximated more closely to the response of the myxoedematous group, while the metabolic response of one diabetic patient (Case 15, Fig. 20, Table 21), treated with salicylate was indistinguishable from that of the convalescent group. No conclusion is drawn from these isolated cases.

It was concluded that over a period of 2-4 weeks, the action of salicylate on the oxygen consumption may differ in different individuals, in particular where thyroid function is absent. In order to clarify the nature of this dissimilarity it was necessary to know whether thyroid function itself was being affected by salicylate. This had in fact been investigated (Alexander & Johnson 1958) by means of radio-iodine tests, and the results indicated that over a period of up to eight weeks, no effect on thyroid as judged by radio-iodine uptake was evident.

Chapter 2.

The Effect of Salicylate on Respiration.

Deepening of the breathing was one of the earliest of the clinical effects observed to follow treatment of acute rheumatism with salicylate (Langmead 1906, Madisson 1934) and after experimental administration of salicylate to man (Odin 1932, Cochran 1952). It is now a well established effect and has more or less empirically been attributed to direct stimulation of the respiratory centre (Goodman & Gilman, 1941). Indirect evidence supporting this view was put forward by Rapoport & Guest (1945), who demonstrated that salicylate induced an alkalosis in monkeys and dogs, which was accompanied by hyperventilation. A similar alkalosis accompanied by hyperventilation has been confirmed in man (Ryder et al 1945, Farber et al 1949, and Reid et al 1952). The reaction change of the blood was attributed by Rapoport & Guest (1945) to stimulation of the respiratory centre leading to the loss of excessive quantities of carbon dioxide from the lungs, which in

turn gave rise to the alkalosis. The mechanism was analogous to the primary respiratory alkalosis induced by voluntary or hysterical overbreathing.

As a refinement to direct stimulation of the respiratory centre, Graham & Parker (1948) suggested that the action of salicylate was at vagal nerve endings, since they claimed that hyperventilation from intravenous injection of salicylate could be prevented by section of the vagus nerves in cats. Cochran & Ramsay (1957), however, employing a more precise method of measuring pulmonary ventilation, could not confirm this claim. They found that section of the vagi did not prevent hyperventilation following injection of sodium salicylate in these animals.

While investigating respiratory gaseous exchanges in rabbits, Reid (1957) observed that increased output of carbon dioxide did in fact result from injection of sodium salicylate, but this was accompanied by a simultaneous and more pronounced increase in the oxygen consumption. These observations, in conjunction with the establishment of the drug as a peripheral metabolic stimulant (Sproull 1954), led to an alternative explanation of the respiratory stimulant action of salicylate. Reid (1957) concluded that the

drug was a primary metabolic stimulant and suggested that the respiratory changes followed the increased oxygen requirement. In his interpretation the alkalosis was secondary to a relative diminution of carbon dioxide production attributable to stimulation of nitrogen katabolism, and confirmed by a fall in respiratory quotient.

Samet (1958) also suggested that the primary action of salicylate might be metabolic rather than respiratory as a result of investigations of the ventilatory response to carbon dioxide in patients with pulmonary emphysema. Several such patients were allowed to breathe air containing differing amounts of carbon dioxide, and measurement of the minute volume was made before and after salicylate therapy. The same increase in ventilation was noted whether the patients breathed 3% or 5% carbon dioxide, so that the slope of the ventilatory response curve during carbon dioxide inhalation was not increased. As a possible clinical application they decided that the depressed ventilatory response in pulmonary emphysema could not be reversed by salicylate, and made the suggestion that the increase in ventilation was secondary to the metabolic response of salicylate.

The possibility that the respiratory stimulation of salicylate in man was secondary to the metabolic stimulation has been investigated directly by measuring increments in pulmonary ventilation and in oxygen consumption resulting from salicylate administration, and comparing these results with the findings already established under physiological conditions such as muscular exercise, when ventilation and oxygen consumption increase proportionately. This was first demonstrated in dogs by Zuntz (1897) and later by Slowtzoff (1903). A similar constancy of the ratio of ventilatory and metabolic increase during exercise was demonstrated in man by Asmussen et al (1943) in a detailed investigation carried out in one subject over a wide range of respiratory stimulation.

In a previous chapter the quantitative relation between serum salicylate concentration and oxygen consumption (and B.M.R.) was established. From the tracings of oxygen consumption with the Benedict-Roth apparatus, measurements of pulmonary ventilation were made. Tidal air was measured to the nearest 50 ml. from the tracing and the respiratory rate was the mean of three or four individual minute counts;

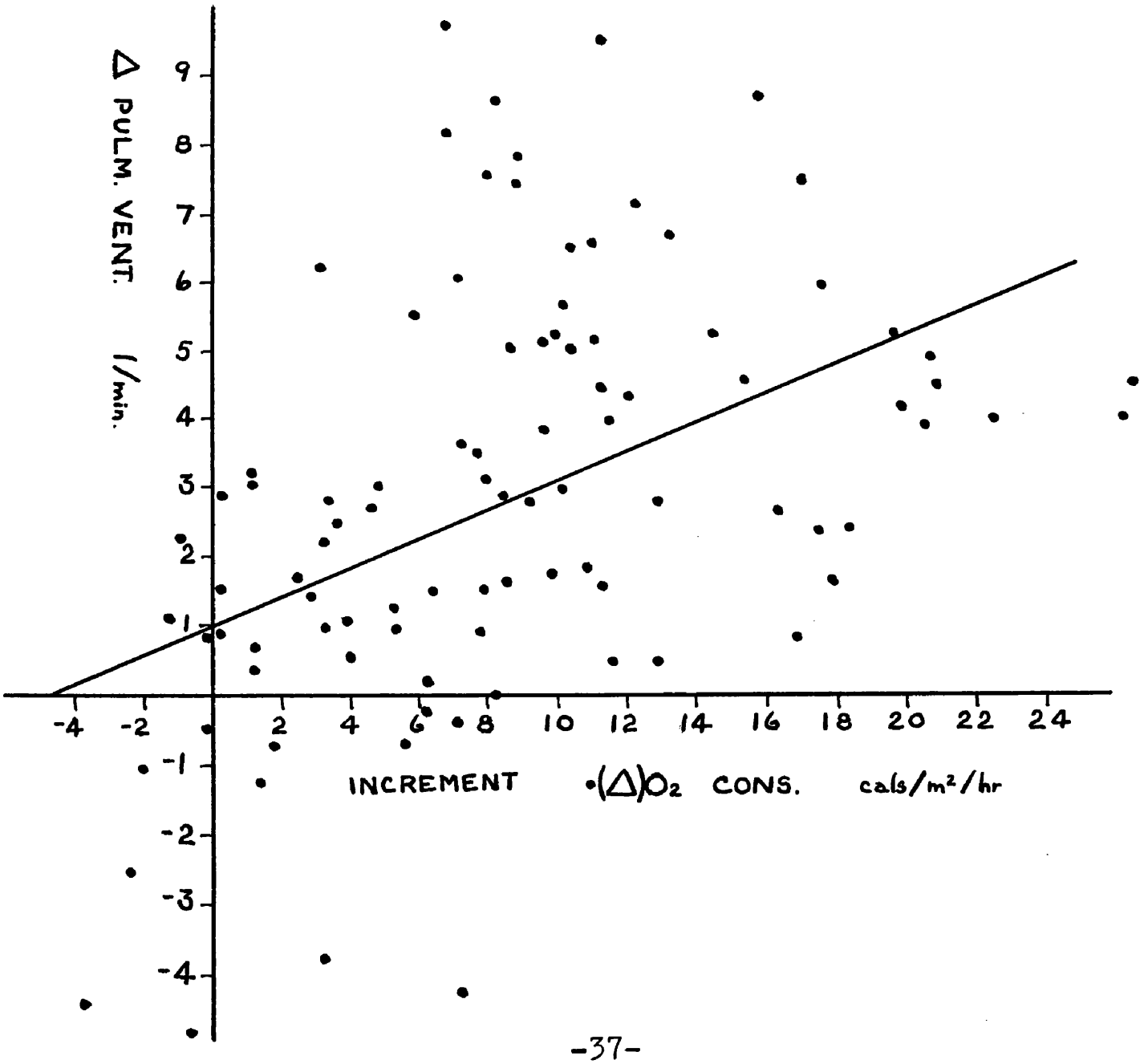
their product, the pulmonary ventilation in litres per minute (l./min.) was then expressed, like the metabolic stimulation as an increment of the patient's pulmonary ventilation value when no salicylate was given. (Tables 22 & 23). The same two main groups, convalescents and myxoedematous patients were considered in turn.

The Relation between Pulmonary Ventilation and Metabolic Stimulation in Convalescent Patients.

Since both oxygen consumption and pulmonary ventilation values were available for each particular serum salicylate concentration over the range 0 to 60 mg./100 ml., it was possible to examine the relationship between them by graphing the 104 pairs of observations (Fig. 21, Table 22), and calculating the regression equation. The relation between the two variables, increment in pulmonary ventilation and increment in oxygen consumption, was not inconsistent with linear function, as evidenced by a correlation coefficient $r = 0.37$, ($P < 0.001$). The scatter of the points was large, which may be accounted for partly by the accuracy with which measurement of tidal air

Fig. 21.

The relationship between pulmonary ventilation and metabolic stimulation in the convalescent patients during salicylate therapy.



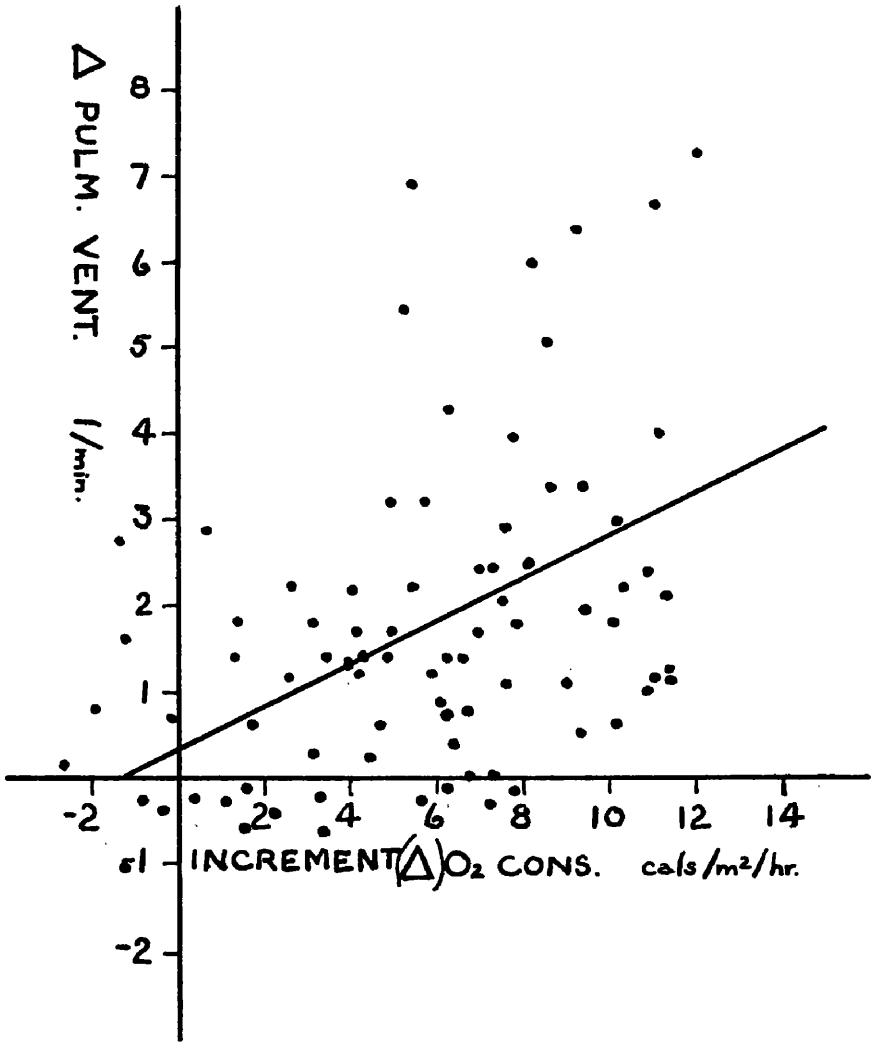
could be made from spirometer tracings. The equation of the regression was $y = 0.22x + 1.0$ where the abscissa represented the increment of oxygen consumption in cals./m^2/hr. and the ordinate the increment in pulmonary ventilation in l./min. It was concluded that, just as during exercise, a direct relationship exists between the respiratory and metabolic stimulation simultaneously induced in man by salicylate.

The Relation between Pulmonary Ventilation and Metabolic Stimulation in Myxoedematous Patients.

The relationship between metabolic stimulation and pulmonary ventilation induced by salicylate was studied in a similar way in the six myxoedematous patients (Nos. 8 to 13). A scatter diagram was drawn of the 82 pairs of observations made over the therapeutic dose range of salicylate. Again the relationship between pulmonary ventilation and oxygen consumption was not inconsistent with a linear function. The correlation coefficient was $r = 0.49$ ($P<0.001$) and the equation of the regression $y = 0.25x + 0.35$ (Fig. 22 Table 23). The scatter of points was much less marked than with the convalescent rheumatic

Fig. 22.

The relationship between pulmonary ventilation and metabolic stimulation in the myxoedematous patients during salicylate therapy.



patients. It was concluded that the metabolic stimulation in myxoedema from the administration of salicylate was accompanied by a proportionate increase in pulmonary ventilation.

From inspection of the two scatter diagrams and the corresponding regression lines (Figs. 21 and 22), it was observed that there was little difference either in slope or intercept of the two lines representing the ratios in the convalescent rheumatic and myxoedematous patients. This visual impression was confirmed by the following analysis.

Comparison of the slopes of the regression lines,

$y_1 = 0.22x_1 + 1.0$, for the convalescents, and

$y_2 = 0.25x_2 + 0.35$, for the myxoedematous,

gave the variance of b_1 (0.22) equal to 0.0016 and the variance of b_2 (0.25) equal to 0.0063. The variance of their difference, $\sigma_{12}^2 = 0.0079$. This gives $t = 0.78$, which is less than $t_{0.05}$ for 182 degrees of freedom, 1.96. Thus there was no significant difference in slope between the two lines.

Comparison of the intercepts made by the two regression lines gave for the expression (a) (Vide chapter 1), the value 0.66. This value is distributed as t. $T_{0.05}$, for 183 degrees of freedom = 1.96. Therefore the

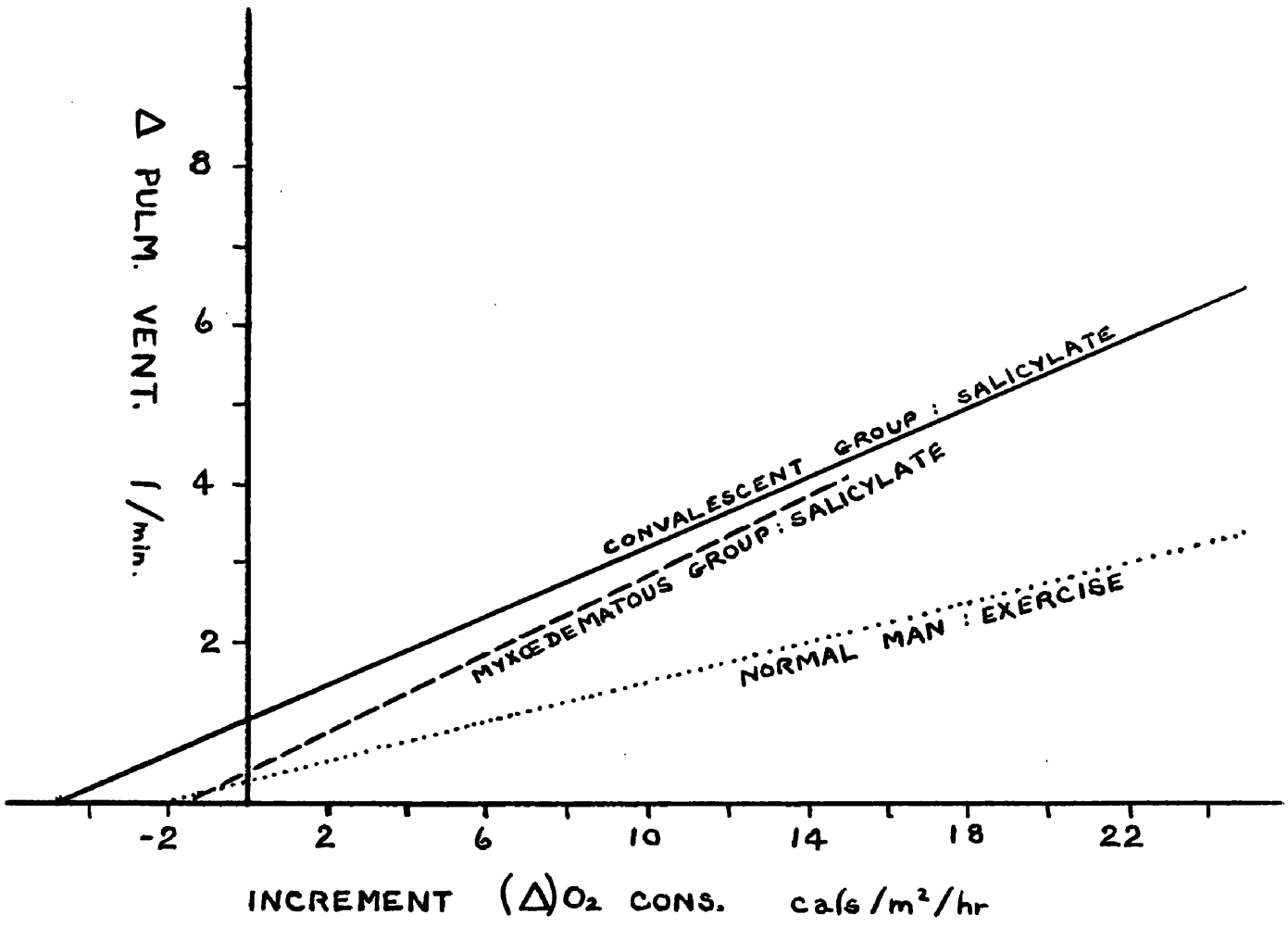
calculated value of $t < t_{0.05}$, indicating that there was at the 5% level of significance no difference in the intercepts made by the two lines.

Thus in both the convalescent and the myxoedematous patients it was shown that the stimulation of oxygen consumption by salicylate was accompanied by a proportionate increase in pulmonary ventilation. It will be remembered that when the increase in metabolic stimulation was plotted against drug concentration, a steeper gradient was seen in the response of the convalescent group (b = 0.46, Fig. 10) than of the myxoedematous group (b = 0.29, Fig. 18,). When however the drug concentration values are eliminated and only the respiratory and metabolic responses are considered, as in this chapter, the difference between the groups is no longer apparent. (Fig. 23). It was thought therefore that although individuals may show a greater or lesser degree of metabolic stimulation, nevertheless the essential mechanism of action of salicylate is likely to be the same, since the ratio of the respiratory response to the metabolic response is almost identical in each case.

In attempting to identify the salicylate response with that of normal exercise, as was done in

Fig. 23.

Comparison of the ratio, pulmonary ventilation : metabolic stimulation during salicylate therapy and during exercise.



..... y = 0.126x + 0.2

_ _ _ y = 0.25x + 0.35

_____ y = 0.22x + 1.0

dogs by Ramsay (1956), it was unfortunate that data for the exercise response in man was confined to meticulous observations in one individual (Asmussen et al 1943). Nevertheless the regression line calculated from his data was found to be $y = 0.126x + 0.2$ and did not materially differ from that obtained for salicylate in both convalescent and myxoedematous patients (Fig. 23). The inference is that increases in pulmonary ventilation to meet increased peripheral demand for oxygen are no different whether they occur as a result of administration of salicylate or voluntary exercise. There is therefore no need to invoke any explanation for respiratory stimulation by salicylate other than the physiological one associated with increased metabolic activity.

Chapter 3.

Respiratory Gaseous Exchange During Salicylate Therapy.

It has been demonstrated that salicylate produces both an increased metabolic rate and a proportionately increased pulmonary ventilation when administered in therapeutic doses to man. Speculation about the particular metabolites affected was made by Cochran (1952), who measured oxygen consumption and carbon dioxide output changes in a one-day experiment using intravenous salicylate, and then over several days using oral salicylate. Barbour & Devenis (1919) had observed no change in respiratory quotient (R.Q.) after a single dose of aspirin, but Cochran demonstrated that if time were allowed for the salicylate concentration in the blood to reach at least 30 to 40 mg./100 ml., a distinct fall in R.Q. would result.

It was decided to reinvestigate the problem of the respiratory gaseous exchange in a few patients receiving aspirin and to pay particular attention to the food intake and appetite over the period, and thus

eliminate R.Q. changes from starvation that might follow the early transient anorexia sometimes encountered in the first few days of full salicylate administration.

While it is recognised that if the R.Q. is to be taken as an indication of the food being oxidised at the time, it is best estimated over a lengthy period (Richardson 1929), nevertheless practical considerations made it necessary to confine the observations to serial and duplicate measurements, each lasting six minutes and the validity of this procedure was confirmed by simultaneous analysis over a longer period with a Haldane gas analyser. The results of this check are described later.

It had been observed (Reid et al 1950) that part of the metabolic changes which result from aspirin administration was an increased protein katabolism evidenced by the excretion of nitrogen in urine and faeces which exceeded the nitrogen intake in food. Faecal nitrogen was small and failure to estimate it would not materially have altered this conclusion. In this work, analysis of urine nitrogen alone was used in the limited nitrogen balance study which was to accompany the investigation of the respiratory exchange.

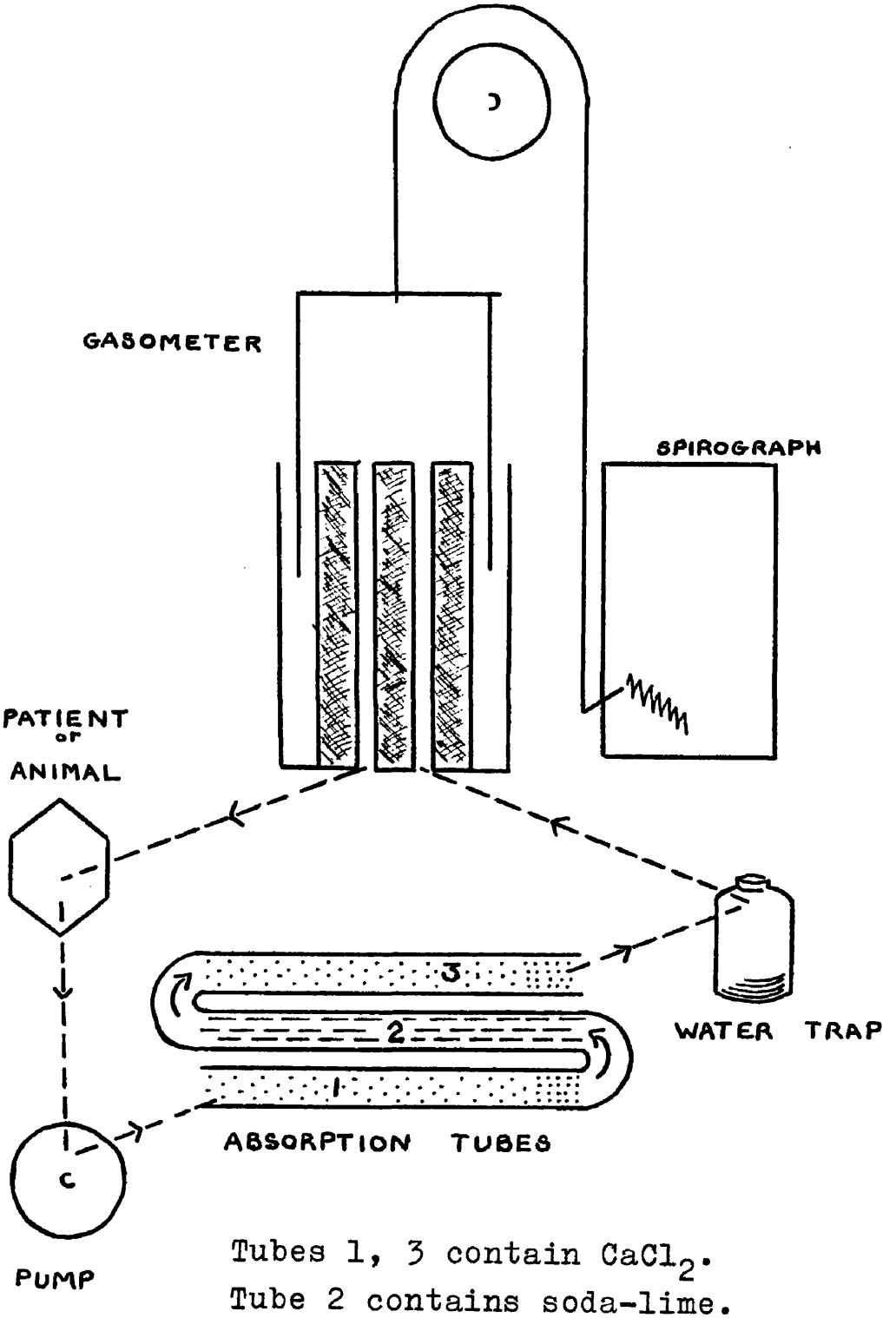
Four rheumatic patients (Cases 16 to 19) were studied. The group included a boy and a girl both aged 16 years and two women aged 29 and 39 respectively. Each patient was given a well-balanced diet, with adequate calories and a known protein intake. Respiratory gaseous exchange and biochemical tests including urinary nitrogen output were carried out before and during administration of salicylate.

Nitrogen intake was calculated from the tables of McCance & Widdowson (1946) and total nitrogen output in the urine was estimated from 24-hour collection by the Kjeldahl method.

Oxygen consumption and carbon dioxide output were measured serially with a modified Knipping spirometer (Fig. 24) at 9 a.m. each day, two and a half hours after a light breakfast consisting of tea, fruit juice and cereal. Oxygen consumption was measured from the spirograph in the usual way; carbon dioxide was trapped in soda lime ("Durasorb") and weighed in the following manner. The Knipping apparatus was modified by replacing the usual carbon dioxide absorbant, a strong solution of KOH, by three "Quickfit" tubes connected in series (after Cameron 1957). Tubes

Fig. 24.

Knipping circuit diagram.



Tubes 1, 3 contain $CaCl_2$.
Tube 2 contains soda-lime.
indicates direction of gas flow.

1 and 3 contained dessicants consisting of 8-14 mesh calcium chloride and a plug of magnesium perchlorate. Tube 2 contained "Durasorb" soda lime as the carbon dioxide absorbant. The tubes were plugged at either end with a little glass wool. The weight of carbon dioxide produced by the patient during the experimental period was measured by the increase in the second and third tubes weighed together. The efficiency of the circuit was demonstrated by the absence of an increase in weight in a second series of tubes inserted after the first.

Duplicate tracings, each of at least 6 minutes, were obtained. Simultaneous determination of expired gases collected with a KM sampler followed by analysis in a Haldane apparatus was performed in two of the patients and showed satisfactory agreement. Results of this comparison are shown in Table 24. Ten sets of observations were made by each method of analysis. The mean oxygen consumption (Haldane) was 250 ± 13.3 ml./min. at s.t.p. and the mean oxygen consumption (Knipping) was 255 ± 14.6 ml./min. at s.t.p. The mean carbon dioxide output (Haldane) was 176 ± 7.1 ml./min. at s.t.p. and the mean carbon dioxide output (Knipping) was 195 ± 5.4 ml./min. at s.t.p.

Table 24.

Comparison of Respiratory Quotients Measured by the Knipping and Haldane Methods.

Case	Date	Haldane			Knipping		
		Oxygen	Carbon Dioxide	R.Q.	Oxygen	Carbon Dioxide	R.Q.
D.G.	3.5.56.	341	202	0.59	372	222	0.59
	4.5.56.	260	169	0.65	247	175	0.71
	7.5.56.	332	203	0.61	345	225	0.67
	17.5.56.	251	191	0.76	257	188	0.73
J.McW.	24.4.56.	199	138	0.69	210	162	0.77
	26.4.56.	166	125	0.75	248	179	0.72
	28.5.56.	233	162	0.69	249	207	0.83
	3.5.56.	301	208	0.69	271	200	0.74
	11.5.56.	215	213	0.99	173	222	1.2
	17.5.56.	202	152	0.75	173	167	0.97
	Sum	2500	1763		2545	1947	
	Mean	250	176		255	195	

(Table 24). Such agreement between the methods indicated that the simpler modified Knipping technique was suitable.

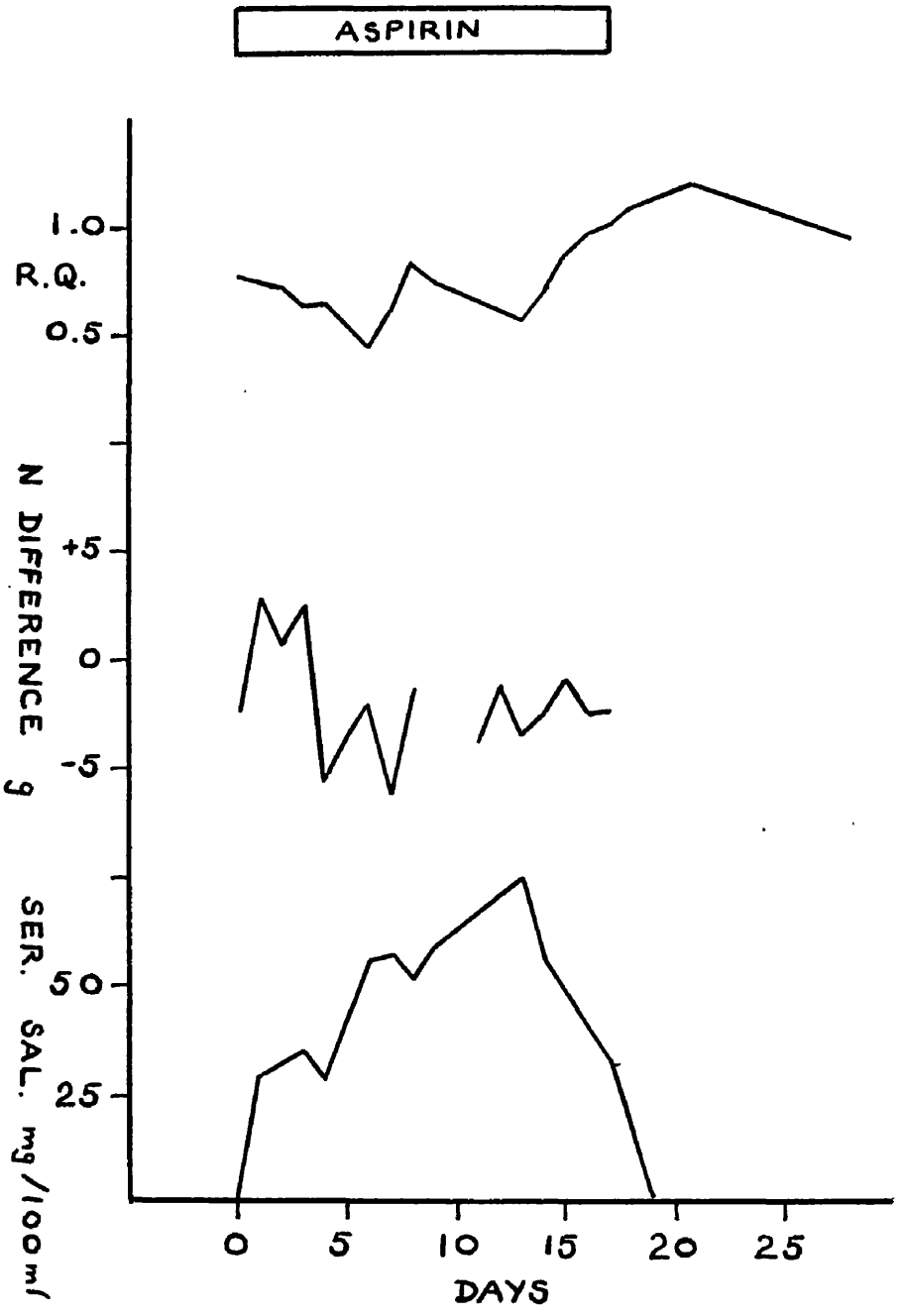
Results of the Determination of Respiratory Quotient.

The respiratory gaseous exchange of the 4 patients will be described and the implications of the findings discussed.

Patient J.McW. (Case 16) was treated with aspirin for 18 days. The serum salicylate concentration rose to 74 mg./100 ml. and the oxygen consumption from a pre-treatment value of 210 ml./min. to 300 ml./min. at the peak level. The pre-treatment carbon dioxide output value was 162 ml./min. and this rose to 175 ml./min. at peak. She was maintained on a diet containing 63 g.protein and entered a phase of negative nitrogen balance after three days of aspirin treatment. It was noted the R.Q. rose dramatically when aspirin was discontinued and then regained its normal value (about 0.8). A graphical representation of these changes is shown in Fig. 25 (Table 25 Appendix).

Fig. 25.

Effect of salicylate on respiratory quotient and nitrogen balance : case 16.



Patient A.I. (case 17) was treated for 27 days. The range of serum salicylate concentration varied from 7 to 62 mg./100 ml. From a pre-treatment oxygen consumption of 287 ml./min., the value reached at the highest drug level was 390 ml./min. The carbon dioxide output rose from 252 to 315 ml./min. This patient was maintained on a high protein intake of about 120 g. per day and was seen to be in negative nitrogen balance after four days treatment with aspirin. The results are expressed graphically in Fig. 26 (Table 26).

Patient D.G. (case 18) was given aspirin for a period of 50 days, during which the serum salicylate reached a concentration of up to 66 mg./100 ml. The pre-treatment oxygen consumption was 253 ml./min. and rose to 345 ml./min. at the peak level. The rise in carbon dioxide output was from 214 ml./min. before treatment to 225 ml./min. at peak. On a diet in which the protein intake was maintained at about 50 g. per day this patient entered a phase of negative nitrogen balance after about four days of aspirin therapy. The results are shown graphically in Fig. 27 (Table 27).

Fig. 26.

Effect of salicylate on respiratory quotient and nitrogen balance : case 17.

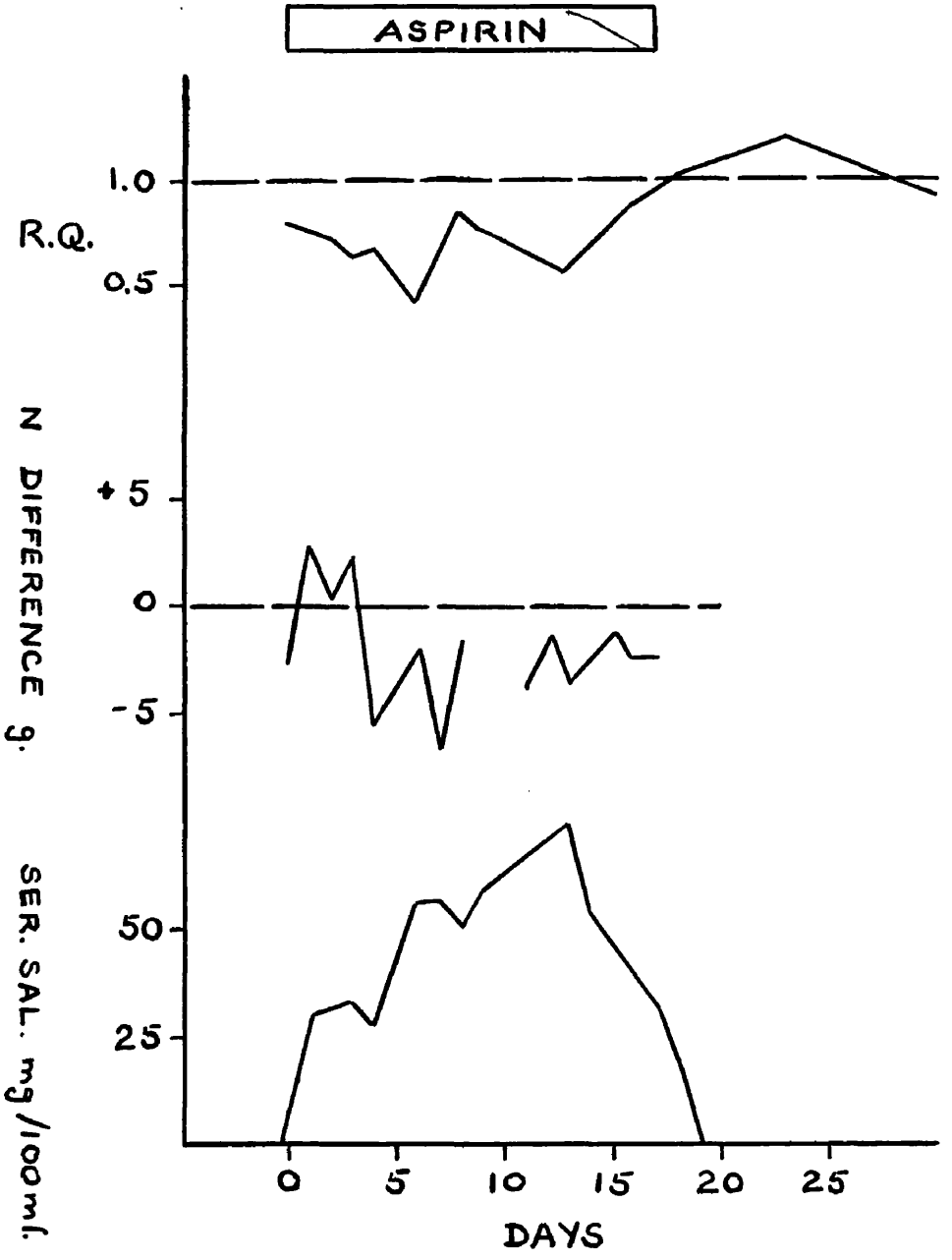
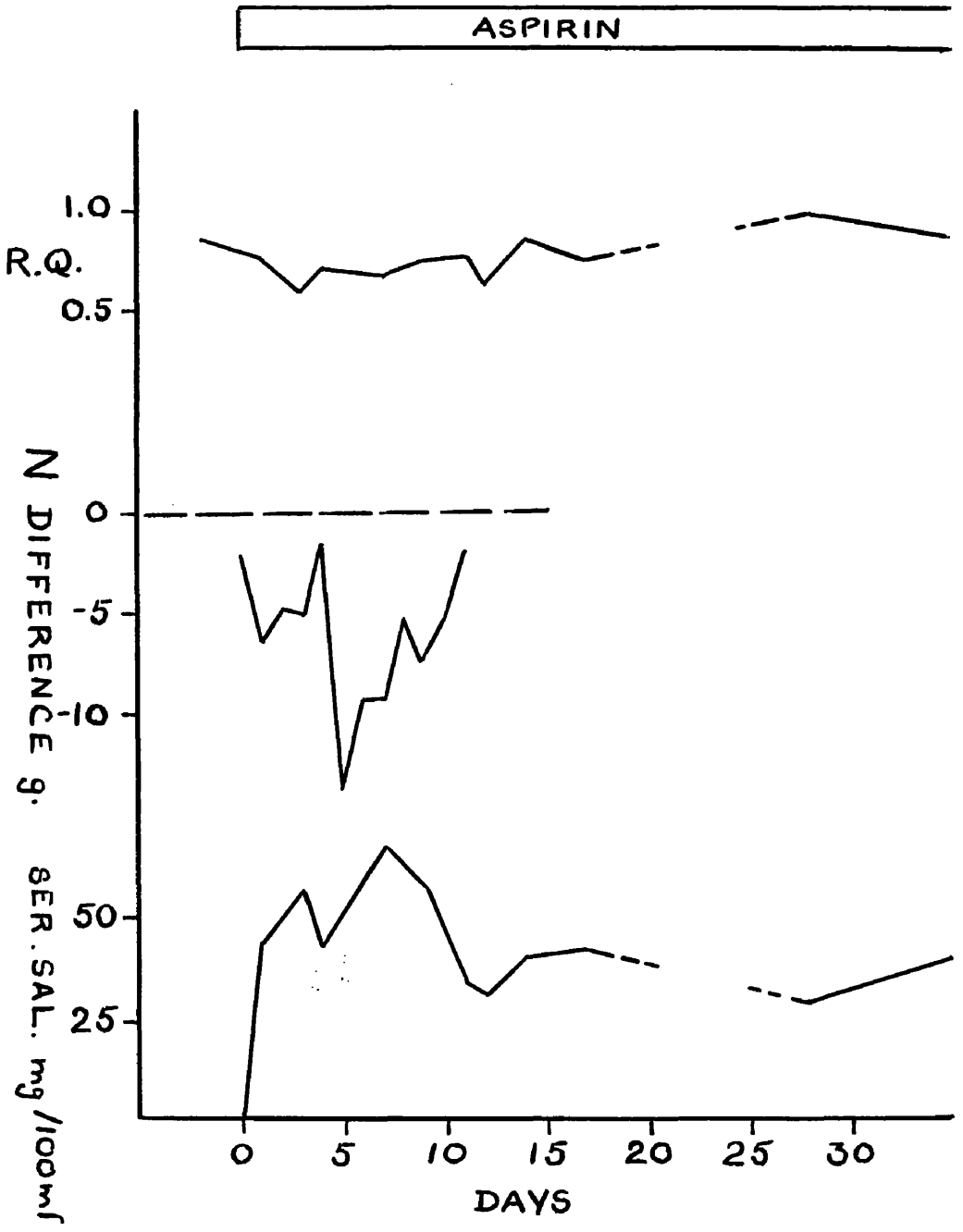


Fig. 27.

Effect of salicylate on respiratory quotient and nitrogen balance : case 18.

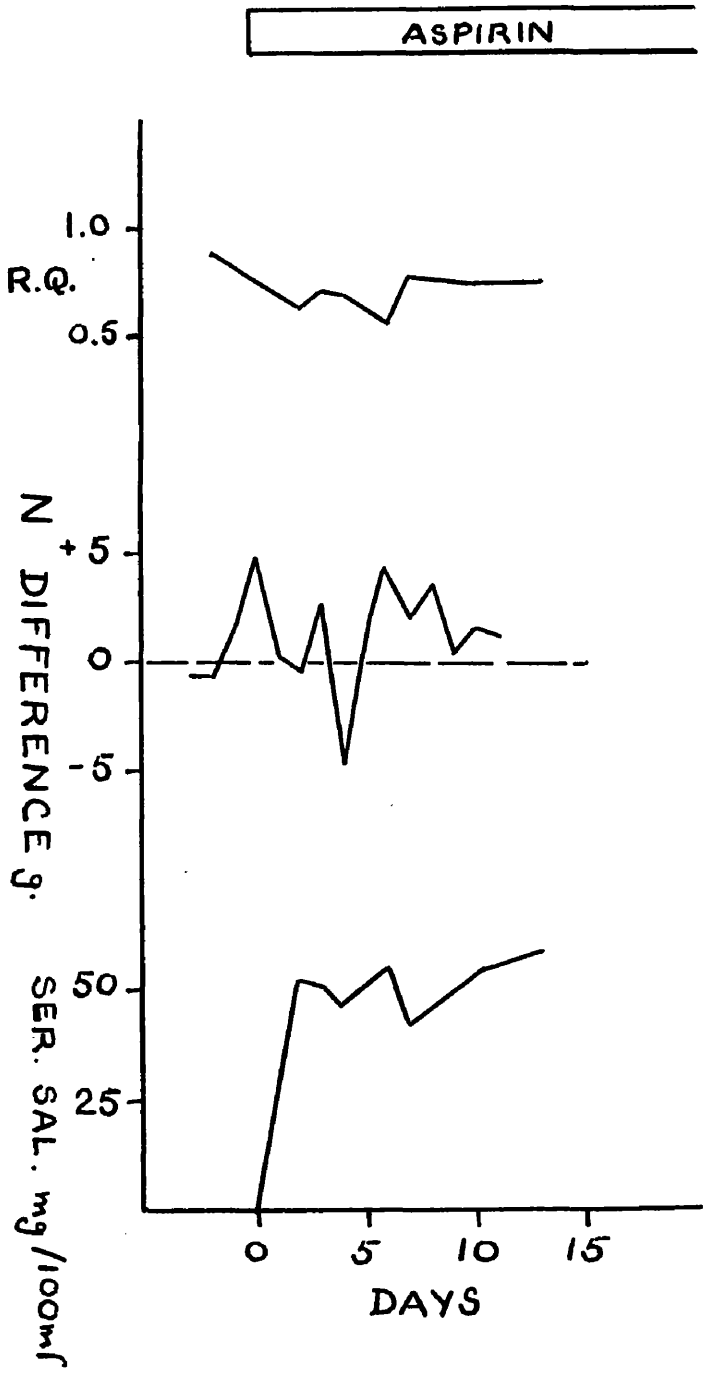


Patient M.McN. (case 19) received salicylate for 13 days. The highest serum concentration of the drug reached was 59 mg./100 ml. Her pre-treatment oxygen consumption was 167 ml./min. and this rose to 233 ml./min. on treatment. The change in carbon dioxide output was from 148 to 178 ml./min. Maintained on a balanced diet containing 63 g. protein, she entered a phase of negative nitrogen balance after about four days of aspirin therapy. A graphical representation of the results are given in Fig. 28.

From inspection of the data of these four patients, it was evident that while both oxygen and carbon dioxide were increased during aspirin therapy, nevertheless the increase in carbon dioxide output was a disproportionate one, with the result that the R.Q. tended to fall. Indeed a definite pattern of R.Q. change was observed. A sharp fall in R.Q. occurred when the serum salicylate concentration reached its first peak level. In case 16, the R.Q. fell from 0.77 before salicylate commenced to 0.46 when the blood concentration had reached 55 mg./100 ml., and again to 0.58 at 74 mg./100 ml.; in case 17, the R.Q. fell from 0.88 before treatment to 0.59 at 47 mg./100 ml. salicylate; in case 18, the R.Q. fell

Fig. 28.

Effect of salicylate on respiratory quotient and nitrogen balance : case 19.

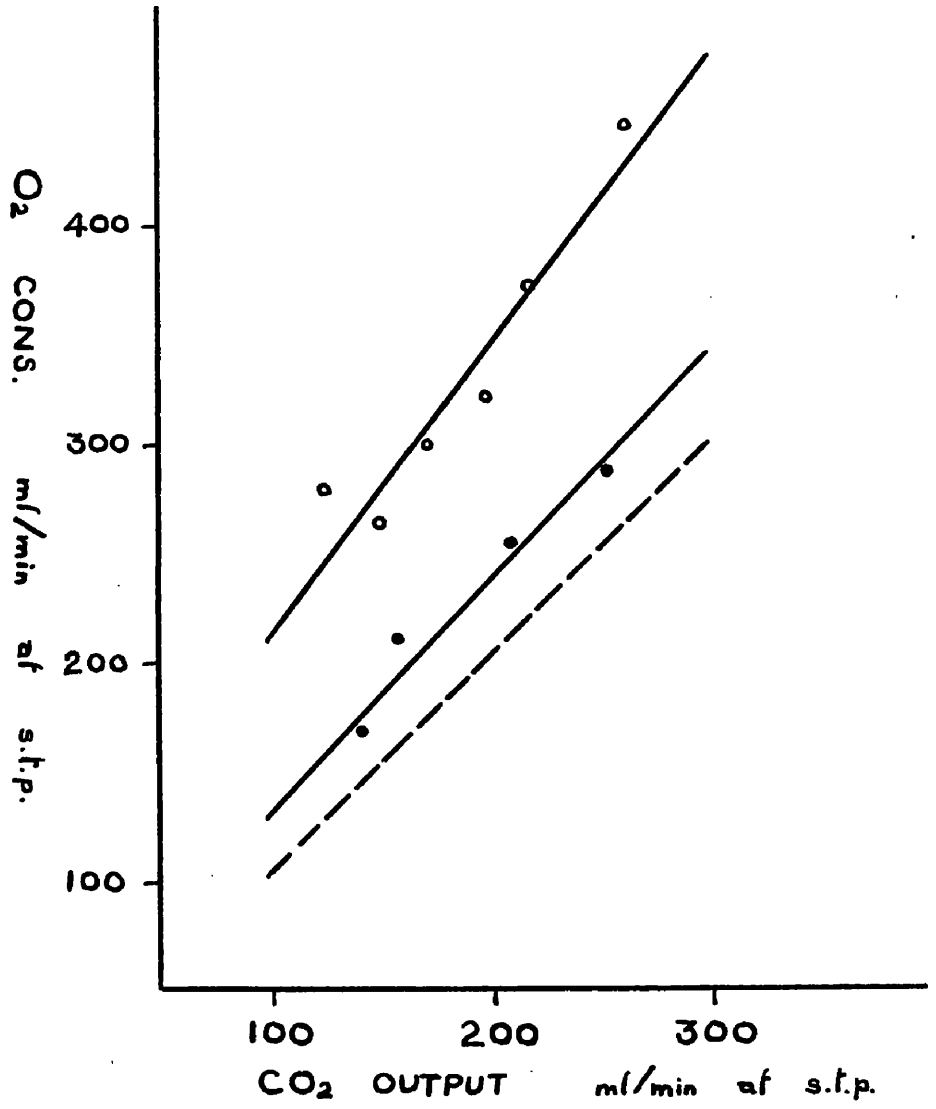


from 0.85 before treatment to 0.60 at 55 mg./100 ml. salicylate; in case 19, the R.Q. fell from 0.89 before to 0.62 at 52 mg./100 ml. and again to 0.58 at 55 mg./100 ml. salicylate. This fall coincided with the point at which the patient began to enter a negative nitrogen balance. On maintaining the salicylate at therapeutic levels, the R.Q. rose slightly although still below the pre-treatment figure. Any subsequent near-toxic dose was accompanied by another sharp fall in R.Q. (cases 16 and 19). On discontinuing the drug, the R.Q. rose to more than 1.0 and after a few days, it returned along with the B.M.R. to normal.

Inspection of the actual R.Q. values before and at peak salicylate concentrations permitted of a more accurate assessment of these changes. A graph of the four pre-treatment values of oxygen consumption and carbon dioxide output ~~were~~ was drawn (Fig. 29). The equation of the line representing these points was $y = 1.06x + 23$. The six pairs of values for oxygen and carbon dioxide production at the peak salicylate concentrations were similarly drawn. The equation representing these points was $y = 1.33x + 78$ (Fig.29). As will be seen, the respiratory response of the four

Fig. 29.

Regression lines of the respiratory quotients before and during salicylate therapy.



•——• Pre-treatment R.Q.'s.

o——o R.Q.'s during salicylate treatment.

--- R.Q. = 1.

patients before salicylate therapy was perceptibly different from that observed after salicylate had been administered.

The regression equations of the two lines were accordingly analysed for difference in slope or intercept:

Equation of the "pre-treatment" regression

$$y_1 = 1.06x_1 + 23.$$

Equation of the regression resulting during salicylate therapy

$$y_2 = 1.33x_2 + 78.$$

Analysis of variance of the regression coefficients

$b_1 = 1.06$ and $b_2 = 1.33$ gave

Weighted average residual variance = 20.28.

Variance of their difference = $0.047 = \sigma_{12}^2$

Calculated $t = (b_1 - b_2)/\sigma_{12} = 1.23.$

$t_{0.05}$ for 10 degrees of freedom = 2.23.

<u>The difference in slope is not evident at this level of significance.</u>

The intercepts of the two lines were then compared.

Expression (a) (vide chapter 1) = 4.6 and was distributed as t. For 7 degrees of freedom, <u>this</u>

value of t was significant at the 5% level.

From the detailed study of the effect of aspirin on the respiratory quotients of four patients further evidence for a metabolic action of the drug has been presented. The R.Q. fell markedly as soon as therapeutic serum salicylate levels had been established and remained subnormal until the drug was discontinued. From the value of the patients' R.Q.'s during treatment, it is suggested that the normal metabolic pathways have been affected. The increased energy requirement, as evidenced by an increased B.M.R. may in part be derived from the combustion of fat in preference to the physiological breakdown of carbohydrate. Whether this is caused however by interference with one of the intermediate breakdown products in carbohydrate metabolism or merely as a response to the suddenly increased need for oxygen is not known.

Chapter 4.

Comparison of the Metabolic Stimulating Effects of Salicylate and Dinitrophenol.

Investigation of the stimulant action of salicylate and support for the hypothesis of a primary metabolic action recalled the properties of another well-known metabolic stimulant, 2:4-dinitrophenol (DNP). Since its relative toxicity has made DNP unsuitable for large-scale investigation in man, much of the evidence of its mode of action has been gained from work on animals and tissue slices. A short review of the literature on the drug, so far as it is relevant, to the stimulation of metabolism and respiration, will be presented and will be followed by description of a carefully controlled study in man and animals carried out to compare the actions of salicylate and DNP.

In 1894, Gibbs & Reichert noticed that oral administration of DNP to dogs stimulated respiration and raised the body temperature. Walko (1901), experimenting with rabbits, and Sander with

mice, confirmed this increase in respiration. Heymans (1934) noted that the DNP-induced hyperthermia in pigeons was closely associated with an increase in oxygen consumption. The first accounts of the pharmacodynamic action of DNP appeared in 1932. Both Magne et al (1932), Hall et al (1933) and Gagliani & Tainter (1936) showed that in dogs DNP caused both an increase in oxygen consumption and in respiration. Magne et al (1932) further claimed that its effect was not of central origin since the hyperpyrexia which accompanied this increase in metabolism was not affected by anaesthetics. They concluded that respiratory stimulation with DNP was a direct consequence of increased oxygen utilisation by cells. In support of this claim of a peripheral action, Alwall & Scheff-Pfeifer (1936) reported that oxygen metabolism was increased in the isolated dog leg, and Dodds & Greville (1933) reported increased respiration of mammalian tissue slices by DNP. More recently Sproull (1954) has shown that both salicylate and DNP stimulate oxygen consumption of tissue slices and Reid (1957) has shown that the action of DNP in rabbits resembled that of salicylate, in that both drugs

stimulate oxygen consumption which results in hyperpyrexia and even death if the doses are large enough. The pharmacological similarity between DNP and salicylate thus extends to the realm of toxicology.

It is realised now that the metabolic action of DNP is not a clear-cut one of stimulation and may depend on substrate (Terner 1952), on environmental temperature (Magne et al 1932, Tainter 1934) and on the drug concentration (Plantefol 1933, Sproull 1954), but its importance, in man at least was first appreciated in connexion with its metabolic stimulating properties. Tainter et al (1933), Dunlop (1934) and Masserman & Goldsmith (1934) had all drawn attention to its possible use as a weight reducer, but its indiscriminate use was found to produce hyperpnoea and fever (Geiger 1933), and prolonged and massive dosage was later suspected of having caused irreversible complications such as cataract, though sole responsibility for this was questioned (Dally 1936, Davis 1937 and Lindahl 1940).

Short-term studies of the metabolic stimulant effect of DNP primarily undertaken to control DNP administration in a study of its action in myxoedema,

diabetes mellitus and other conditions provided data for a comparison with salicylate.

The first group of patients considered consisted of four middle-aged diabetics in whom the effect on blood sugar was being studied, and one patient with hypercholesterolaemia (cases 20 to 24). All had resting B.M.R.'s within normal limits when no drug was given, and were afebrile throughout the period of investigation.

The second group comprised three patients with myxoedema in whom the effect on the subnormal metabolism and hypercholesterolaemia was being investigated (cases 25 to 27). At no time during treatment did adverse symptoms or pyrexia develop.

Metabolic and respiratory investigations were made in exactly the same manner as in the salicylate studies and the plasma concentration of DNP was estimated by the method of Parker (1949) to allow concentration-response studies to be undertaken.

Plasma DNP Concentration and the Metabolic Rate in the Diabetic Group. Measurement of the oxygen consumption and simultaneous estimation of plasma DNP were made during two weeks of DNP administration to each of the patients in the first group

(cases 20 to 24). Linear correlation was established in each case between concentration and response. The regression lines which represented the pairs of observations were constructed and were drawn together in Fig. 30. A summary of the clinical data of the individual patients is given in Table 29. A summary of the regression data is given in Table 30.

Conforming to earlier practice, each value of the metabolic rate was expressed as the increment of oxygen consumption above the patient's resting value when no treatment was given. The forty-five points were plotted on one graph (Fig. 31, Table 31, Appendix), covering a plasma DNP concentration of 6 to 51 mg./l. Linear correlation was established, the correlation coefficient $r = 0.78$, with a high degree of significance ($P < 0.001$), and 95% confidence limits of the line were ± 5.98. The equation of the regression was $y = 0.27x + 3.3$ (Fig. 31).

Plasma Concentration of DNP and Metabolic Stimulation in Myxoedema. The relationship between drug concentration and metabolic rate in the myxoedematous patients was found to be linearly correlated in each case and the three regression lines were drawn (Fig.32).

Fig. 30.

Summary of concentration-response curves

cases 20 to 24.

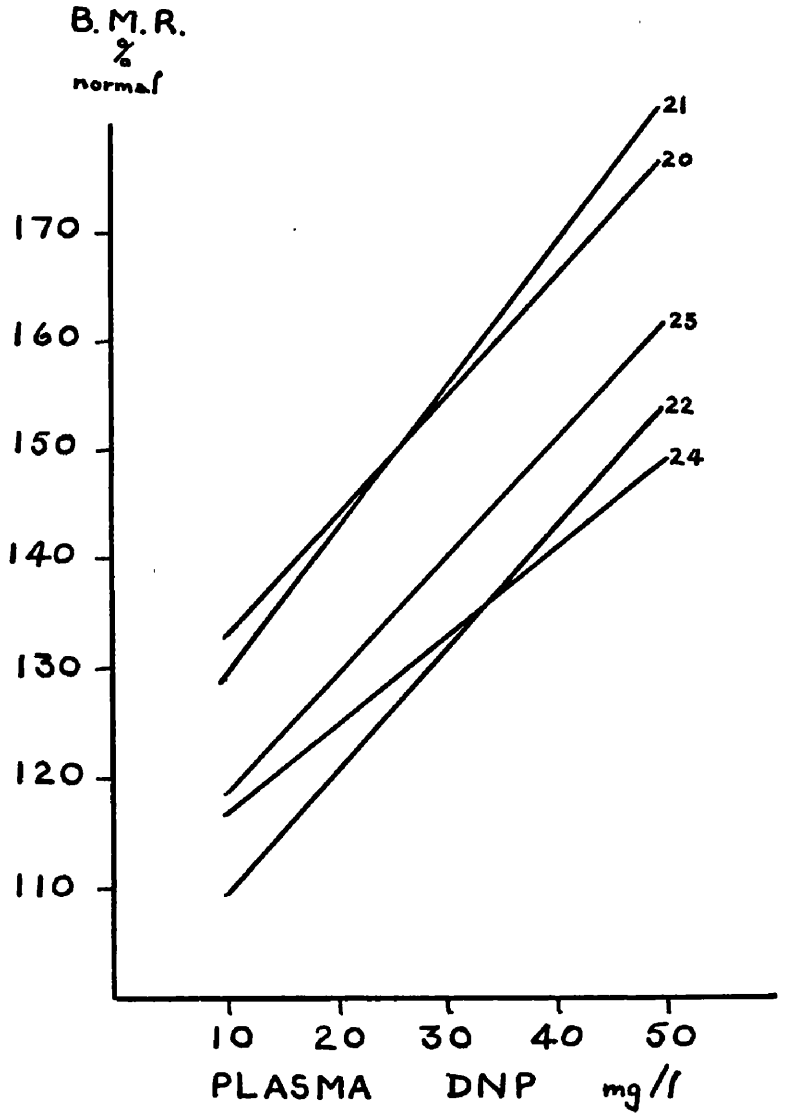


Fig. 31.

Composite regression line : diabetic patients

cases 20 to 24.

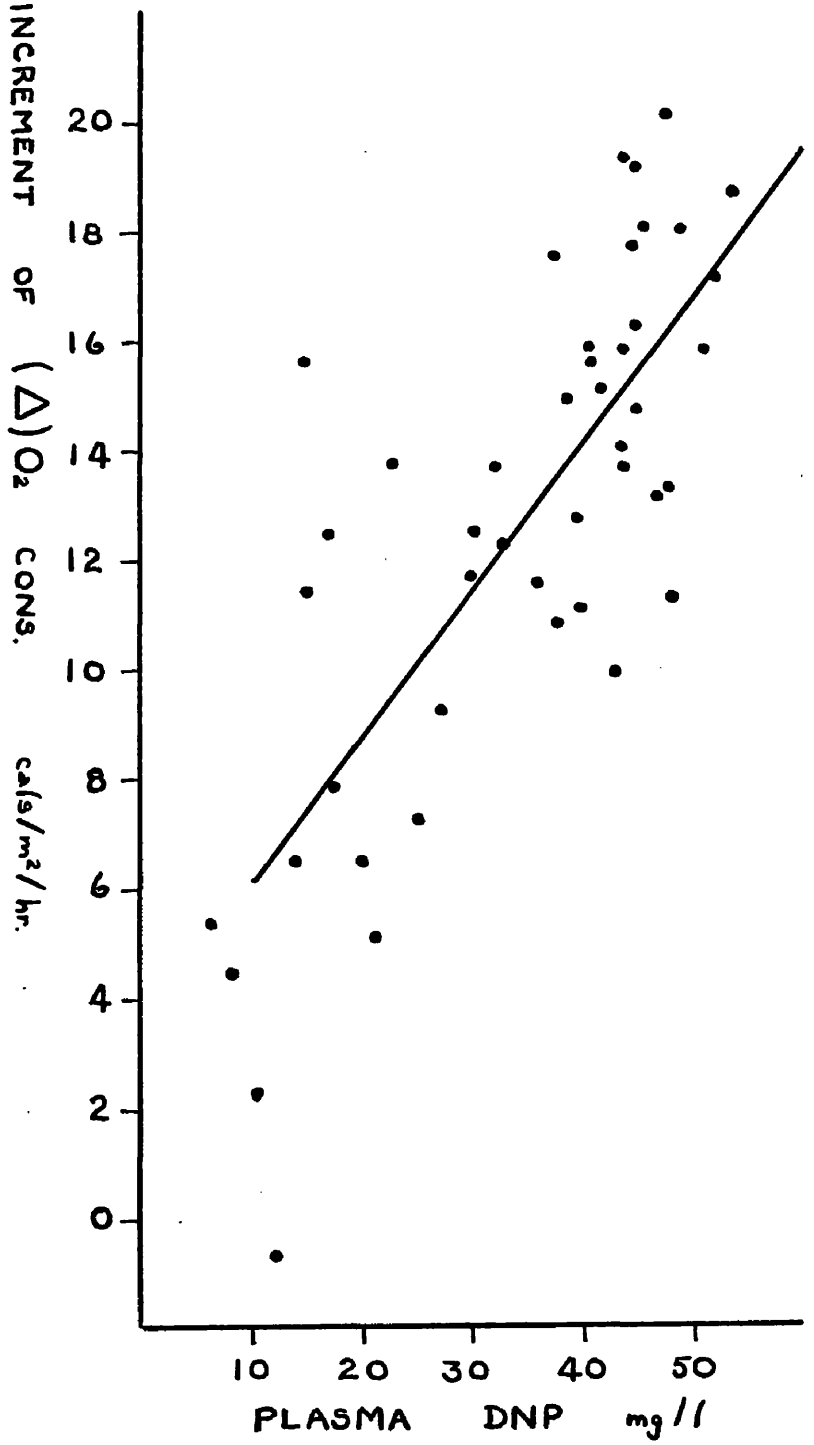
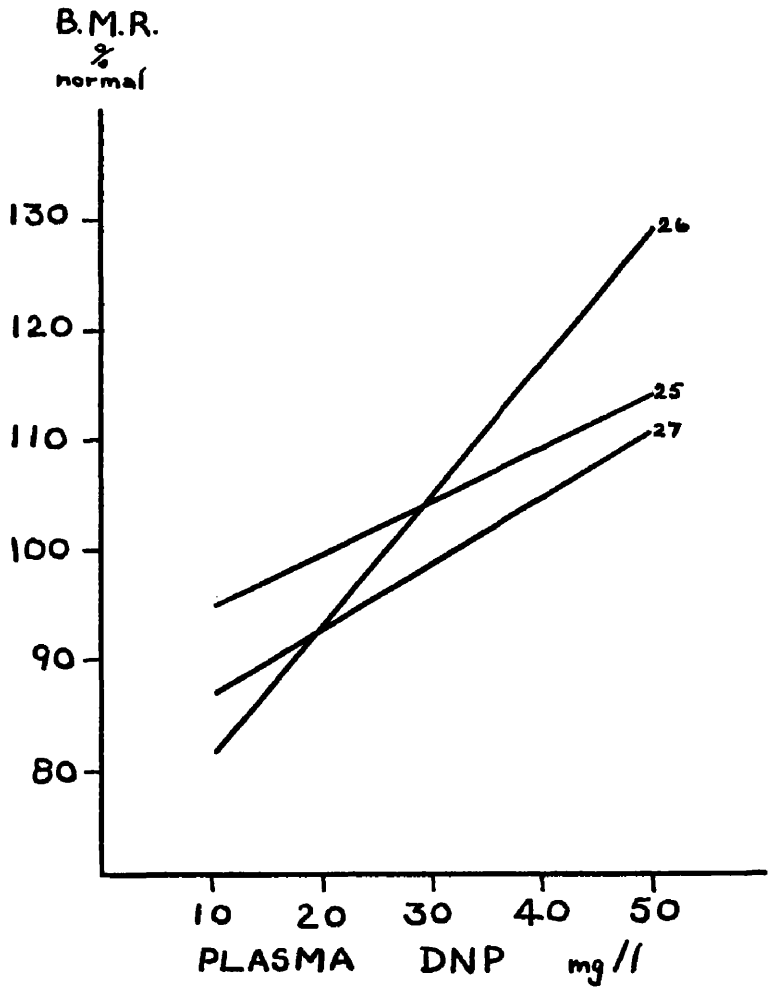


Fig. 32.

Summary of concentration-response curves

cases 25 to 27.



A summary of the clinical data of the individual patients are given in Table 29, and of the regression data in Table 30 (Appendix).

The composite regression curve constructed from the thirty-seven pairs of observations gave a linear correlation with a coefficient $r = 0.86$ and the 95% confidence limits of the line ± 5.1. The equation representing this regression was $y = 0.29x - 2.0$ (Fig. 33, Table 32).

The impression formed from visual inspection of the regression lines of the diabetic and myxoedematous groups (Figs. 31 and 33) was that while the intercepts were slightly different, the slopes were similar. This impression was tested by statistical analysis.

The slopes of the two lines represented by

$y_1 = 0.27x_1 + 3.3$ for the diabetics,

and $y_2 = 0.29x_2 - 2.0$ for the myxoedematous,

were examined by comparing their regression coefficients b_1 and b_2.

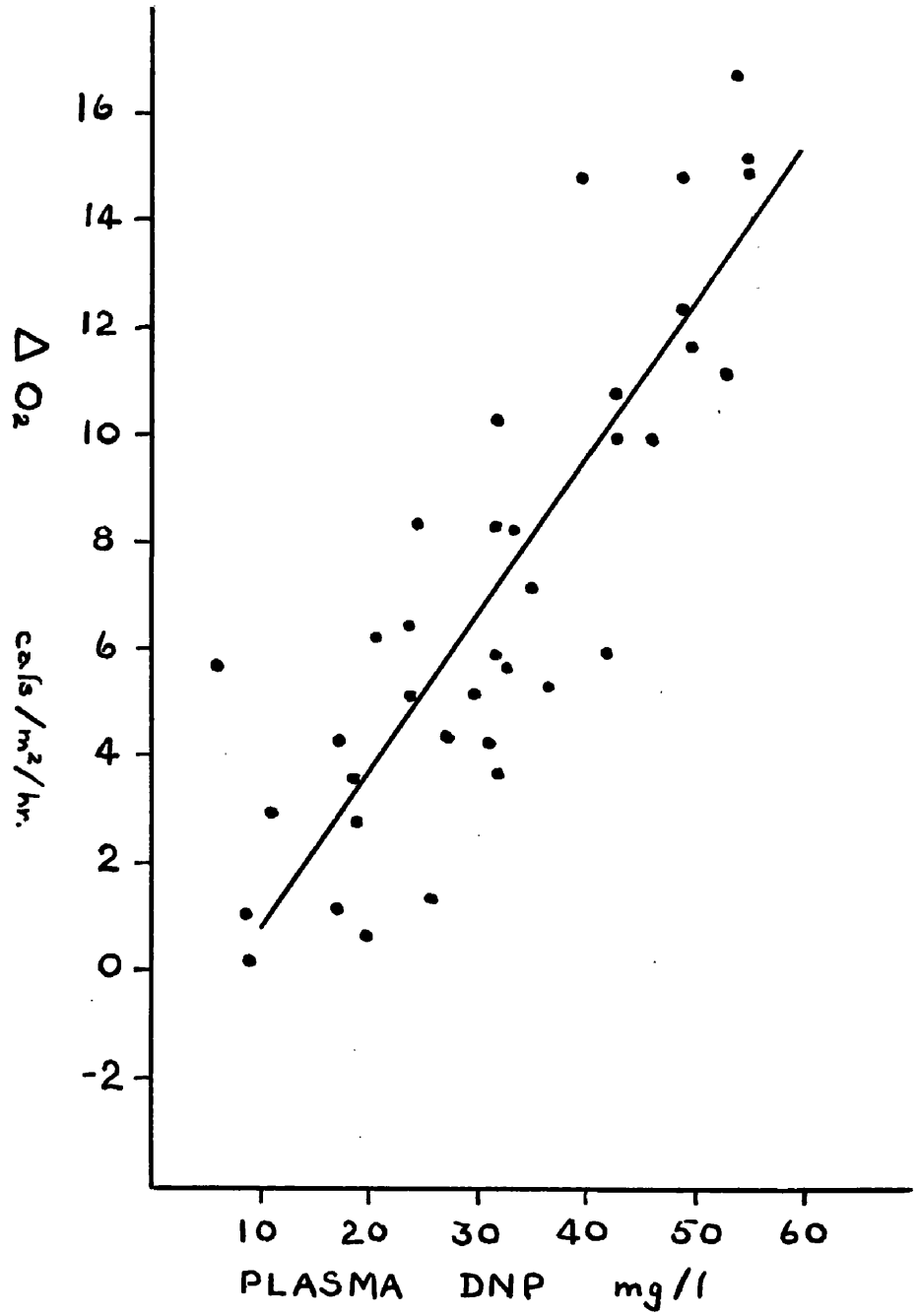
The variance of $b_1 = 0.00089$ and of $b_2 = 0.00099$,

The variance of their difference $\sigma_{12}^2 = 0.0018$.

The value of $t = (b_1 - b_2)/\sigma_{12} = 0.465$. For $t_{0.05}$,

Fig. 33.

Composite regression line : myxoedematous patients cases 25 to 27.



and 78 degrees of freedom, the estimate of t = 1.99. Thus the calculated $t < t_{0.05}$, indicating that there was no significant difference between the gradients of the lines.

Comparison of the intercepts of the two regression lines gave, for the expression

$$\frac{a_1 - a_2}{s\sqrt{\frac{1}{n_1} + \frac{1}{n_2} + \frac{\bar{x}_1^2}{\Sigma(x_1 - \bar{x}_1)^2} + \frac{\bar{x}_2^2}{\Sigma(x_2 - \bar{x}_2)^2}}} \qquad \text{(a)}$$

a value of 2.73. This is greater than the estimated value of $t_{0.05}$ for N - 3 i.e. 79 degrees of freedom, 1.99. It was concluded that there was a significant difference in intercept between the two lines.

In contrast to the findings of patients whose metabolism had been stimulated with salicylate, it was observed that DNP stimulated both myxoedematous and patients with normal thyroid function to the same degree, although in both cases, as was expected, a different intercept was observed probably due to the lower initial starting level of the hypothyroid subjects.

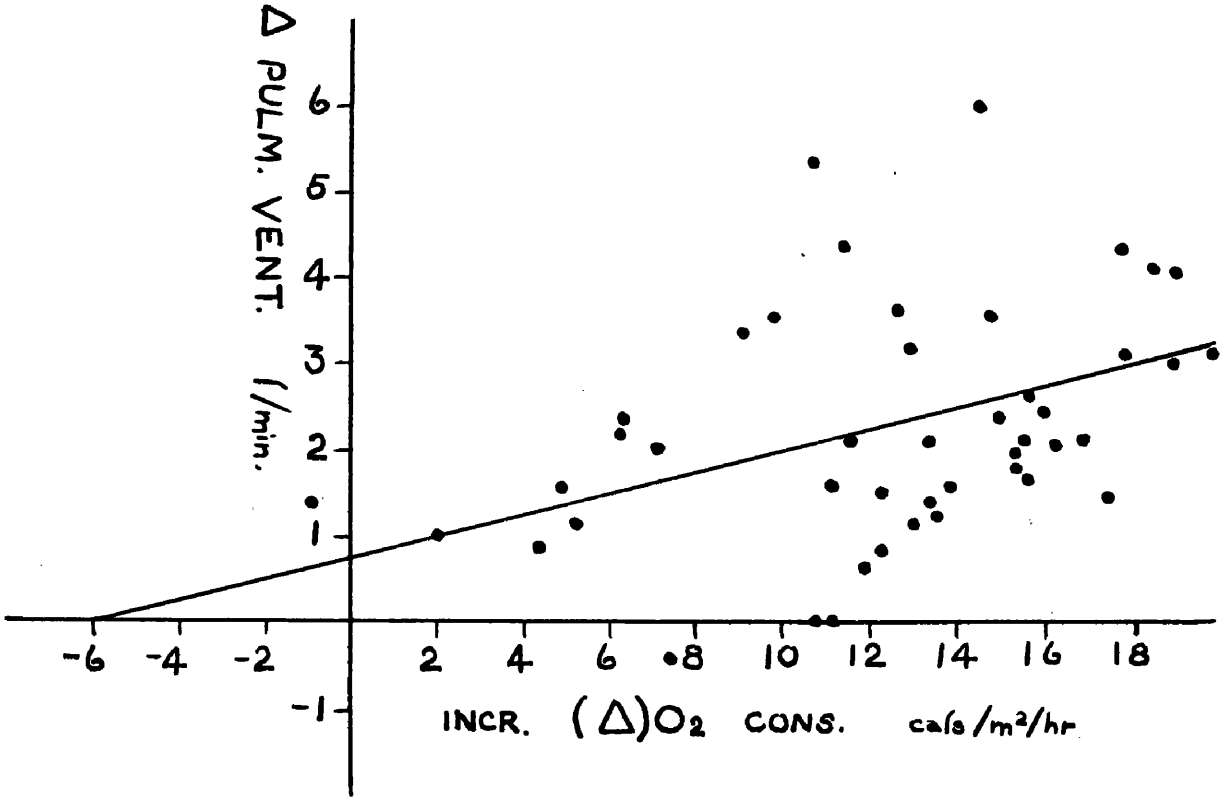
The relation between oxygen consumption and pulmonary ventilation resulting from DNP administration was next investigated using methods

similar to those used in the salicylate studies.

DNP and Pulmonary Ventilation and Metabolic Stimulation in the Diabetic Group. The same five patients who had taken part in the study of the metabolic response to DNP were reconsidered to evaluate the respiratory response. Measurement of pulmonary ventilation was made from the tracings obtained in the estimation of oxygen consumption. Since each particular respiratory estimation was made at the same plasma concentration of the drug as the oxygen consumption values, pulmonary ventilation and metabolic stimulation were compared directly by plotting the pairs of observations. Figure 34 represents the scatter diagram formed from the 45 pairs of observations in the diabetics. A linear correlation was established between the increment in pulmonary ventilation (y) and the increment in oxygen consumption (x). The correlation coefficient $r = 0.36$ ($p = 0.01$) and the equation of the regression was $y = 0.126x + 0.72$ (Fig. 34, Table 33). It was thus shown that the administration of DNP to man resulted in a stimulation of metabolism which was associated with a corresponding increase in pulmonary ventilation.

Fig. 34.

The relationship between pulmonary ventilation and metabolic stimulation in the diabetic patients during DNP administration.



DNP and Pulmonary Ventilation and Metabolic Stimulation in the Myxoedematous Group. The increase in pulmonary ventilation shown by the three myxoedematous patients while they were receiving DNP was investigated in the same manner and the results were compared with the simultaneous estimates of oxygen consumption.

A scatter diagram consisting of 37 pairs of observations is shown in Fig. 35. Analysis suggested a linear correlation between the increase in metabolic stimulation (x) and the increase in pulmonary ventilation (y). The correlation coefficient $r = 0.359$ ($0.05 > P < 0.02$), and the equation of the regression was $y = 0.15x + 0.98$ (Fig. 35 Table 34).

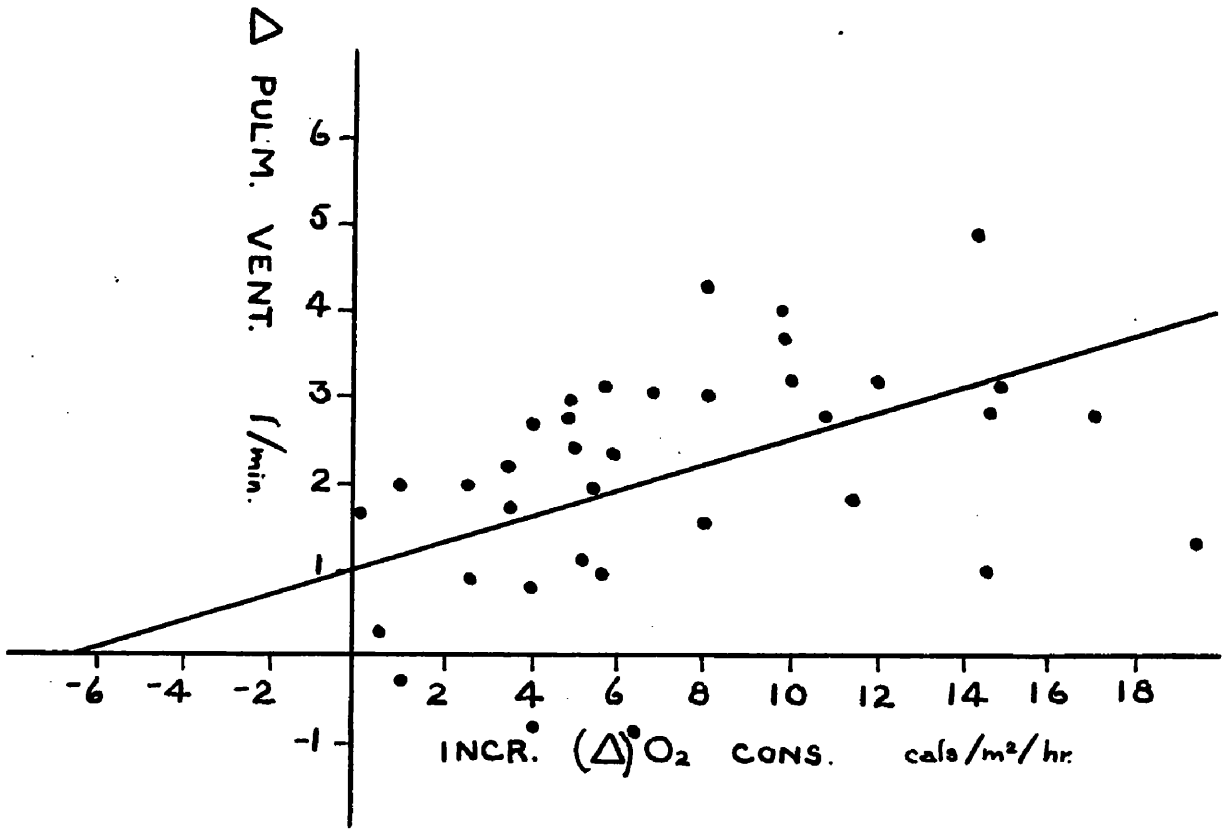
It was thus shown that during administration of DNP to the myxoedematous patient there was a proportional increase between increase in oxygen consumption and increase in pulmonary ventilation.

Inspection of the lines representing this ratio in the diabetic and in the myxoedematous patient appeared to be roughly similar in slope, and an analysis of both gradient and intercept was done to establish the exact relationship.

Comparison of the slopes of the lines,

Fig. 35.

The relationship between pulmonary ventilation and metabolic stimulation in the myxoedematous patients during DNP administration.



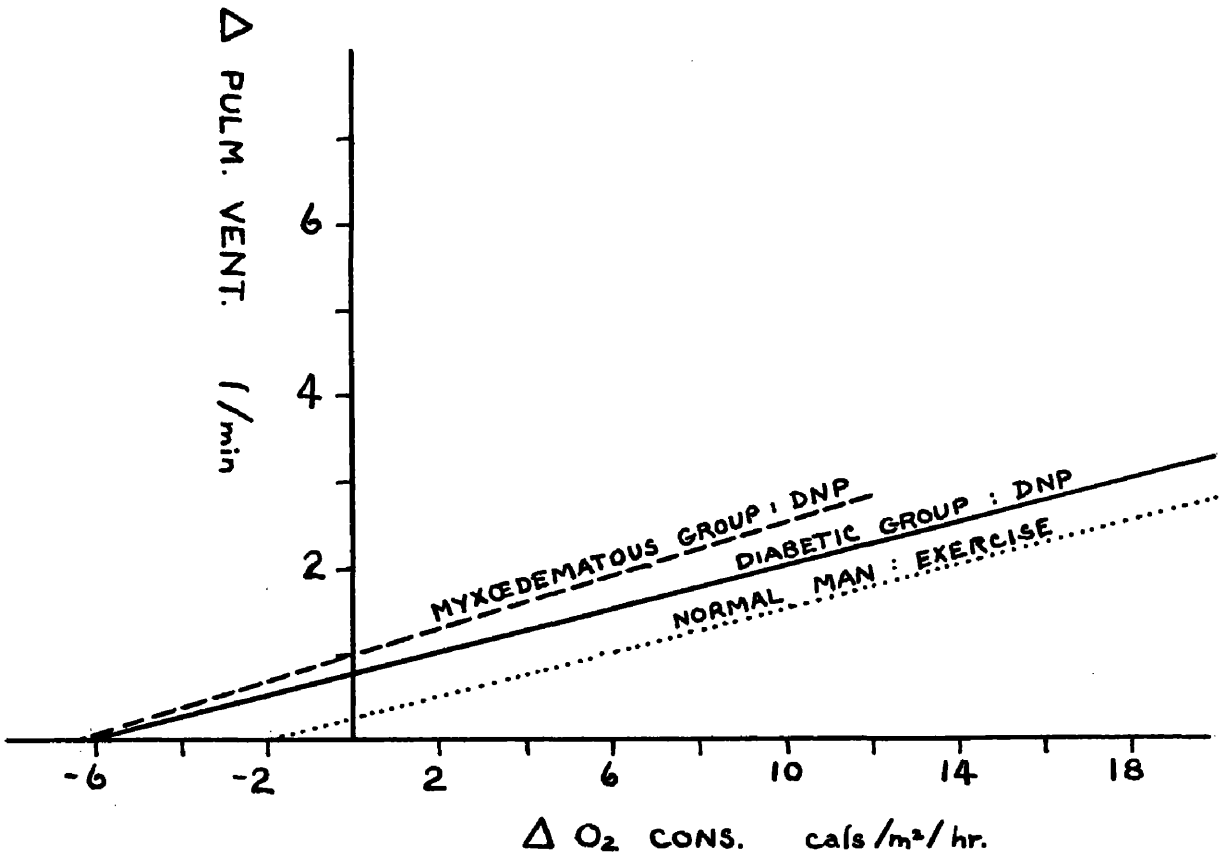
$y_1 = 0.126x_1 + 0.72$, for the diabetic group, and $y_2 = 0.15x_2 + 0.98$, for the myxoedematous group, gave
The variance of $b_1 = 0.0018$ and of $b_2 = 0.0022$,
The variance of their difference $\sigma^2_{12} = 0.0040$.
The value of $t = b_1 - b_2/\sigma_{12} = 1.2$. For 78 degrees of freedom, the estimated value of $t_{0.05} = 1.99$. Thus the calculated t was less than $t_{0.05}$, indicating that there was no significant difference in the slopes of the two lines.

Comparison of the intercepts of the two regression lines, gave by means of the above formula, ((a)) the value of 1.65, in the t distribution. This was less than the value of $t_{0.05}$ for 79 degrees of freedom 1.99. It was concluded that there was no significant difference between the intercepts formed by the two regressions.

The impression formed from inspection of the diagrams, Figs. 34 and 35, was thus confirmed: the ratio between metabolic stimulation and pulmonary ventilation after DNP was the same. Fig. 36 shows the representation of the DNP-induced pulmonary ventilation/oxygen consumption ratio compared with the Asmussen (1943) representation of the results of voluntary exercise in one normal man. Inspection

Fig. 36.

Comparison of the ratio, pulmonary ventilation : metabolic stimulation during DNP administration and during exercise.



—— y = 0.126x + 0.72

--- y = 0.15x + 0.98

..... y = 0.126x + 0.2

of the diagram showed that the three lines were similar in both slope and intercept, which supports the contention that respiratory stimulation in man induced by DNP was similar to that induced by exercise stimulus in dogs (Ramsay 1956).

Summary of the Comparison of the Pulmonary Ventilation/Metabolic Stimulation Ratio with Salicylate and Dinitrophenol.

The metabolic and respiratory stimulant action of both salicylate and DNP was studied in four main groups of patients. In order to compare the effects of the two drugs, the relationship between the ventilatory and metabolic responses was investigated in each group, and the following equations were derived:

$y = 0.22x + 1.0$ for the convalescents with salicylate administration,

$y = 0.25x + 0.35$ for the myxoedematous with salicylate administration,

$y = 0.126x + 0.72$, for the diabetics with DNP administration, and $y = 0.15x + 0.98$ for the myxoedematous with DNP administration.

It was concluded that there was little difference between the metabolic-respiratory response

to salicylate , and to DNP. Furthermore, when these equations were compared with the equation derived from data from the results of exercise (Asmussen 1943), the results were not inconsistent with the conclusion that respiratory stimulation following increased oxygen consumption from either DNP or salicylate does not differ from the physiological exercise stimulus.

Chapter 5.

Comparison of the Glycogenolytic Effects of Salicylate and 2:4-dinitrophenol.

Both salicylate and 2:4-dinitrophenol have been shown to stimulate oxygen consumption of the whole animal and of tissue slices. Similarity in their effects on the ratio of increased oxygen consumption to increased pulmonary ventilation, and on the R.Q. in man has already been described. Furthermore, Brody (1956) showed that salicylate stimulated the oxygen consumption of mitochondria without a commensurate effect on the uptake of organic phosphate. This dissociation of oxidation and phosphorylation had previously led Loomis and Lipmann (1948) to introduce the concept of the uncoupling of oxidative phosphorylation in explanation of the action of dinitrophenol. Other similarities between the drugs included the initial depletion of liver and muscle glycogen after administration of a large single dose of either salicylate (Lutwak-Mann 1942, Smith 1952 and Sproull 1954) or of DNP (Barnes

(1953).

Barnes (1953) had also shown that prolonged administration of DNP to rats had a different effect on liver glycogen than a single large dose: a single dose depleted liver glycogen, whereas prolonged administration increased it. It was therefore decided to find out whether salicylate also possessed this paradoxical action and to compare it with DNP.

Wistar rats were chosen as suitable experimental animals and the drugs were given for ten days. The rats were weighed and oxygen consumption was measured at intervals throughout the period of investigation and again just before sacrifice. This was done by placing the rats in groups of four in a desiccator divided into four compartments. The desiccator was connected to the modified Knipping spirometer previously described (Fig. 24), which circulated oxygen and removed carbon dioxide with soda lime absorbers. At the end of ten days, the rats were sacrificed by guillotine without anaesthetic. Liver samples were excised for the estimation of glycogen content by the method of Good et al (1933). Blood samples were collected in oxalate-fluoride tubes from the great vessels at the neck for estimation

of drug concentration (salicylate by Trinder's 1954 method; DNP by Parker's 1949 method), and also for blood sugar estimation by the Lehmann & Silk (1952) modification of the Folin & Wu method.

Salicylate and DNP had to be administered to the rats in such a way that an effective blood concentration was maintained throughout the twenty-four hours of the day so that the effect of the drugs would be continuous. The best procedure to achieve this was to mix the substances with ordinary powdered M.R.C. "Diet 41" and feed the rats ad lib. A preliminary trial of this method was made and a group of sixteen rats (Group I) was fed with ordinary diet in powdered form until a steady gain in weight was achieved - about three weeks. Then eight were changed to a mixture containing 5% sodium salicylate, and eight to one containing 0.1% DNP. After five days, i.e. half way through the proposed experimental period, the animals were sacrificed and blood concentrations estimated at six-hourly intervals throughout one day.

The results of this feeding trial (Table 35) show that the mean plasma salicylate concentration obtained was 34.4 mg./100 ml. over a range of 26 to 45 mg./100 ml., and the mean plasma DNP concentration

Table 35.

Sixteen Rats - Group I.

Time	Rat No.	Plasma Salicylate mg./100 ml.	Rat No.	Plasma DNP mg./l.
3 p.m.	1	32	9	40
	2	26	10	17
9 p.m.	3	26	11	15
	4	30	12	23
3 a.m.	5	44	13	51
	6	40	14	45
9 a.m.	7	32	15	37
	8	45	16	-

Drug concentrations in the blood of sixteen rats, estimated at intervals throughout 24 hours.

32.6 mg./l. over a range of 15 to 51 mg./l. This method of administering the drugs was therefore considered suitable for the main investigation.

Two further groups of sixteen rats (Groups II and III) were then caged in pairs and allowed to accustom themselves to ordinary powdered diet for one month. A normal weight gain was achieved after a slight initial loss due to changed conditions. Several measurements of the rats' oxygen consumption were made to establish the mean untreated basal reading. Eight animals from each group were then fed on the 5% salicylate mixture or on the 0.1% DNP mixture. The remaining eight in each group acted as controls and were left untreated. Special feeding was continued for ten days, when both treated and untreated animals were sacrificed. Liver and blood samples were taken immediately after death.

The mean blood concentrations of the drug obtained from the salicylate-treated animals (Group II) at sacrifice varied from 15 to 41 mg./100 ml., the mean being 32.1 mg./100 ml., which was similar to that obtained in the trial Group I (mean 34.4 mg./100 ml., range 26 to 45 mg./100 ml.). The blood DNP concentrations of the other eight animals (Group III)

ranged from 18 to 31 mg./l., the mean being 24.9 mg./l. (cf. the trial DNP group with a mean of 32.6 mg./l. and a range of 15 to 51 mg./l.).

The blood levels of salicylate and DNP were of the same order as those used in their therapeutic applications and the effect of these concentrations on rat liver glycogen and blood sugar, oxygen consumption and body weight will now be described.

Prolonged Salicylate Administration. Continued administration of sodium salicylate to normal rats for ten days produced a marked decrease in liver glycogen compared with that of the controls. The mean value of the eight salicylate-treated rats was 2.05 $\pm$ 0.64%, while that of the untreated rats was 5.84 $\pm$ 2.13%. Comparison of the results by Student's t-test showed the difference observed to be significant ($t = 3.88$ $p > .01$) (Table 36).

No change was noted between the blood sugar concentrations of the treated rats, 102.3 $\pm$ 13.5 mg./100 ml., and that of the controls, 101.6 $\pm$ 3.8 mg./100 ml. Owing to the method of administering the drug, fasting levels were not available, but from the results obtained it was possible to conclude that there was no material difference between the groups.(Table 36).

Table 36.

The Effect of Salicylate on Liver Glycogen and Blood Sugar.

Group II	No. of Rats	Blood Sugar* mg./100 ml.	Liver Glycogen+ g./100 g.
Treated	8	102.3±13.5	2.05±0.64
Untreated	8	101.6± 3.8	5.84±2.13

* Mean values ± standard error are given for liver glycogen and blood sugar.

+ Statistical significance of the difference between the results for the treated and untreated groups: $t = 3.88$, $P > 0.01$.

The salicylate-fed animals began treatment with a mean body weight of 357 g. At the end of ten days it had fallen to 307 g. i.e. a decrease of 14%. Although it was not possible to keep the rats in metabolic cages, no obvious decrease in food intake was noted: on the contrary, the food containers of the treated group required more frequent refilling than those of the controls. Change in body weight of the control group was negligible - a decrease of only 1%, from 388 g. to 384 g. (Table 37).

Salicylate produced an increase in oxygen consumption throughout the experimental period (Table 37). After five days of treatment, the salicylate-fed group showed an increase of 69%, and immediately before the animals were sacrificed, an increase of 50%, compared with an increase of 5% and 11% respectively in the controls. All these figures were expressed with respect to the pre-treatment values for the particular group.

Prolonged DNP Administration. After ten days of DNP administration the mean liver glycogen of the treated group was 6.94 $\pm$ 2.78% and that of the untreated group 6.87 $\pm$ 2.63%, and there was no significant difference between these values when examined by Student's t-test. (Table 38). In this DNP differed from salicylate

Table 37.

The Effect of Salicylate on Body Weight and Oxygen Consumption.

Group II	No. of Rats	Initial Weight* g.	Day 1 Weight g.	Day 1 Oxygen cons.+	Day 5 Weight g.	Day 5 Oxygen cons.	Day of sacrifice Weight g.	Day of sacrifice Oxygen cons.
Treated	8	320	357	4.2	328	7.1 (+69%)	307	6.3(+50%)
Untreated	8	354	388	3.6	386	3.8 (+5%)	384	4.0(+11%)

* Average body weight of the group.

\+ Oxygen consumption is expressed as $ml.x10^{-2}/min./g.$ body weight, the estimation on Day 1 being the mean of four pre-treatment values.

Table 38.

The Effect of 2:4-Dinitrophenol on Liver Glycogen and Blood Glucose.

Group III	No. of Rats	Blood Sugar* mg./100 ml.	Liver Glycogen g./100 g. wet weight
Treated	8	95.2±8.8	6.94±2.78
Untreated	8	103.0±8.3	6.87±2.63

* Mean values ± standard error are given for liver glycogen and blood sugar.

which depleted liver glycogen.

There was no difference between the mean blood sugar concentration of the treated group, 95.2 ± 8.8 mg./100 ml. and that of the untreated group, 103.0 ± 8.3 mg./100 ml. at sacrifice (Table 38).

The mean body weights of the rats given DNP decreased by only 4% over the experimental period, falling from a mean of 201 g. to 193 g.; the control group however showed a slight increase from 201 g. to 205 g. i.e. 2% (Table 39).

The treated rats showed an increase in oxygen consumption amounting to 43% after 5 days and 58% after 10 days. This compared with increases of only 8% and 11% respectively in the untreated group (Table 39).

Summary of the Results.

These results showed that oral administration of the drugs was practical and that blood concentrations of the same order as those used therapeutically were maintained over the whole day. Administered over a period of ten days, sodium salicylate caused an increase in oxygen consumption, depletion of liver glycogen,

Table 39.

The Effect of 2:4-Dinitrophenol on Body Weight and Oxygen Consumption.

Group III	No. of Rats	Initial Weight* g.	Day 1 Weight g.	Day 1 Oxygen cons.+	Day 5 Weight g.	Day 5 Oxygen cons.	Day of sacrifice Weight g.	Day of sacrifice Oxygen cons.
Treated	8	179	201	5.1	201	7.3(+43%)	193	8.0(+58%)
Untreated	8	174	201	4.7	206	5.1(+ 8%)	205	5.2(+11%)

* Average body weight of the group.

+ Oxygen consumptions are expressed as ml. x 10^{-2}/min./g. body weight, the estimation on Day 1 being the mean of four pre-treatment values.

loss in body weight and no change in non-fasting blood sugar concentration. For the same order of metabolic stimulation, DNP produced a slight weight loss, and no change in liver glycogen content or blood sugar concentration. It was concluded that the effects of prolonged administration of salicylate and DNP on liver glycogen of rats were not identical.

Discussion.

In the foregoing chapters the study of the respiratory and metabolic effects of salicylate and their comparison with dinitrophenol (DNP) has provided a quantitative analysis of some of the well-known results of salicylate therapy.

Although dose-response curves were constructed for the effect of salicylate on the metabolic rate of tissue slices (Sproull 1954) and rabbits (Reid 1957), no detailed investigation of the response in man had been derived. Qualitative stimulation of metabolism had been established by Cochran (1952) but the effect of aspirin on the oxygen consumption of man has been quantitatively studied only in this work and it has been shown that oxygen consumption and serum salicylate concentration are directly related to one another over the complete therapeutic range of concentration. The first group of patients examined in this way were convalescent rheumatics and were normal, clinically and biochemically, each patient having already received aspirin over a period of at least four weeks previously

in the treatment of the disease.

When concentration-response curves of these patients were compared with those of a group of hypothyroid patients, a significant difference was found. The main difference between the patients was obviously the function of the thyroid gland in both groups and the possibility was considered that this was connected with the quantitative difference observed. It has been shown however (Alexander & Johnson 1958) that in both euthyroid and hypothyroid individuals treated with aspirin for at least as long as the patients under consideration here, no alteration in thyroid function, as measured by ^{131}I uptake by the thyroid gland, was detected.

Another possibility, that some interaction between aspirin and circulating thyroxine occurred, was suggested because of the lesser degree of stimulation seen in the myxoedematous group. A specific experiment to test this hypothesis has not however been performed.

Salicylate increases oxygen consumption and stimulates respiration to the extent of causing hyperventilation. The relation between the increased metabolic rate and the simultaneous increase in

pulmonary ventilation was examined in the same groups of patients, and the ratio between the two responses was found to be similar in each group, and also similar to that obtained during muscular exercise (Asmussen et al 1943). This indicated that the action of therapeutic doses of salicylate was in no way different from the exercise stimulus in these respects and that respiratory stimulation was a direct result of metabolic stimulation.

Comparison with another recognised metabolic stimulant, dinitrophenol, was made. In studying the respiratory and metabolic effects of DNP in man, it was found that while the increase in oxygen consumption of all the subjects was the same, irrespective of thyroid function (this in contrast to the salicylate effect), nevertheless the ratio of oxygen consumption to pulmonary ventilation was again indistinguishable from that resulting from stimulation by exercise. This was in agreement with the results obtained by Ramsay (1957) experimenting with rats under DNP administration.

Among the metabolic effects mentioned in the preliminary reports on increased oxygen consumption in man (Cochran 1952), a lowering of the respiratory

quotient after single doses of salicylate was noted. This aspect of the work was re-examined in four patients on whom balance studies were being conducted. A prolonged depression of the R.Q. was noted, which commenced when the patient's excessive excretion of nitrogen caused him to enter a phase of negative balance. This confirmed the suggestion that the prime effect of salicylate was of metabolic origin, and from the low levels of the R.Q. one may reasonably be led to the postulate that there is a preferential breakdown of fat, rather than carbohydrate, to meet the energy requirements.

Finally, the possible interference in the metabolism of carbohydrate was investigated on a limited scale by assessing the effect of prolonged administration of salicylate to rats. Again comparison was made with DNP by carrying out an identical experiment with that drug. Whereas it had been shown that single doses of both DNP (Barnes 1953) and salicylate (Smith 1954) to rats caused an initial depletion in the normal liver glycogen which was followed by a return to normal after twenty-four hours, in these experiments the depression was seen to persist with the continued administration of salicylate

but not with DNP. The animals in both treated groups lost weight when compared with the control sibling rats, but the amount lost by the salicylate-fed group was considerably greater.

Thus it has been shown that many of the respiratory effects of salicylate may be likened to those of another metabolic stimulant, dinitrophenol, but that their action is not wholly identical. The prime action of salicylate would seem to be metabolic in origin and the purely respiratory results which occur to be sequential rather than causal. The many facets of salicylate action still remain relatively unconnected and it may well be that the action itself is a complex one, altered by certain other physiological or pathological conditions.

Summary.

I. The effect of salicylate on the basal metabolic rate, the pulmonary ventilation and the respiratory quotient was quantitatively studied in man over the therapeutic dose range.

(a) A linear correlation was established between the serum salicylate concentration and the basal metabolic rate in the afebrile convalescent, the diabetic and the myxoedematous subject. The response of the myxoedematous patients was not the same as that of the convalescent, but no alteration in thyroid function was detected.

(b) Increased oxygen consumption due to salicylate was accompanied by a commensurate increase in pulmonary ventilation and the ratio of these responses was similar to the exercise stimulus.

(c) The respiratory quotient was depressed over a considerable period of salicylate administration, the first peak coinciding with the onset of nitrogen katabolism.

(d) Studies in the rat showed that salicylate sufficient to stimulate metabolism by fifty per cent interfered with normal carbohydrate metabolism, inducing depletion of liver glycogen and loss in body weight.

II. Comparative metabolic and respiratory studies were carried out with 2:4-dinitrophenol in diabetic and myxoedematous patients, and comparison of the glycogenolytic action was studied in the rat.

(a) The metabolic rate was linearly correlated with the plasma DNP concentration. Unlike salicylate, DNP induced the same response in all subjects regardless of thyroid function.

(b) Increased oxygen consumption due to DNP was accompanied by a commensurate increase in pulmonary ventilation and the ratio of these responses was similar to the exercise stimulus.

(c) Studies in the rat showed that DNP differed from salicylate in that, though the same degree of metabolic stimulation was induced, no effect on the liver glycogen was detected and the loss in body weight was less marked.

Appendix.

Table 1.

Comparison of dose-response and concentration-response curves. (Fig. 1).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Dose gr./day	Conc. mg./100 ml.
11.7.55.	155	83	50	18
12.7.55.	173	94	55	21
13.7.55.	176	95	62.5	31
14.7.55.	174	94	62.5	31
15.7.55.	190	102	65	36
16.7.55.	199	107	65	34
20.7.55.	182	98	55	23
21.7.55.	188	102	75	30
22.7.55.	188	102	77.5	36
23.7.55.	218	117	77.5	44
25.7.55.	205	111	82.5	43

Data of the Regressions.

Dose-response	Conc.-response
n = 11	n = 11
r = 0.79 $P \leq 0.01$	r = 0.88, $P \leq 0.001$
y = 0.68x + 55.25	y = 0.98x + 69.5
σ_r = 5.95	σ = 4.64
$t\sigma_r = \pm 13.27$	$t\sigma_r = \pm 10.49$

Table 3.

Clinical data of the individuals in the salicylate investigation.

Case	Name	Diagnosis	Sex	Age yrs.	S.A.+ m^2	N.B.M.R.* cals/m^2/hr.
1	G.W.	Rheumatic fever	M	25	2.04	37.1
2	S.H.	Rheumatic fever	F	24	1.43	33.9
3	R.C.	Rheumatic fever	M	23	1.70	37.6
4	A.W.	Rheumatic fever	M	18	1.62	39.2
5	C.McC.	Rheumatic fever	F	37	1.40	34.0
6	J.McW.	Rheumatic fever	F	16	1.44	36.0
7	M.Gr.	Rheumatic fever	F	14	1.36	37.8
8	M.McM.	Myxoedema	M	52	1.80	33.8
9	A.McL.	Myxoedema	F	65	1.74	31.0
10	I.McG.	Myxoedema	F	72	1.84	30.7
11	F.F.	Myxoedema	F	72	1.64	30.7
12	M.B.	Myxoedema	F	43	1.56	32.5
13	F.A.	Myxoedema	F	52	1.72	31.9
14	M.G.	Obesity	F	67	1.73	31.0
15	W.B.	Diabetes mellitus	M	58	1.88	33.4

+S.A. = surface area calculated from weight and standing height (Du Bois).

* N.B.M.R. = normal basal metabolic rate.

Fig. 2.

Concentration-response curve : case 1.

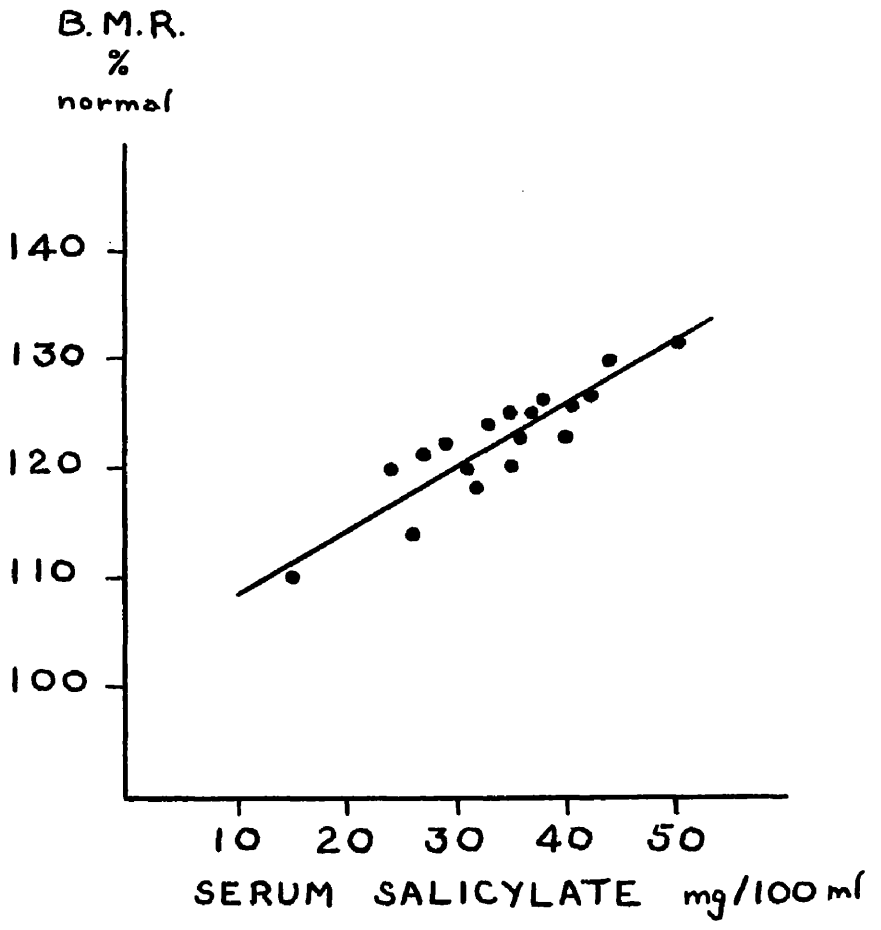


Table 4.

Basal metabolic rates and serum salicylate concentrations: case 1 (Fig. 2).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
1.12.55.	314	120	24
1.12.55.	317	121	27
2.12.55.	319	122	29
3.12.55.	324	124	33
5.12.55.	313	120	31
6.12.55.	297	114	26
6.12.55.	305	118	32
7.12.55.	326	125	35
7.12.55.	325	125	37
9.12.55.	322	123	40
9.12.55.	328	126	40
10.12.55.	313	120	35
11.12.55.	331	127	42
13.12.55.	322	123	35
14.12.55.	329	126	38
14.12.55.	338	130	44
15.12.55.	343	132	50
16.12.55.	286	110	15
19.12.55.	268	103	0
20.12.55.	260	99	0

Data of the Regression.

$n = 18$

$r = 0.91$, $P < 0.001$

$y = 0.59x + 102.5$

$\sigma_r = 2.26$

$t\sigma_r = \pm 4.79$.

Fig. 3.

Concentration-response curve : case 2.

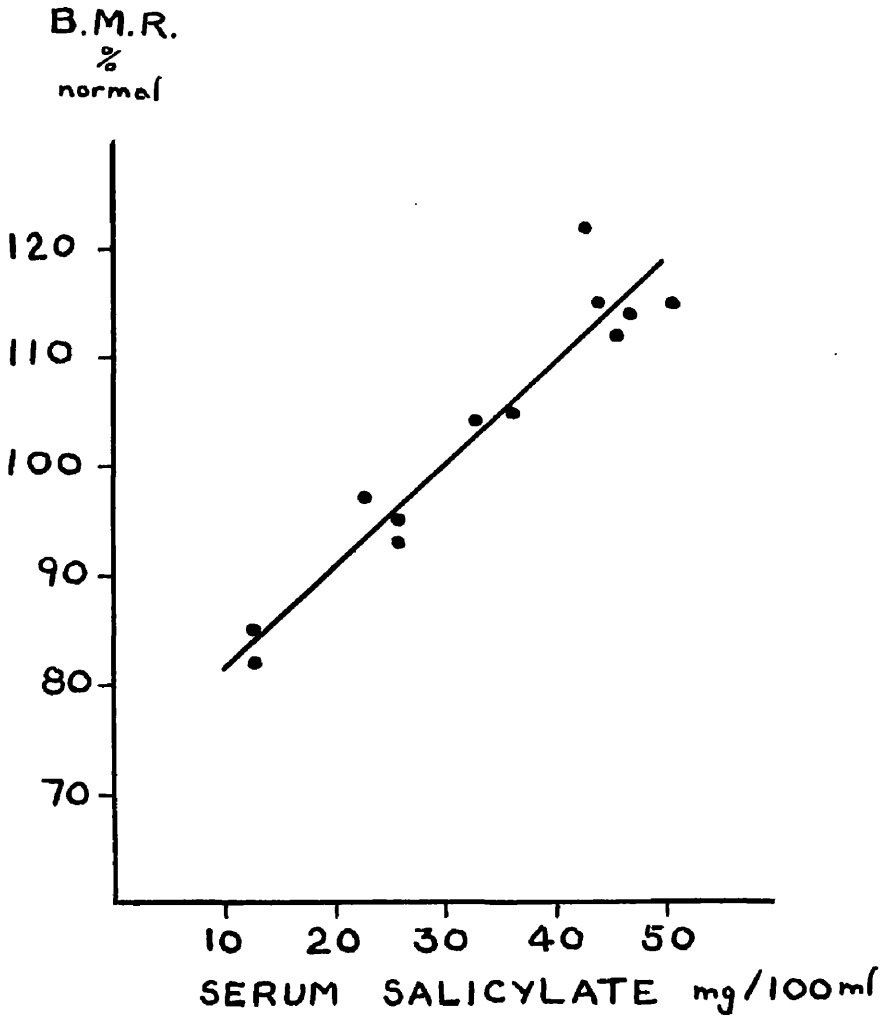


Table 5.

Basal metabolic rates and serum salicylate concentrations: case 2 (Fig. 3).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
20.6.56.	203	122	43
22.6.56.	192	115	44
22.6.56.	189	114	47
23.6.56.	186	112	46
25.6.56.	173	104	33
28.6.56.	192	115	51
29.6.56.	154	93	26
29.6.56.	157	95	26
1.7.56.	176	105	36
3.7.56.	161	97	23
4.7.56.	136	82	13
4.7.56.	139	84	13
6.7.56.	138	83	0

Data of the Regression.

$n = 12$

$r = 0.92$, $P < 0.001$

$y = 0.94x + 71.8$

$\delta_r = 5.49$

$t\delta_r = \pm 12.24$

Fig. 4.

Concentration-response curve : case 3.

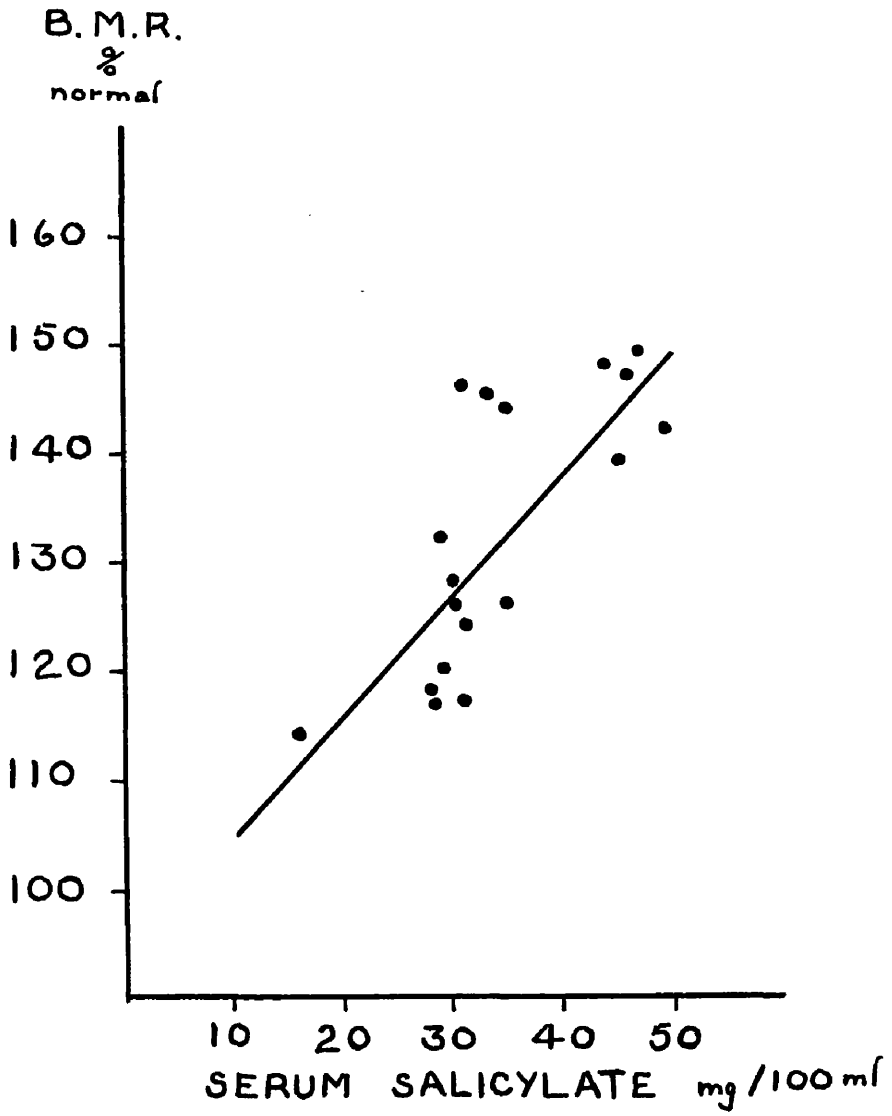


Table 6.

Basal metabolic rates and serum salicylate concentrations: case 3 (Fig. 4).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
14.1.56.	329	149	47
16.1.56.	313	142	49
17.1.56.	307	139	45
18.1.56.	327	148	44
21.1.56.	276	126	30
21.1.56.	264	120	29
22.1.56.	271	124	31
23.1.56.	278	126	35
24.1.56.	317	144	35
24.1.56.	322	146	31
25.1.56.	284	128	30
26.1.56.	288	132	29
28.1.56.	320	145	33
29.1.56.	324	147	46
30.1.56.	257	117	31
31.1.56.	257	117	28
31.1.56.	259	118	28
2.2.56.	250	114	16
9.2.56.	256	116	0
10.2.56.	258	118	0
10.2.56.	256	116	6

Data of the Regression.

$n = 18$

$r = 0.76$, $P < 0.001$

$y = 1.11x + 93.7$

$\delta_r = 8.43$

$t\delta_r = \pm 17.87.$

Fig. 5.

Concentration-response curve : case 4.

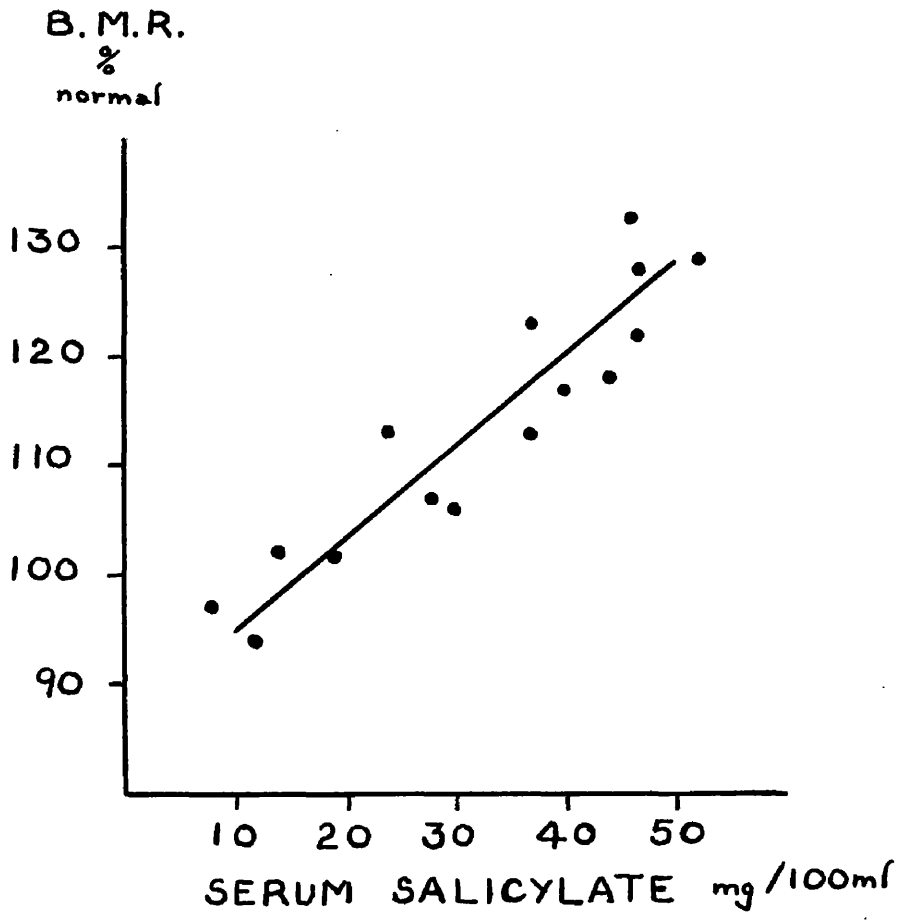


Table 7.

Basal metabolic rates and serum salicylate concentrations: case 4 (Fig. 5).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
1.7.55.	289	133	46
7.7.55.	267	122	47
8.7.55.	279	128	47
9.7.55.	281	129	52
11.7.55.	269	123	37
12.7.55.	255	117	40
14.7.55.	258	118	44
18.7.55.	221	102	19
19.7.55.	204	94	12
21.7.55.	246	113	24
22.7.55.	231	106	30
23.7.55.	246	113	37
25.7.55.	233	107	28
26.7.55.	223	102	14
27.7.55.	211	97	8
28.7.55.	223	102	0
1.8.55.	226	104	0

Data of the Regression.

$n = 15$

$r = 0.93$, $P < 0.001$

$y = 0.85x + 86.2$

$\delta_r = 4.66$

$t\,\delta_r = \pm 10.07$.

Fig. 6.

Concentration-response curve : case 5.

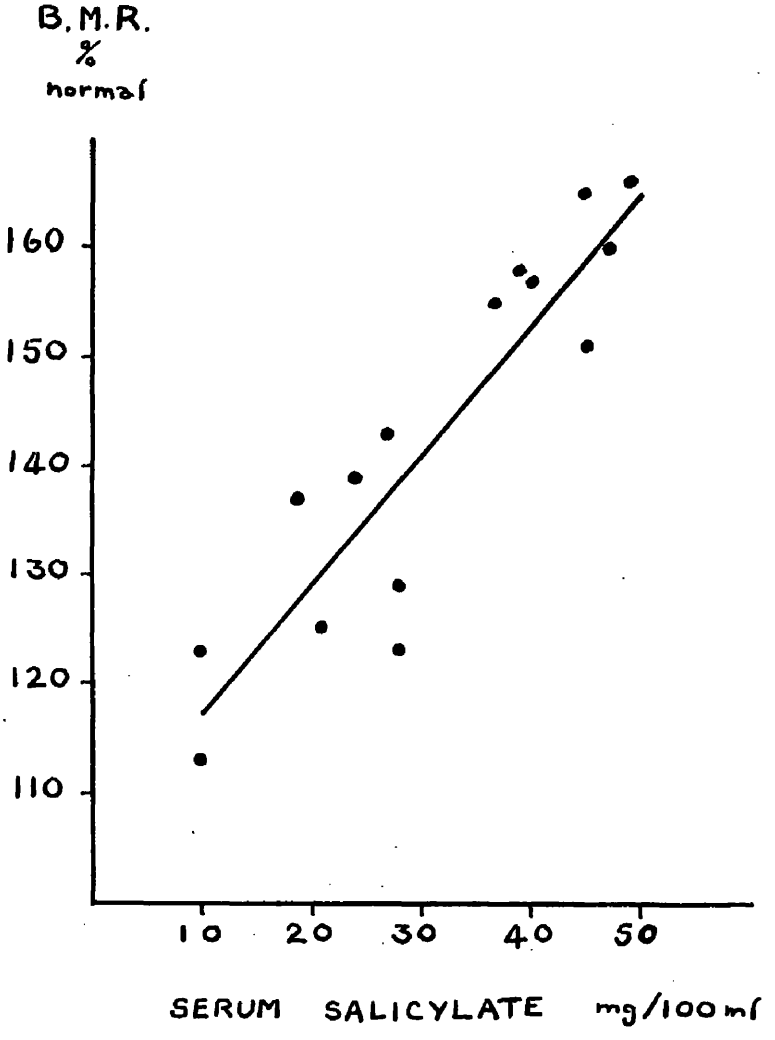


Table 8.

Basal metabolic rates and serum salicylate concentrations: case 5 (Fig. 6).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
8.2.56.	264	165	45
10.2.56.	241	151	45
13.2.56.	265	166	49
14.2.56.	255	160	47
20.2.56.	251	157	40
21.2.56.	253	158	39
21.2.56.	248	155	37
23.2.56.	228	143	27
24.2.56.	222	139	24
27.2.56.	206	129	28
27.2.56.	196	123	28
28.2.56.	200	125	21
29.2.56.	197	123	10
29.2.56.	180	113	10
1.3.56.	218	137	19
5.3.56.	167	102	0

Data of the Regression.

$n = 15$

$r = 0.91$, $P < 0.001$

$y = 1.20x + 105.25$

$\delta_r = 7.38$

$t\delta_r = \pm 15.94$.

Fig. 7.

Concentration-response curve : case 6.

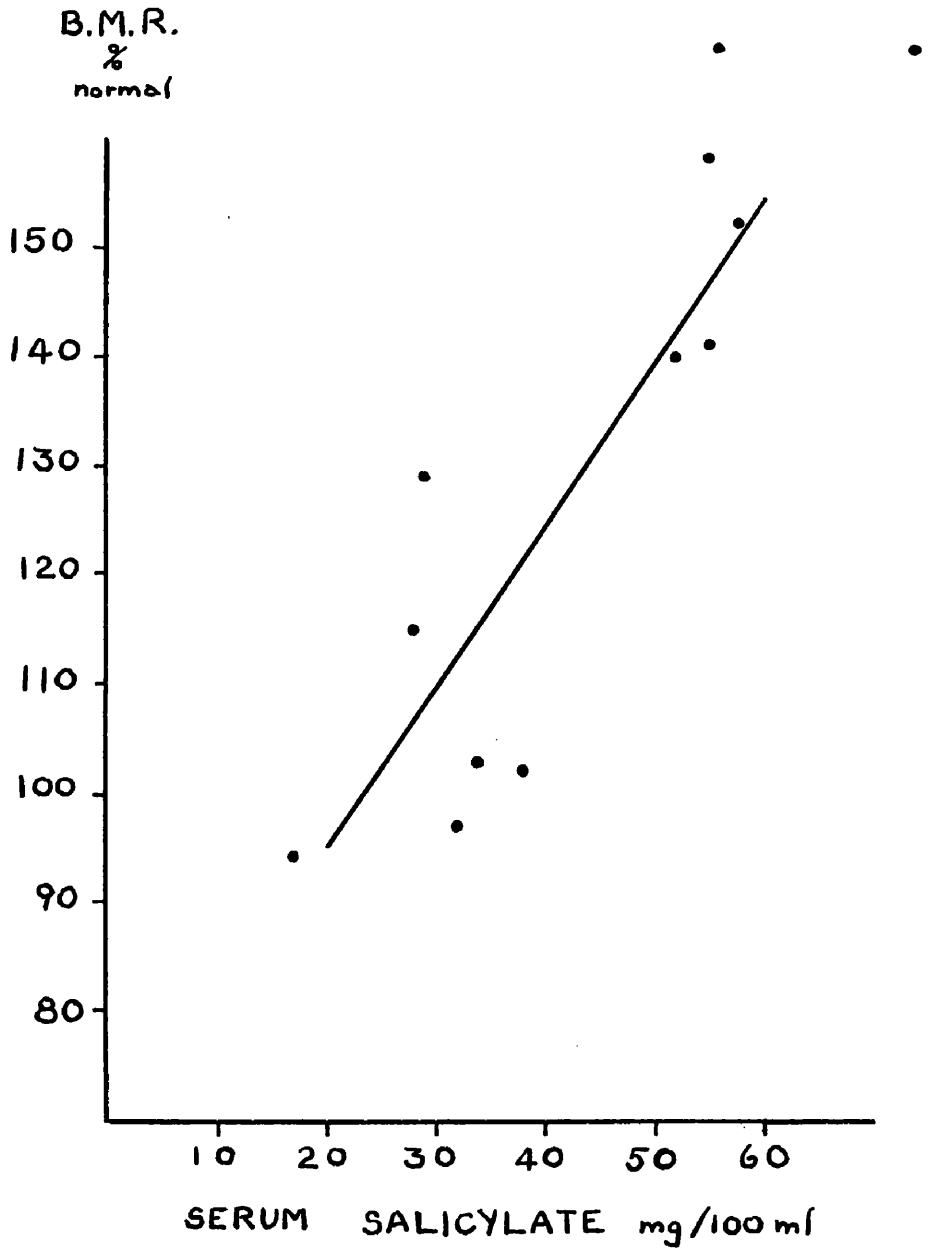


Table 9.

Basal metabolic rates and serum salicylate concentrations: case 6 (Fig. 7).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
24.4.56.	210	118	0
25.4.56.	230	129	29
27.4.56.	184	103	34
28.4.56.	205	115	28
30.4.56.	280	158	55
1.5.56.	298	168	56
2.5.56.	249	140	52
3.5.56.	271	152	58
7.5.56.	300	168	74
8.5.56.	252	141	55
10.5.56.	183	102	38
11.5.56.	173	97	32
12.5.56.	167	94	17
14.5.56.	154	87	0
17.5.56.	173	97	0
25.5.56.	184	103	0

Data of the Regression.

$n = 12$

$r = 0.88$, $P < 0.001$

$y = 1.48x + 65.5$

$\delta_r = 13.83$

$t\delta_r = \pm 30.1$

Fig. 8.

Concentration-response curve : case 7.

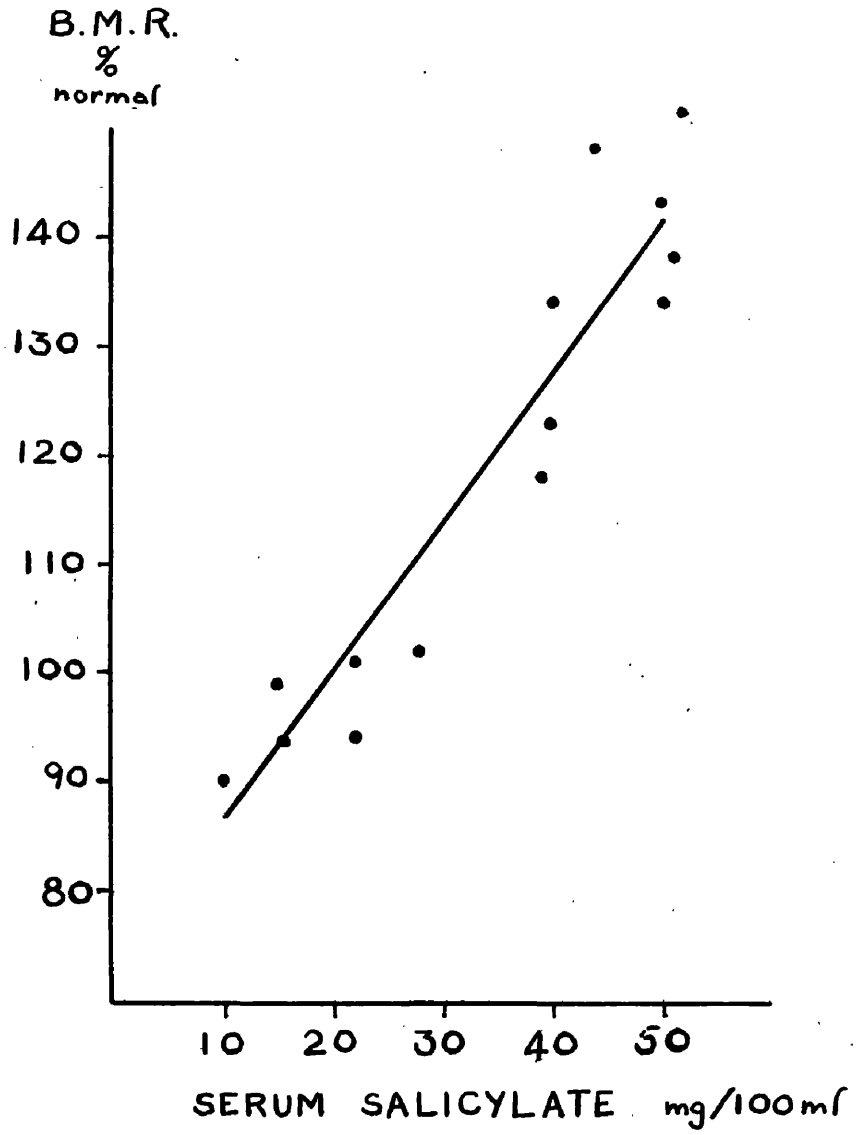


Table 10.

Basal metabolic rates and serum salicylate concentrations: case 7 (Fig. 8).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
20.6.55.	262	148	44
21.6.55.	217	123	40
22.6.55.	266	151	52
23.6.55.	253	143	50
24.6.55.	238	134	50
27.6.55.	243	138	51
28.6.55.	223	134	40
30.6.55.	208	118	39
1.7.55.	166	94	22
2.7.55.	198	112	28
4.7.55.	178	101	22
5.7.55.	159	90	10
5.7.55.	167	95	16
6.7.55.	174	99	15
16.7.55.	169	96	0
18.7.55.	168	95	0

Data of the Regression.

$n = 14$

$r = 0.95$, $P < 0.001$

$y = 1.37x + 73.1$

$\delta_r = 7.06$

$t\delta_r = \pm 15.2.$

Table 11.

Data of the regression lines of individuals in the salicylate investigation.

Case	Name	B.M.R. without treatment % normal+	Conversion factor*	No. of Observations	r	P	Equation of the Regression	95% confidence limits
1	G.W.	101	2.61	18	0.91	<0.001	y=0.59x+102.5	±4.8
2	S.H.	83	1.66	12	0.92	<0.001	y=0.94x+ 71.8	±12.2
3	R.C.	117	2.20	18	0.76	<0.001	y=1.11x +93.7	±17.9
4	A.W.	103	2.19	15	0.93	<0.001	y=0.85x +86.2	±10.1
5	C.McC.	102	1.64	15	0.91	<0.001	y=1.20x+105.1	±15.9
6	J.McW.	95	1.79	12	0.88	<0.001	y=1.48x +65.5	±30.1
7	M.Gr.	96	1.77	14	0.95	<0.001	y=1.37x +73.1	±15.2
8	M.McM.	76	2.10	9	0.97	<0.001	y=1.08x +59.1	±6.8
9	A.McL.	85	1.86	15	0.93	<0.001	y=0.99x +69.2	±10.3
10	I.McG.	61	1.95	17	0.96	<0.001	y=0.88x +50.6	±6.1
11	F.F.	80	1.74	15	0.94	<0.001	y=0.83x +69.4	±7.7
12	M.B.	78	1.75	13	0.95	<0.001	y=0.93x +62.3	±9.8
13	F.A.	80	1.89	13	0.92	<0.001	y=0.73x +68.3	±10.3
14	M.G.	102	1.85	15	0.67	<0.01	y=0.38x+108.9	±16.6
15	W.B.	110	2.16	7	0.92	<0.001	y=1.53x +90.2	±25.8

+Robertson & Reid (1952) standards.

* To convert B.M.R. to oxygen consumption ml./min. at s.t.p.

Table 12.

Serum salicylate concentrations and increments of oxygen consumption: cases 1 to 7 (Fig. 10).

Patient G.W. Case 1.

Ser. sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
24	7.1
27	7.5
29	7.8
33	8.5
31	6.8
26	4.7
32	5.8
35	8.9
37	8.8
40	8.2
40	9.1
35	6.9
42	9.5
35	8.2
38	9.1
44	10.4
50	11.3
15	3.1

Table continued overleaf

Table 12 (continued).

Patient S.H. Case 2.

Ser. sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
43	13.2
44	11.0
47	10.3
46	9.6
33	7.1
51	11.0
26	3.2
26	3.8
36	7.7
23	4.6
13	-0.4
13	0.1

Patient R.C. Case 3.

Ser. sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
47	12.2
49	9.5
45	8.7
44	12.0
30	3.2
29	1.1
31	2.4
35	3.5
35	10.1
31	11.2
30	4.5
29	5.1
33	10.8
46	11.2
31	0.0
28	0.0
28	0.2
16	-1.4

Table continued overleaf

Table 12.(continued).

Patient A.W. Case 4.

Ser. sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
46	11.6
47	7.6
47	9.8
52	9.9
37	7.9
40	5.6
44	5.9
19	-0.5
12	-3.7
24	3.8
30	1.2
37	3.9
28	1.4
14	-0.4
8	-2.4

Patient C.McC. Case 5.

Ser. sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
45	20.0
45	15.3
49	20.5
47	18.4
40	17.5
39	17.9
37	16.9
27	12.7
24	11.5
28	8.1
28	6.1
21	7.0
10	6.3
10	2.8
19	10.8

Table continued overleaf.

Table 12. (continued).

Patient J. McW. Case 6.

Ser. sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
29	12.6
34	3.3
28	7.7
55	22.5
56	26.3
52	16.3
58	20.9
74	26.6
55	17.1
38	3.1
32	1.1
17	-0.1

Patient M.Gr. Case 7.

Ser. sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
44	19.8
40	10.2
52	20.7
50	17.7
50	14.5
51	15.8
40	11.4
39	8.3
22	-0.6
28	6.2
22	1.9
10	-2.1
16	-0.3
15	1.2

Fig. 11.

Concentration-response curve : case 8.

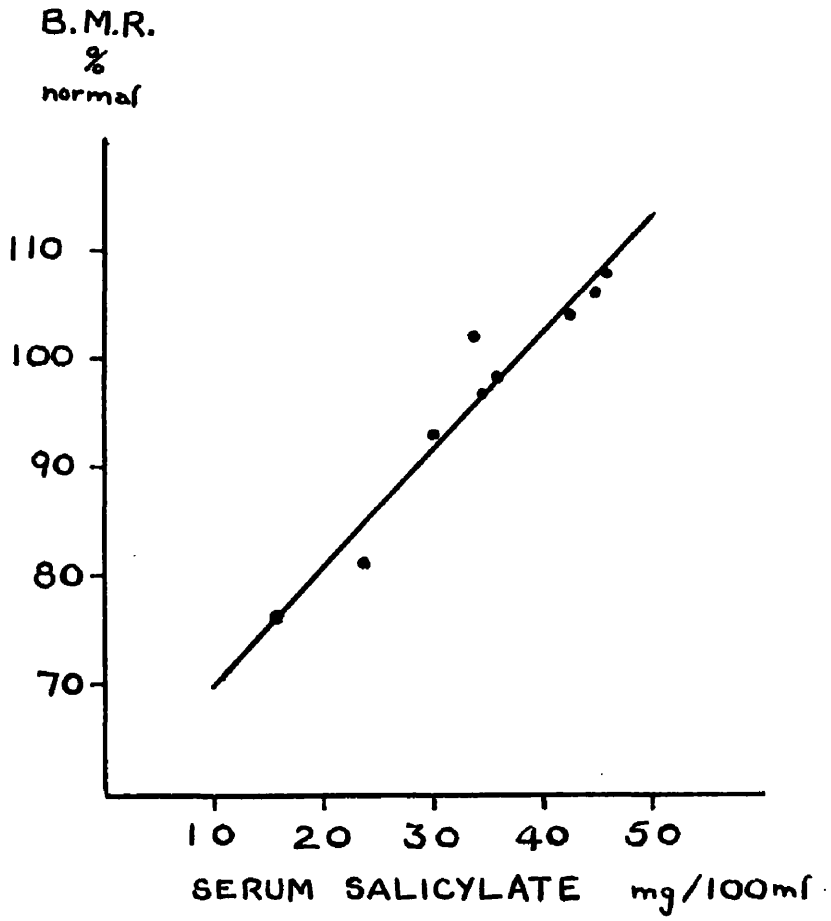


Table 13.

Basal metabolic rates and serum salicylate concentrations: case 8 (Fig. 11).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
21.4.55.	163	78	0
22.4.55.	152	73	0
29.4.55.	170	81	24
2.5.55.	206	98	36
4.5.55.	195	93	30
6.5.55.	203	97	35
9.5.55.	219	104	43
10.5.55.	221	106	45
11.5.55.	227	108	46
12.5.55.	214	102	34
13.5.55.	159	76	16

Data of the Regression.

$n = 9$

$r = 0.97$, $P<0.001$

$y = 1.08x + 59.1$

$\delta_r = 2.87$

$t\delta_r = \pm 6.8$.

Fig. 12.

Concentration-response curve : case 9.

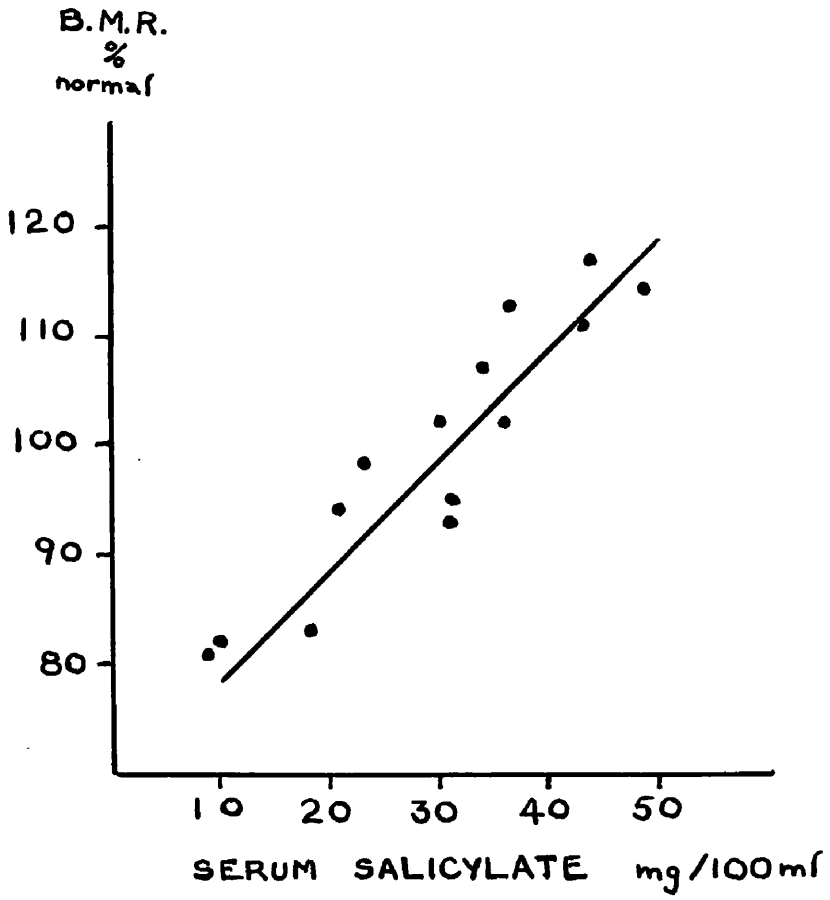


Table 14.

Basal metabolic rates and serum salicylate concentrations: case 9 (Fig. 12).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
7.7.55.	158	85	0
8.7.55.	160	86	0
9.7.55.	157	84	0
11.7.55.	155	83	18
12.7.55.	173	94	21
13.7.55.	176	95	31
14.7.55.	174	93	31
15.7.55.	190	102	36
16.7.55.	199	107	34
19.7.55.	207	112	37
20.7.55.	182	98	23
21.7.55.	188	102	30
22.7.55.	188	102	36
23.7.55.	218	117	44
25.7.55.	205	111	43
26.7.55.	210	114	49
28.7.55.	153	82	10
29.7.55.	151	81	9

Data of the Regression.

$n = 15$

$r = 0.93$, $P < 0.001$

$y = 0.99x + 69.2$

$\delta_r = 4.78$

$t\delta_r = \pm 10.3$.

Fig. 13.

Concentration-response curve : case 10.

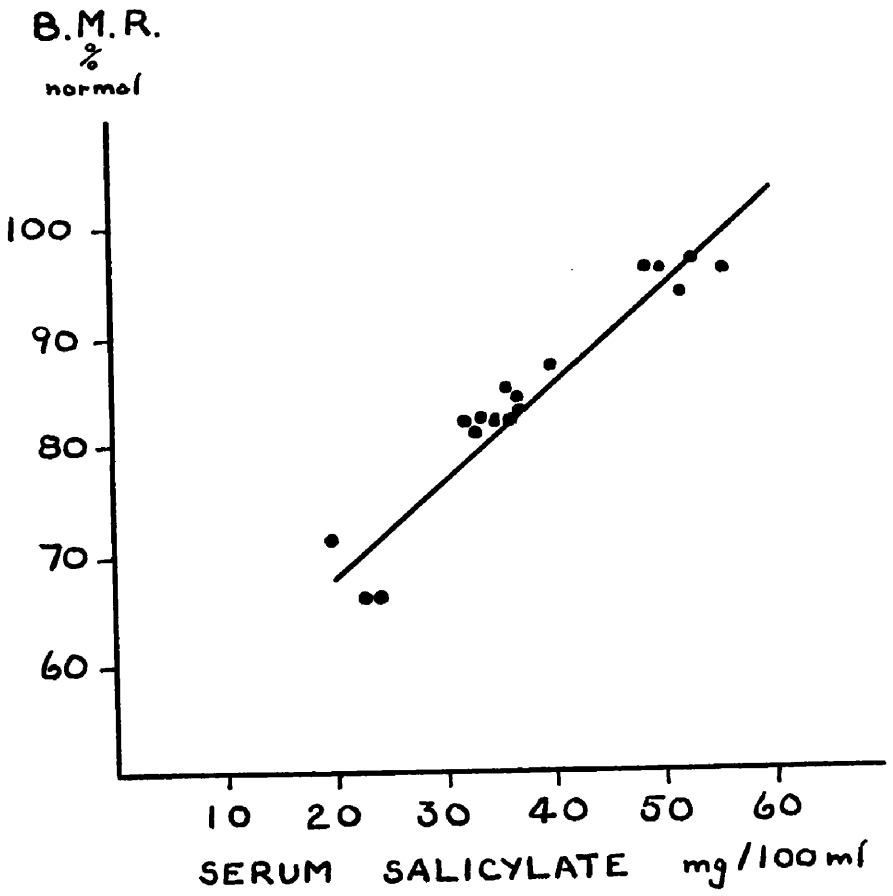


Table 15.

Basal metabolic rates and serum salicylate concentrations: case 10 (Fig. 13).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
14.9.55.	122	63	0
15.9.55.	119	61	0
16.9.55.	116	60	0
16.9.55.	117	60	0
21.9.55.	160	82	32
22.9.55.	161	83	37
22.9.55.	160	82	36
24.9.55.	169	87	40
26.9.55.	159	82	34
27.9.55.	158	82	35
28.9.55.	165	85	36
29.9.55.	187	96	49
30.9.55.	187	96	56
2.10.55.	187	96	50
4.10.55.	189	97	53
5.10.55.	183	94	52
6.10.55.	164	84	37
6.10.55.	158	81	33
7.10.55.	128	66	24
7.10.55.	128	66	23
8.10.55.	139	71	20

Data of the Regression.

$n = 17$

$r = 0.96$, $P < 0.001$

$y = 0.88x + 50.6$

$\delta_r = 2.85$

$t\delta_r = \pm 6.1$

Fig. 14.

Concentration-response curve : case 11.

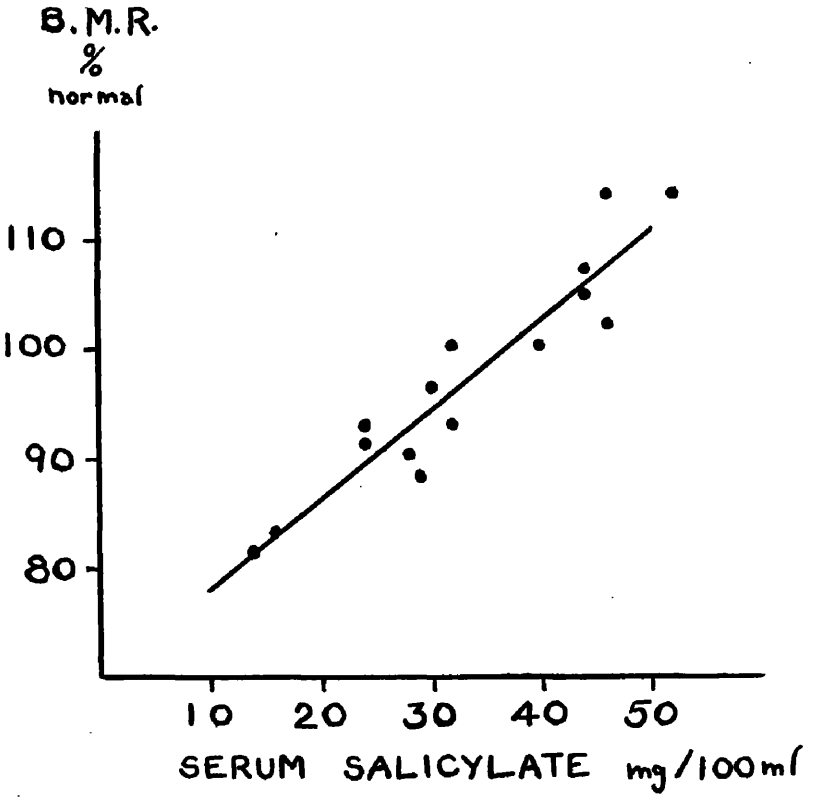


Table 16.

Basal metabolic rates and serum salicylate concentrations: case 11 (Fig. 14).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
10.9.55.	141	81	0
12.9.55.	141	81	0
12.9.55.	130	79	0
13.9.55.	128	78	0
14.9.55.	131	80	0
21.9.55.	151	91	24
22.9.55.	159	96	30
23.9.55.	174	100	32
24.9.55.	160	93	32
27.9.55.	152	88	29
29.9.55.	173	100	40
30.9.55.	185	107	44
2.10.55.	176	102	46
3.10.55.	197	114	46
4.10.55.	198	114	52
5.10.55.	182	105	44
6.10.55.	156	90	28
6.10.55.	161	93	24
7.10.55.	143	83	16
8.10.55.	140	81	14

Data of the Regression.

$n = 15$

$r = 0.94$, $P < 0.001$

$y = 0.83x + 69.4$

$\delta_r = 3.58$

$t\delta_r = \pm 7.7$.

Fig. 15.

Concentration-response curve : case 12.

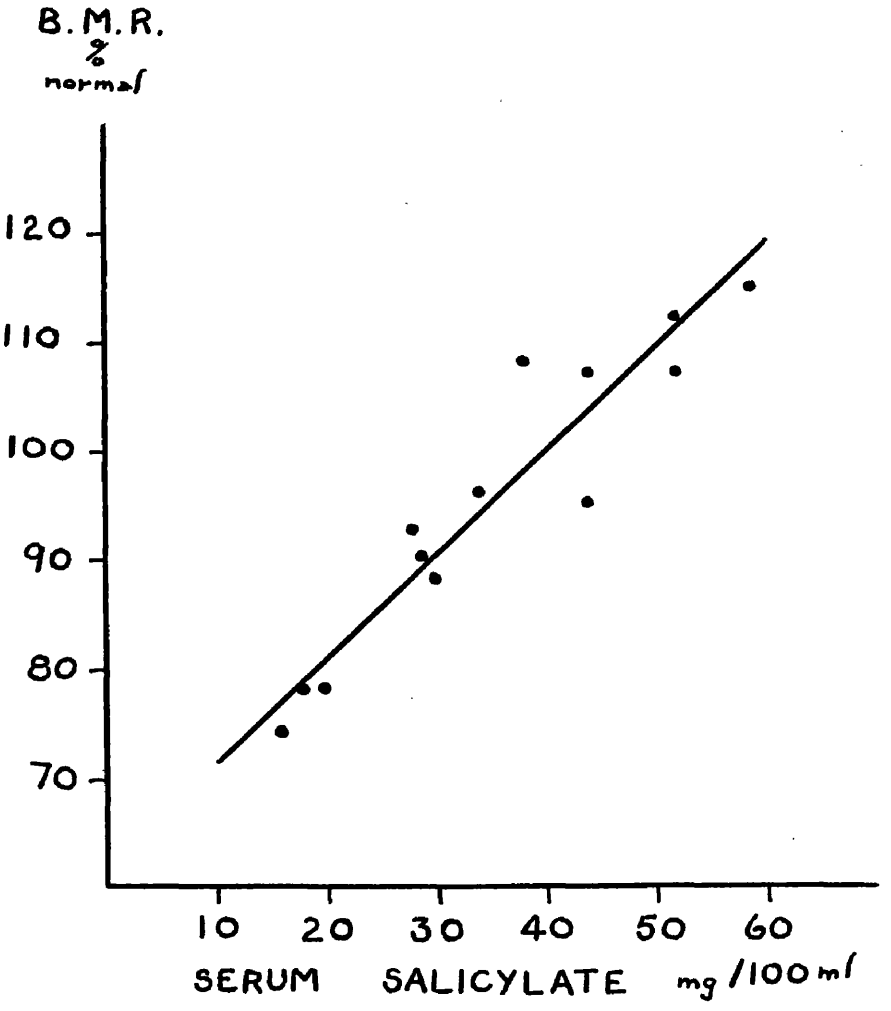


Table 17.

Basal metabolic rates and serum salicylate concentrations: case 12 (Fig. 15).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
15.9.55.	135	77	0
16.9.55.	137	78	0
21.9.55.	162	93	28
21.9.55.	157	90	29
22.9.55.	168	96	34
26.9.55.	188	108	38
28.9.55.	187	107	44
29.9.55.	196	112	52
30.9.55.	201	115	59
2.10.55.	186	107	52
4.10.55.	166	95	44
5.10.55.	155	88	30
7.10.55.	137	78	20
7.10.55.	135	78	18
8.10.55.	130	74	16
12.10.55.	136	78	0

Data of the Regression.

$n = 13$

$r = 0.95$, $P<0.001$

$y = 0.93x + 62.3$

$\delta_r = 4.43$

$t\delta_r = \pm 9.8$.

Fig. 16.

Concentration-response curve : case 13.

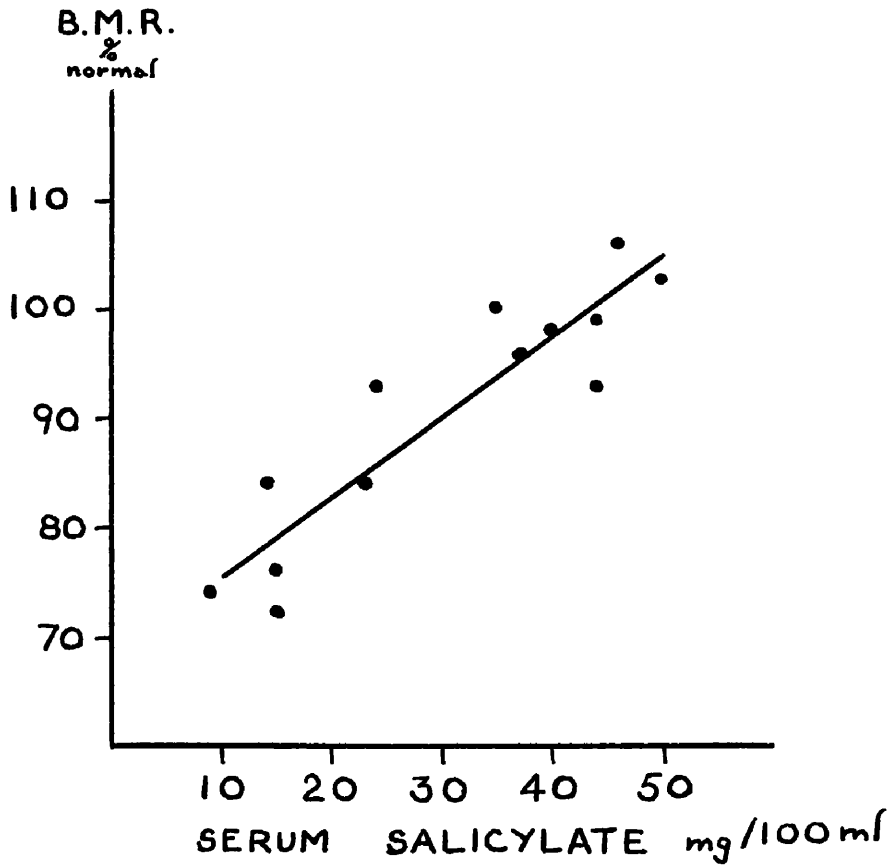


Table 18.

Basal metabolic rates and serum salicylate concentrations: case 13 (Fig. 16).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
16.7.55.	156	83	0
18.7.55.	146	78	0
20.7.55.	136	72	15
21.7.55.	159	84	14
22.7.55.	158	84	23
23.7.55.	188	100	35
25.7.55.	185	98	40
26.7.55.	194	103	50
27.7.55.	174	93	44
28.7.55.	188	99	44
29.7.55.	200	106	46
30.7.55.	182	96	37
1.8.55.	175	93	24
3.8.55.	143	76	15
4.8.55.	139	74	9

Data of the Regression.

$n = 13$

$r = 0.92$, $P < 0.001$

$y = 0.73x + 68.3$

$\delta_r = 4.67$

$t\delta_r = \pm 10.3$.

Table 19.

Serum salicylate concentrations and increments of oxygen consumption: cases 8 to 13 (Fig. 18).

Patient M.McM. Case 8.

Ser. Sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
24	2.1
36	7.8
30	6.2
35	7.5
43	10.0
45	10.3
46	11.2
34	9.2
16	0.3

Patient A.McL. Case 9.

Ser. Sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
18	-0.6
21	2.5
31	3.0
31	2.6
36	5.3
34	6.8
37	8.1
23	4.0
30	4.9
36	4.9
44	10.1
43	7.7
49	8.6
10	-0.9
9	-1.3

Table continued overleaf

Table 19. (continued).

Patient I. McG. Case 10.

Ser. Sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
32	6.5
37	6.7
36	6.5
40	7.9
34	6.3
35	6.1
36	7.3
49	10.8
56	10.8
50	10.8
53	11.0
52	10.1
37	7.1
33	6.2
24	1.5
23	1.5
20	3.2

Patient F.F. Case 11.

Ser. Sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
24	3.0
30	4.4
32	7.0
32	4.6
29	3.2
40	6.9
44	9.0
46	7.5
46	11.1
52	11.3
44	8.5
28	3.9
24	4.8
16	1.6
14	1.1

Table continued overleaf

Table 19.(continued).

Patient M.B. Case 12.

Ser. Sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
28	4.8
29	3.7
34	5.9
38	9.4
44	9.3
52	11.0
59	12.0
52	9.1
44	5.4
30	3.3
20	-0.1
18	-0.4
16	-1.3

Patient F.A. Case 13.

Ser. Sal. mg./100 ml.	ΔO_2 cons. Cals./m^2/hr.
15	-2.6
14	1.3
23	1.2
35	6.2
40	5.7
50	7.2
44	3.9
44	6.2
46	8.2
37	5.1
24	4.0
15	-1.4
9	-2.1

Fig. 19.

Concentration-response curve: case 14.

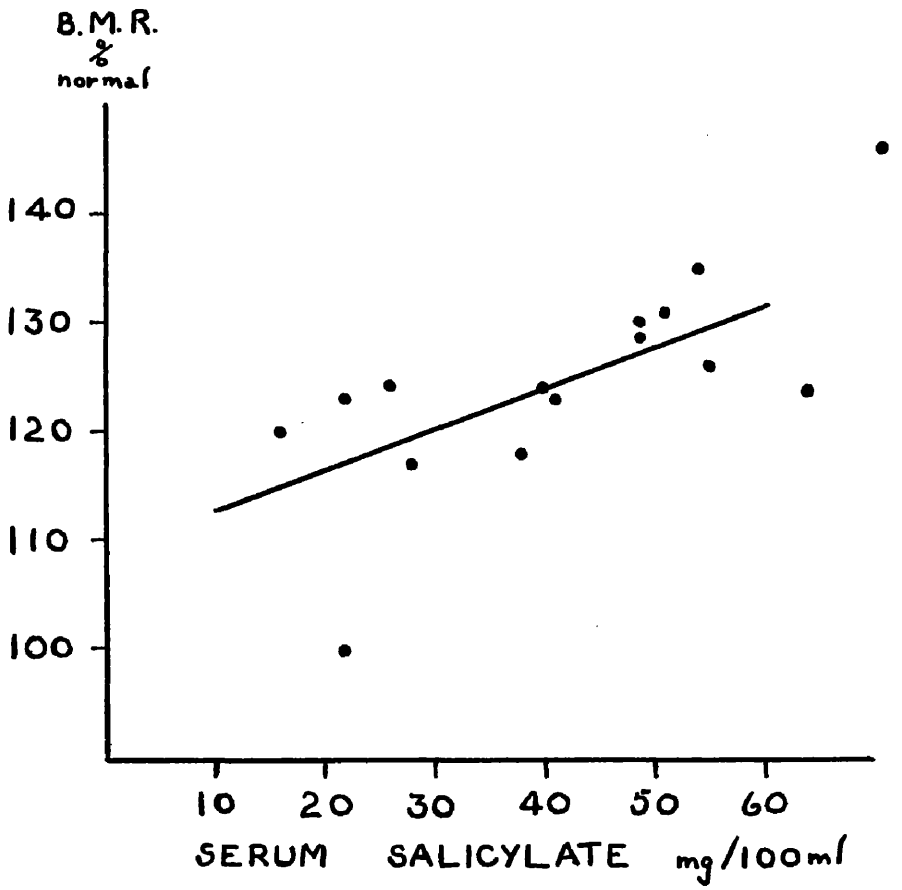


Table 20.

Basal metabolic rates and serum salicylate concentrations: case 14 (Fig. 19).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
16.10.56.	238	129	49
19.10.56.	227	123	41
23.10.56.	216	117	28
26.10.56.	240	130	49
30.10.56.	228	124	40
2.11.56.	218	118	38
6.11.56.	229	124	64
7.11.56.	270	146	71
8.11.56.	242	131	51
9.11.56.	250	135	54
10.11.56.	233	126	55
11.11.56.	184	100	22
14.11.56.	189	102	0
11.12.56.	227	123	22
28.11.57.	223	120	16
29.3.57.	230	124	26

Data of the Regression.

$n = 15$

$r = 0.67$, $P < 0.01$

$y = 0.38x + 108.9$

$\delta_r = 7.70$

$t\delta_r = \pm 16.6$.

Fig. 20.

Concentration-response curve: case 15.

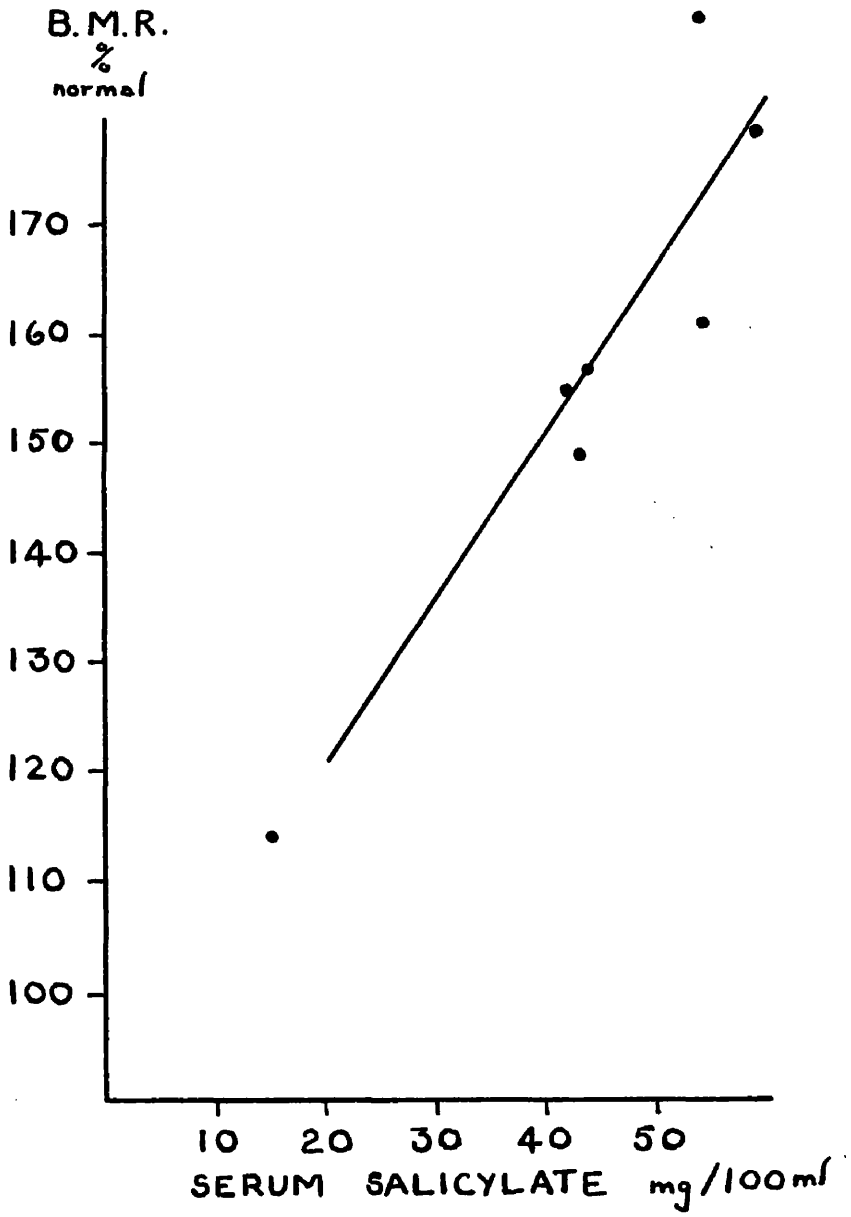


Table 21.

Basal metabolic rates and serum salicylate concentrations: case 15 (Fig. 20).

Date	O_2 ml./min. at N.T.P.	B.M.R. % Normal	Ser. Sal. mg./100 ml.
28.11.56.	242	112	0
30.11.56.	339	157	44
3.12.56.	400	179	59
5.12.56.	415	189	52
7.12.56.	347	161	54
10.12.56.	335	155	42
12.12.56.	321	149	43
14.12.56.	247	114	15
15.12.56.	235	108	0
17.12.56.	240	111	0

Data of the Regression.

$n = 7$

$r = 0.92$, $P < 0.001$

$y = 1.53x + 90.2$

$\delta_r = 10.56$

$t\delta_r = \pm 25.88$.

Table 22.

Increase in pulmonary ventilation and oxygen consumption in convalescent patients. (Fig. 21).

Patient G.W. Case 1.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
1.12.55.	7.1	6.0
1.12.55.	7.5	3.4
2.12.55.	7.8	3.1
3.12.55.	8.5	1.6
5.12.55.	6.8	9.7
6.12.55.	4.7	3.0
6.12.55.	5.8	5.5
7.12.55.	8.9	7.8
7.12.55.	8.8	7.4
9.12.55.	8.2	11.1
9.12.55.	9.1	13.1
10.12.55.	6.9	8.2
11.12.55.	9.5	10.3
13.12.55.	8.2	8.6
14.12.55.	9.1	2.7
14.12.55.	10.4	5.0
15.12.55.	11.3	9.5
16.12.55.	3.1	6.2

Table continued overleaf

Table 22. (continued).

Patient S.H. Case 2.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
20.6.56.	13.2	6.6
22.6.56.	11.0	6.5
22.6.56.	10.3	6.5
23.6.56.	9.6	5.1
25.6.56.	7.1	3.6
28.6.56.	11.0	5.1
29.6.56.	3.2	1.0
29.6.56.	3.8	1.0
1.7.56.	7.7	1.5
3.7.56.	4.6	0.9
4.7.56.	-0.4	2.9
4.7.56.	0.1	2.9

Table continued overleaf

Table 22. (continued).

Patient R.C. Case 3.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
14.1.56.	12.2	7.1
16.1.56.	9.5	3.8
17.1.56.	8.7	5.0
18.1.56.	12.0	4.3
21.1.56.	3.2	2.8
21.1.56.	1.1	3.1
22.1.56.	2.4	1.7
23.1.56.	3.5	2.5
24.1.56.	10.1	2.9
24.1.56.	11.2	4.4
25.1.56.	4.5	2.7
26.1.56.	5.1	1.3
28.1.56.	10.8	1.7
29.1.56.	11.2	1.5
30.1.56.	0	1.5
31.1.56.	0	0.9
31.1.56.	0.2	0.9
2.2.56.	-1.4	1.1

Table continued overleaf

Table 22. (continued).

Patient A.W. Case 4.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
1.7.55.	11.6	-9.1
7.7.55.	7.6	-4.1
8.7.55.	9.8	1.7
9.7.55.	9.9	5.2
11.7.55.	7.9	7.5
12.7.55.	5.6	-0.7
14.7.55.	5.9	-5.3
18.7.55.	-0.5	-3.9
19.7.55.	-3.7	-4.2
21.7.55.	3.8	-3.7
22.7.55.	1.2	0.4
23.7.55.	3.9	0.5
25.7.55.	1.4	-1.2
26.7.55.	-0.4	-4.7
27.7.55.	-2.4	-2.6

Table continued overleaf

Table 22. (continued).

Patient C. McC. Case 5.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
8.2.56.	20.0	4.1
10.2.56.	15.3	4.5
13.2.56.	20.5	3.8
14.2.56.	18.4	2.3
20.2.56.	17.5	2.3
21.2.56.	17.9	1.6
21.2.56.	16.9	0.8
23.2.56.	12.7	2.7
24.2.56.	11.5	0.4
27.2.56.	8.1	0.0
27.2.56.	6.1	-1.3
28.2.56.	7.0	-0.4
29.2.56.	6.3	0.2
29.2.56.	2.8	1.4
1.3.56.	10.8	-1.2

Table continued overleaf

Table 22. (continued).

Patient J.McW. Case 6.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
25.4.56.	12.6	0.4
27.4.56.	3.3	2.8
28.4.56.	7.7	0.9
30.4.56.	22.5	3.9
1.5.56.	26.3	3.9
2.5.56.	16.3	2.6
3.5.56.	20.9	4.4
7.5.56.	26.6	4.4
8.5.56.	17.1	7.4
10.5.56.	3.1	2.2
11.5.56.	1.1	3.2
12.5.56.	-0.1	-0.4

Table continued overleaf

Table 22. (continued).

Patient M.Gr. Case 7.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
20.6.55.	19.8	5.2
21.6.55.	10.2	5.7
22.6.55.	20.7	4.8
23.6.55.	17.7	5.9
24.6.55.	14.5	7.2
27.6.55.	15.8	8.7
28.6.55.	11.4	3.9
30.6.55.	8.3	2.8
1.7.55.	-0.6	2.2
2.7.55.	6.2	1.4
4.7.55.	1.9	-0.6
5.7.55.	-2.1	-1.0
5.7.55.	-0.3	-0.9
6.7.55.	1.2	0.7

Table 23.

Increase in pulmonary ventilation and oxygen consumption in myxoedematous patients. (Fig. 22).

Patient M.M. Case 8.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
29.4.55.	2.1	-0.4
2.5.55.	7.8	1.8
4.5.55.	6.2	-0.1
6.5.55.	7.5	2.1
9.5.55.	10.0	1.8
10.5.55.	10.3	2.2
11.5.55.	11.2	1.2
12.5.55.	9.2	0.5
13.5.55.	0.3	-0.2

Table continued overleaf

Table 23. (continued).

Patient A. McL. Case 9.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
11.7.55.	0.6	2.9
12.7.55.	2.5	1.2
13.7.55.	3.0	1.8
14.7.55.	2.6	2.2
15.7.55.	5.3	2.2
16.7.55.	6.8	1.1
19.7.55.	8.1	2.5
20.7.55.	4.0	1.7
21.7.55.	4.9	3.2
22.7.55.	4.9	1.7
23.7.55.	10.1	3.0
25.7.55.	7.7	4.0
26.7.55.	8.6	3.4
28.7.55.	-0.9	-0.2
29.7.55.	-1.3	-1.0

Table continued overleaf

Table 23. (continued).

Patient I.McG. Case 10.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
21.9.55.	6.5	0.0
22.9.55.	6.7	0.8
22.9.55.	6.5	1.4
24.9.55.	7.9	-0.2
26.9.55.	6.3	0.4
27.9.55.	6.1	0.9
28.9.55.	7.3	0.0
29.9.55.	10.8	1.0
30.9.55.	10.8	1.0
2.10.55.	10.8	2.4
4.10.55.	11.0	1.1
5.10.55.	10.1	0.6
6.10.55.	7.1	-0.3
6.10.55.	6.2	0.8
7.10.55.	1.5	-0.1
7.10.55.	1.5	-0.5
8.10.55.	3.2	-0.2

Table continued overleaf

Table 23. (continued).

Patient F.F. Case 11.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
21.9.55.	3.0	0.3
22.9.55.	4.4	0.2
23.9.55.	7.0	1.7
24.9.55.	4.6	0.6
27.9.55.	3.2	-0.6
29.9.55.	6.9	2.4
30.9.55.	9.0	1.1
2.10.55.	7.5	2.9
3.10.55.	11.1	4.0
4.10.55.	11.3	2.1
5.10.55.	8.5	5.2
6.10.55.	3.9	1.2
6.10.55.	4.8	1.2
7.10.55.	1.6	0.6
8.10.55.	1.1	-0.2

Table continued overleaf

Table 23. (continued).

Patient M.B. Case 12.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
21.9.55.	4.8	1.4
21.9.55.	3.7	1.3
22.9.55.	5.7	3.2
26.9.55.	9.4	1.9
28.9.55.	9.3	3.4
29.9.55.	11.0	6.7
30.9.55.	12.0	7.3
2.10.55.	9.1	6.4
4.10.55.	5.4	6.9
5.10.55.	3.3	1.4
7.10.55.	-0.1	0.7
7.10.55.	-0.4	-0.3
8.10.55.	-1.3	1.6

Table continued overleaf

Table 23. (continued).

Patient F.A. Case 13.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
20.7.55.	-2.6	0.2
21.7.55.	1.3	1.8
22.7.55.	1.2	1.4
23.7.55.	6.2	4.3
25.7.55.	5.7	-0.3
26.7.55.	7.2	2.4
27.7.55.	3.9	2.2
28.7.55.	6.2	1.4
29.7.55.	8.2	6.0
30.7.55.	5.1	5.5
1.8.55.	4.0	1.4
3.8.55.	-1.4	2.8
4.8.55.	-2.1	0.8

Table 25.

Effect of salicylate on respiratory quotient and nitrogen balance: Case 16 (Fig. 25).

Date	Gaseous Exchange ml./min. at s.t.p. O_2	CO_2	R.Q.	Serum Salicylate mg./100 ml.	Nitrogen diff. g.
24.4.56.	210	162	0.77	0	-2.68
25.4.56.	230	-	-	29	+2.8
26.4.56.	248	179	0.72	-	+0.71
27.4.56.	184	118	0.64	34	+2.22
28.4.56.	205	131	0.64	28	-5.4
29.4.56.					-3.6
30.4.56.	280	129	0.46	55	-2.31
1.5.56.	298	179	0.60	56	-6.26
2.5.56.	249	207	0.83	52	-1.62
3.5.56.	271	200	0.74	58	-2.91*
4.5.56.					-2.63*
5.5.56.					-3.98
6.5.56.					-1.37
7.5.56.	300	175	0.58	74	-3.6
8.5.56.	252	177	0.70	55	-2.62
9.5.56.					-1.01
10.5.56.	183	157	0.86	38	-2.48
11.5.56.	173	167	0.97	32	-2.41
12.5.56.	167	172	1.03	17	
13.5.56.					
14.5.56.	154	167	1.09	0	
15.5.56.					
16.5.56.					
17.5.56.	173	222	1.20	0	
25.5.56.	184	176	0.96	0	

* Patient vomited.

Table 26.

Effect of salicylate on respiratory quotient and nitrogen balance: Case 17 (Fig. 26).

Date	Gaseous Exchange ml./min. at s.t.p. O_2	CO_2	R.Q.	Serum Salicylate mg./100 ml.	Nitrogen diff. g.
7.3.56.	287	252	0.88	0	+3.54
8.3.56.	345	276	0.80	26	+10.12
9.3.56.					+2.97
10.3.56.	412	272	0.66	43	-6.64
11.3.56.					+5.55
12.3.56.	448	264	0.59	47	-0.65
13.3.56.	457	279	0.61	52	+2.73
14.3.56.					+7.43
15.3.56.	406	350	0.86	49	+6.65
16.3.56.					-1.9
17.3.56.					+4.3
18.3.56.					+1.45
19.3.56.	416	308	0.74	47	+1.54
20.3.56.					+3.72
21.3.56.					+10.37
22.3.56.					+5.15
23.3.56.					+8.95
24.3.56.	294	211	0.72	37	-
25.3.56.					-
26.3.56.	324	246	0.76	48	+3.64
27.3.56.					+3.78
28.3.56.					+8.23
29.3.56.					+8.83
30.3.56.	394	295	0.75	57	+0.52
31.3.56.					+5.36
1.4.56.					+0.88
2.4.56.					+7.04
3.4.56.	390	315	0.81	62	+3.28
4.4.56.	241	270	1.12	32	+2.19
5.4.56.	261	293	1.12	7	+6.42
6.4.56.	209	263	1.26	0	+4.57
7.4.56.					+1.21
8.4.56.					+6.03
9.4.56.					+7.29
10.4.56.					
11.4.56.					
12.4.56.	224	184	0.825	0	

Table 27.

Effect of salicylate on respiratory quotient and nitrogen balance: Case 18 (Fig. 27).

Date	Gaseous Exchange ml./min. at s.t.p. O_2	CO_2	R.Q.	Serum Salicylate mg./100 ml.	Nitrogen diff. g.
28.4.56.	253	214	0.85	0	
29.4.56.				0	-3.91
30.4.56.				0	-2.12
1.5.56.	332	253	0.76	43	-6.29
2.5.56.					-4.99
3.5.56.	372	222	0.60	55	-5.07
4.5.56.	247	175	0.71	42	-1.85
5.5.56.					-13.83
6.5.56.					-9.29
7.5.56.	345	225	0.67	66	-9.3
8.5.56.					-5.23
9.5.56.	300	222	0.74	56	-7.33
10.5.56.					-5.18
11.5.56.	231	178	0.77	33	-2.05
12.5.56.	305	190	0.62	30	
13.5.56.					
14.5.56.	230	195	0.85	39	
15.5.56.					
16.5.56.					
17.5.56.	257	188	0.73	41	
18.5.56.					
19.5.56.					
20.5.56.					
21.5.56.					
28.5.56.	215	214	1.0	29	
4.6.56.	225	200	0.89	39	
11.6.56.	230	181	0.79	50	
18.6.56.	205	200	0.97	41	

Table 28.

Effect of salicylate on respiratory quotient and nitrogen balance: Case 19 (Fig. 28).

Date	Gaseous Exchange ml./min. at s.t.p. O_2	CO_2	R.Q.	Serum Salicylate mg./100 ml.	Nitrogen diff. g.
15.5.56.				0	-0.79
16.5.56.	167	148	0.89	0	-0.70
17.5.56.	168	-	-	0	+1.51
18.5.56.				0	+4.82
19.5.56.				-	+0.13
20.5.56.	323	200	0.62	52	-0.07
21.5.56.	292	205	0.70	50	+2.4
22.5.56.	234	165	0.705	46	-4.56
23.5.56.					+1.37
24.5.56.	265	152	0.575	55	+4.23
25.5.56.	225	175	0.78	42	+2.08
26.5.56.					+3.48
27.5.56.					+0.52
28.5.56.	272	203	0.75	54	+1.42
29.5.56.					+1.19
30.5.56.					
31.5.56.	233	178	0.76	59	

Table 29.

Clinical data of the individuals in the DNP investigation.

Case	Name	Diagnosis	Sex	Age yrs.	S.A.+ m^2	N.B.M.R.* Cals./m^2/hr.
20	N.M.	Diabetes mellitus	F	55	1.88	31.6
21	A.B.	Diabetes mellitus	F	57	1.54	31.6
22	M.S.	Diabetes mellitus	F	55	1.60	31.6
23	M.D.	Diabetes mellitus	F	76	1.30	30.7
24	D.McP.	Hypercholesterolaemia	F	43	1.40	36.0
25	M.A.	Myxoedema	F	55	1.62	31.6
26	M.I.	Myxoedema	F	58	1.73	31.6
27	W.M.	Myxoedema	M	56	2.00	33.4

+ S.A. = Surface area calculated from weight and standing height (Du Bois).

* N.B.M.R. = Normal basal metabolic rate.

Table 30.

Data of the regression lines of individuals in the DNP investigation.

Case	Name	Pre-treatment B.M.R. % normal+	*Conv. factor	Number of observations	r	P<	Equation of the regression	95% confidence limits
20	N.M.	131	2.04	7	0.88	0.01	y=1.09x+121.6	±18.8
21	A.B.	128	1.68	8	0.94	0.001	y=1.32x+115.4	±16.6
22	M.S.	98	1.74	8	0.93	0.001	y=1.11x +98.0	±16.1
23	M.D.	98	1.38	10	0.89	0.001	y=1.08x+107.3	±28.9
24	D.McP.	102	1.74	12	0.80	0.01	y=0.80x+108.6	±16.9
25	M.A.	89	1.77	8	0.79	0.01	y=0.66x +87.6	±14.9
26	M.I.	84	1.88	9	0.95	0.001	y=1.20x +68.9	±17.1
27	W.M.	77	2.30	20	0.74	0.001	y=0.60x +80.2	±14.7

+Robertson and Reid (1951) Standards.

* To convert B.M.R. to oxygen consumption ml./min. at N.T.P.

Table 31.

Plasma DNP concentrations and increments of oxygen consumption: cases 20 to 24 (Fig. 31).

Patient N.M. Case 20.

Plasma DNP mg./l.	ΔO_2 cons. Cals./m^2/hr.
40	11.0
36	11.5
33	12.2
48	13.3
43	9.9
23	13.7
15	11.3

Patient A.B. Case 21.

Plasma DNP mg./l.	ΔO_2 cons. Cals./m^2/hr.
47	13.1
54	18.7
38	10.8
42	15.1
52	17.1
48	11.2
21	5.0
12	-0.8

Table continued overleaf

Table 31. (continued).

Patient M.S. Case 22.

Plasma DNP mg./l.	ΔO_2 cons. Cals./m^2/hr.
45	16.2
45	19.2
49	18.0
45	14.7
40	12.7
27	9.2
17	7.8
6	5.3

Patient M.D. Case 23.

Plasma DNP mg./l.	ΔO_2 cons. Cals./m^2/hr.
30	11.6
44	19.3
15	15.6
48	20.1
46	18.0
39	14.9
44	15.8
20	6.4
14	6.4
9	4.4

Table continued overleaf

Table 31. (continued).

Patient D.McP.

Plasma DNP mg./l.	ΔO_2 cons. Cals./m^2/hr.
19	12.4
32	13.6
38	17.5
30	12.4
44	14.0
45	17.7
41	15.6
51	15.8
44	13.6
41	15.8
25	7.2
10	2.2

Table 32.

Plasma DNP concentrations and increments of oxygen consumption: cases 25 to 27 (Fig. 33).

Patient M.A. Case 25.

Plasma DNP mg./l.	ΔO_2 cons. Cals./m^2/hr.
32	8.3
32	3.7
37	5.3
35	7.1
33	8.3
19	2.8
11	2.9
9	0.2

Patient M.I. Case 26.

Plasma DNP mg./l.	ΔO_2 cons. Cals./m^2/hr.
40	14.9
62	19.8
55	15.2
50	11.7
54	16.7
55	15.0
27	4.3
20	0.7
17	1.1

Table continued overleaf

Table 32. (continued).

Patient W.M. Case 27.

Plasma DNP mg./l.	ΔO_2 cons. Cals./m^2/hr.
19	3.6
21	6.2
31	4.2
26	1.3
24	5.1
24	6.4
32	5.9
32	10.3
42	5.9
30	5.1
53	11.1
33	5.7
46	10.0
49	12.3
49	14.8
43	10.0
43	10.9
25	8.4
17	4.3
6	3.7

Table 33.

Increase in pulmonary ventilation and oxygen consumption in diabetic patients.

(Fig. 34).

Patient N.M. Case 20.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
17.5.57.	11.0	0.0
22.5.57.	11.5	4.4
24.5.57.	12.2	0.7
25.5.57.	13.3	1.2
27.5.57.	9.9	3.6
30.5.57.	13.7	1.3
1.6.57.	11.3	0.0

Patient A.B. Case 21.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
3.7.57.	2.73	3.2
5.7.57.	3.89	4.2
8.7.57.	10.8	5.4
10.7.57.	15.1	2.4
12.7.57.	17.1	2.15
15.7.57.	11.2	1.6
17.7.57.	5.0	1.6
19.7.57.	-0.8	1.4

Table continued overleaf

Table 33. (continued).

Patient H.S. Case 22.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
13.5.57.	16.2	2.5
15.5.57.	19.2	3.0
16.5.57.	18.0	4.4
22.5.57.	14.7	6.0
24.5.57.	12.7	3.7
26.5.57.	9.2	3.4
28.5.57.	7.8	-0.4
30.5.57.	5.3	1.2

Patient M.D. Case 23.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
19.9.57.	11.6	2.2
20.9.57.	19.3	4.1
24.9.57.	15.6	1.8
25.9.57.	20.1	3.1
28.9.57.	18.0	3.1
30.9.57.	14.9	3.6
2.10.57.	15.8	2.7
3.10.57.	6.4	2.4
4.10.57.	6.4	2.3
6.10.57.	4.4	0.9

Table continued overleaf

Table 33. (continued).

Patient M.McP. Case 24.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
24.10.56.	12.4	0.9
26.10.56.	13.6	1.4
27.10.56.	17.5	2.1
29.10.56.	12.4	1.5
31.10.56.	14.0	1.6
2.11.56.	17.7	1.5
3.11.56.	15.6	2.0
6.11.56.	15.8	1.7
8.11.56.	13.6	2.1
11.11.56.	15.8	2.1
12.11.56.	7.2	2.1
15.11.56.	2.2	1.0

Table 34.

Increase in pulmonary ventilation and oxygen consumption in myxoedematous patients.

Patient M.A. Case 25.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
31.10.57.	8.3	1.5
2.11.57.	3.7	1.7
4.11.57.	5.3	2.4
6.11.57.	7.1	3.0
7.11.57.	8.3	4.3
8.11.57.	2.8	2.0
11.11.57.	2.9	0.9
13.11.57.	0.2	1.7

Patient M.I. Case 26.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
21.1.58.	14.9	1.0
23.1.58.	19.8	1.3
25.1.58.	15.2	3.1
28.1.58.	11.7	1.8
30.1.58.	16.7	2.8
1.2.58.	15.0	2.8
4.2.58.	4.3	-0.8
5.2.58.	0.7	0.3
6.2.58.	1.1	-0.3

Table continued overleaf

Table 34. (continued).

Patient W.M. Case 27.

Date	ΔO_2 cons. Cals./m^2/hr.	Δ Pulm. Vent. l./min.
7.7.56.	3.6	2.2
8.7.56.	6.2	2.3
9.7.56.	4.2	0.8
10.7.56.	1.3	2.0
11.7.56.	5.1	2.8
12.7.56.	6.4	-0.9
14.7.56.	5.9	0.9
16.7.56.	10.3	3.2
17.7.56.	5.9	3.1
19.7.56.	5.1	2.9
21.7.56.	11.1	2.8
23.7.56.	5.7	1.0
26.7.56.	10.0	3.7
27.7.56.	12.3	3.2
28.7.56.	14.8	4.9
30.7.56.	10.0	8.0
31.7.56.	10.9	4.0
2.8.56.	8.4	3.0
4.8.56.	4.3	2.7
6.8.56.	5.7	-1.9

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