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SOME BIOCHEMICAL ASPECTS OF ACUTE CHOLERA.

by

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INTRODUCTION.

The treatment of cholera may be briefly described, both historically and therapeutically, under three headings, that directed against the dehydration, that directed against the causative organisms and their toxins, and that directed against the acidosis. A surprisingly small amount of this treatment is based on laboratory findings concerning the biochemical changes which occur in the blood during the acute stages. Nor is it difficult to see why the biochemical method of approach has not been more used; cholera is so rapid in its effects and such large numbers of patients are usually involved in a short time in any epidemic, that anything like a thorough chemical investigation of each case is well nigh impossible.

Our experience of cholera, small though it is, has convinced us that a further advance in the treatment can only be made if a thorough biochemical study of the fluid loss is made including a corresponding study of the body fluids in acute untreated cases. With this aim in view we took advantage of the opportunity, during the 1937 Hong Kong epidemic, of carrying out a number of biochemical studies; those on convalescent cases and cases developing oedema we have already described (Ride *et al* 1938); in this paper we propose to give the results of further investigations in acute cases. These investigations (the methods used are indicated in brackets) were, blood pH (Cullen 1929), sedimentation rates (Ride, 1936), cell volumes (Millar, 1925), whole blood, plasma and cell chlorides (Patterson, 1928), urea (Ling & Cheng, 1937), non-protein nitrogen (Ling & Cheng, 1937a), pyruvic acid, glucose, together with urinary chlorides and urea. The methods used are described in more detail in the paper (Ride *et al* 1938) referred to above. It should be noted that although we described our findings as being those of acute cases it was only very rarely that blood was

taken from cases before any treatment at all had been given; hence these investigations were really carried out on blood taken from patients suffering from acute cholera plus biochemical interference. Where possible we shall indicate the extent of this interference in various cases.

INVESTIGATIONS.

pH.

The results of plasma pH determination in 21 acute cases are given in Table 1 along with those of 17 convalescent cases for comparison.

TABLE I.

ACUTE			CONVALESCENT		
No. of Cases.	*Range*	*Mean pH Values.*	*No. of Cases.*	*Range*	*Mean pH Values.*
21	6.88—7.39	7.120 ± .034	17	7.24—7.64	7.444 ± .032

Showing the average values and range for blood plasma pH of 21 acute and 17 convalescent cholera cases.

These figures provide direct evidence of acidosis in acute cholera. This acidosis must not be confused with the acidosis found during the anuric stage which so frequently precedes death from this disease. Most of these pH estimations were made before the development of anuria, and hence the primary cause of this acidosis is not retention of acids.

Peters and Van Slyke (1931) on p. 776, quote the work of Holt, Courtney and Fales (1915) (whose paper is not available here) who found that in diarrhoea of infancy, potassium and sodium usually excreted by the kidneys were diverted to the faeces and that the output of these bases in the stools was increased enormously. These authors quote Hoag and Marples (1929) (original papers not available here) who found an excess of base over acid (1.2 : 1) in diarrhoeal stools, and hence although we did not measure the alkali content of the stools, it seems reasonable to assume, until the contrary is proved, that a similar base loss occurs in cholera. The early acidosis of acute cholera demonstrated above is thus due primarily to excessive loss of fixed base via the bowel, and hence belongs to the group of non-gaseous acidoses (Haldane, J.B.S., 1921).

Concerning the actual pH values recorded, Peters and Van Slyke (1931) state that the range "in man appears to be approximately 7.0-7.8. Values lower than 7.0 are seldom encountered..... A pH_s of 6.95 was in one instance detected by Cullen (unpublished) electrometrically." Our determinations were all made electrometrically on plasma separated as soon as possible from venous blood as

previously described (Ride *et al,* 1938). We found 5 cases out of 38 under 7.00; the values recorded were, 6.94, 6.93, 6.92, 6.91 and 6.88. All of these cases died except the first, a female aged 33 who was pregnant and at full term. On the second day after admission, and hence after a number of infusions, her pH was 6.94; 8 days after admission she was convalescent, pH=7.27, and two days later the pH was 7.33. (This case No. 1254 will be mentioned later as she was one of the cases treated with *Betaxin*). Two of the other determinations, 6.88 and 6.91 were the first of the group to be made and hence personal and experimental errors may have operated there to a maximum. On the other hand determinations were in every case repeated a number of times and hence we feel that these figures are trustworthy.

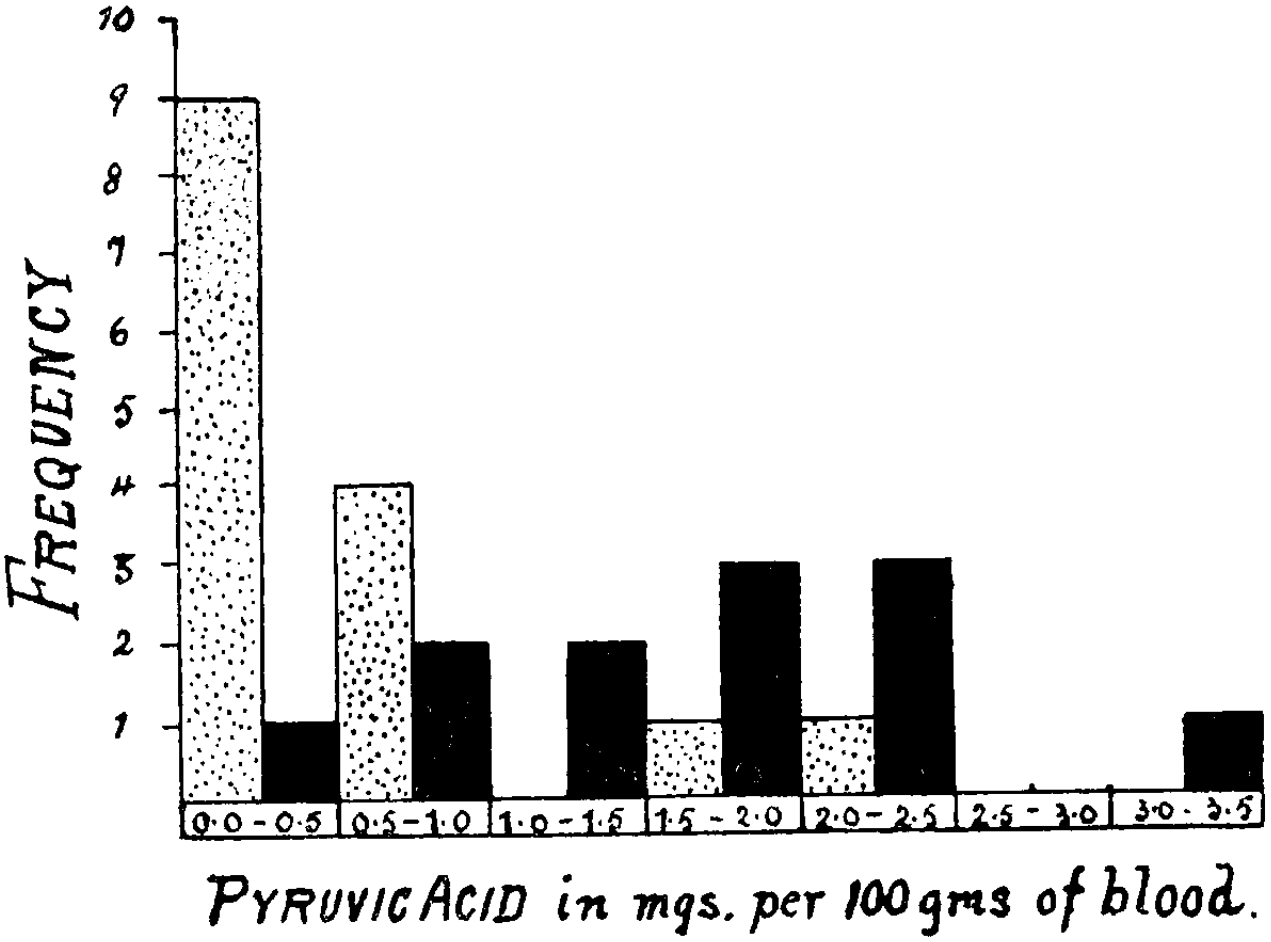
We made only two observations on the effect of intravenous infusion on the pH. Case No. 1256 admitted on 21st October, 1937 had a plasma pH of 7.07 on the 25th; after one pint of sodium bicarbonate solution had been infused into one arm, blood was taken from the vein of the other arm; the pH was then found to be 7.21; a pint of Roger's solution was then given and 10 minutes later the pH was 7.04. Case No. 1260 admitted on the 25th October, 1937 had a plasma pH of 7.27; the blood being taken immediately on admission and before any treatment had been given. After 1 pint of sodium bicarbonate and ¾ pint Roger's solution it was 7.26, and 10 minutes after 1 pint of sodium bicarbonate solution and 3 pints of Roger's solution had been infused, it was still 7.26. Both these examples seem to indicate that the beneficial change in pH following bicarbonate infusion is only short lived.

We have no specific records concerning the plasma pH of a large enough group of those suffering from anuria and its consequent uraemia, but the clinical picture of congested mucous membranes and conjunctivae and flushed malar skin, gradually increasing depth of respiration and somnolence, leading to coma and death, leaves no doubt as to the justification of concluding along with Sellards (1914) that this later condition is also one of acidosis, also of Haldane's non-gaseous type, but in these cases due to abnormal retention of acid radicles following depressed kidney function.

Pyruvic Acid.

We have already given figures for blood pyruvic acid in convalescent cases (Ride *et al,* 1938) and although we do not yet know the average values in healthy Chinese the data was of use in camparing the oedematous and non-oedematous cases. The acute cases have been grouped according to the result, recovery or death, and the figures are set out in Table II and in Figure 1; a further grouping into those cases treated and those not treated with Betaxin will be found in the next section.

Figure 1.



Bar-diagram showing the frequency of blood pyruvic acid values among acute cholera cases, recovery frequencies shown in shaded rectangles, fatal shown in black. The pyruvic acid values are indicated in mgs. per 100 gms. of blood.

TABLE II.

BLOOD PYRUVIC ACID IN THE ACUTE STAGES OF CHOLERA.

FATAL CASES		RECOVERY CASES	
No.	*Mean Values.*	*No.*	*Mean Values.*
12	1.58 ± .198	15	0.62 ± .158
Difference = 0.963 ± .252			

Mean values of blood pyruvic acid in acute cholera cases, 12 fatal and 15 recovery cases; values expressed in mgms. per 100 gms. of blood.

The data given in Table II and figure 1, show that the mean blood pyruvic acid value in fatal cases was definitely higher than that of the recovery cases. A further point worth mentioning in this connection is that the highest pyruvic acid values in the recovery

group, 2.43 and 1.64 mgs. per cent., were both treated with intravenous injections of *Betaxin*.

The significance of these findings we shall discuss when we have given the blood urea data, but there are one or two points of interest concerning vitamin B_1 therapy worth mentioning here. Case No. 873, a female, aged 37, a domestic servant, was admitted on the 4th September, 1937; convalescence, which began on the 10th, was uneventful until about 10 days later when she developed a boil on her buttock. About this time her blood pyruvic acid was 0.26 mgms. per cent. On the 12th October she developed an abscess in the muscles of the right shoulder and on the 15th her pyruvic acid had mounted to 1.80 mgms. per cent. She developed uraemia and died on the 17th of October. These findings are very similar to the effects of infection on pyruvic acid level of the blood in beri-beri cases. Case No. 1234, admitted on the 12th October 1937, was a female, aged 35 years and six months pregnant. On the 18th she was still passing a number of typical cholera stools per day, and in view of the almost certain abortion and its effect on the blood-pyruvic acid, she was given 5 mgs. of *Betaxin* intravenously; on the next day her pyruvic acid was 0.13 mgs. per cent. Her condition was not causing any grave alarm until she aborted when her pyruvic acid rose to 2.09 mgs. per cent. She was given another 5 mgs. of *Betaxin* intravenously and although her pyruvic acid level 24 hours later was down to 0.18, she developed fatal uraemia. Case No. 1254 already mentioned on page was pregnant at full term; her blood pyruvic acid levels on the 19th and 22nd of October were 0.73 and 0.80 mgs. per cent. respectively. On the 25th she gave birth to a dead child and her pyruvic acid shot up to 4.42 mgs. per cent. She was treated with 5 mgs. of *Betaxin* intravenously and on the 28th her pyruvic acid was down to 1.40 mgs. per cent. She made an uneventful recovery and was discharged on the 1st November, 1937.

The effect on blood pyruvic acid of sepsis, child birth and B_1 therapy are typical of that found in avitaminosis B_1 and just as we have previously demonstrated the prevalence of this condition amongst the convalescent cases, so these data show its prevalence amongst the acute cases. These figures however go further than that; they show that those with low pyruvic acid values stand the strain of the acute stage better than those with high values, and that those of the latter group stand a better chance of recovery if treated with *Betaxin*.

Blood Non-Protein Nitrogen.

The N.P.N. content of the blood depends on the rate of protein katabolism, the rate of nitrogen excretion and on the blood volume. In Table III will be found the average blood non-protein nitrogen and urea values found in a number of acute cases.

TABLE III.

N. P. N.		UREA.		
No. of Cases	*Average value mgs. per cent.*	*No. of Cases.*	*Average Value.*	
			mgs. per cent.	*mgs. of N2 p.c.*
18	116.67 ± 9.82	34	128.82 ± 12.2	60.03

Showing the average blood N. P. N. and urea values in acute cholera cases.

In spite of the decreased blood-plasma volume and the diminution in urine formation, these large increases in blood nitrogen must indicate large increases in protein katabolism, and in view of the absence of protein intake, the nitrogen must all come from the break down of body proteins; in fact these conditions of restricted protein intake, and high protein break down must inevitably lead to a great loss of plasma protein, which after the return to a normal blood volume during convalescence must result in the low level of plasma proteins referred to in our earlier article as a contributory cause of oedema. The protein katabolism is further stimulated by the excessive dehydration, and the raising of the blood volume by saline or bicarbonate (without protein) infusions completes a human experiment almost identical with the plasmaphoresis experiments of Whipple *et alia* (1934). The only difference is that Whipple's experimental animals were able to maintain a normal blood nitrogen by efficient kidney function, but in cholera on top of the protein upset we have the marked rise in non-protein nitrogen as well. This difference must therefore be due to depressed function in the case of the cholera kidneys.

Evidence of depressed kidney function in cholera is obtainable on every hand; the clinician sees it in the progressive oliguria leading up to anuria, and in the onset of acidosis; the biochemist sees it in the rise in the blood non-protein nitrogen and urea. The cumulative effect of this depressed function is shown in the scatter diagram of Figure 2, in which the blood urea values of 39 acute cases are plotted against the duration of the disease. The correlation coefficient of $+0.64 \pm 0.09$ shows how closely the urea values increase progressively with the duration of the acute stage. In the diagram the black dots indicate fatal cases, and the open circles indicate those cases which recovered, while the concentric rings show those cases treated with *Betaxin*. Is this impaired renal function due primarily to mal-function of the kidneys or to extra-renal causes?

In our earlier paper we reported on the urine of 77 cases that had recovered from the acute stages and the outstanding findings were the low specific gravity and the absence of albumin or casts.

This latter finding shows that these kidneys suffered no organic damage during the acute stages and hence we conclude that the renal disorder in these stages is a functional one consequent upon extra-renal factors. The slow circulation through the kidneys due to low blood pressure and raised blood viscosity results in renal anoxia which further diminishes the powers of the renal cells and thus a vicious circle is set up resulting in the evidence of steadily increasing renal failure illustrated by the findings given above. The formation of low specific gravity urine after the acute stage is over is evidence of

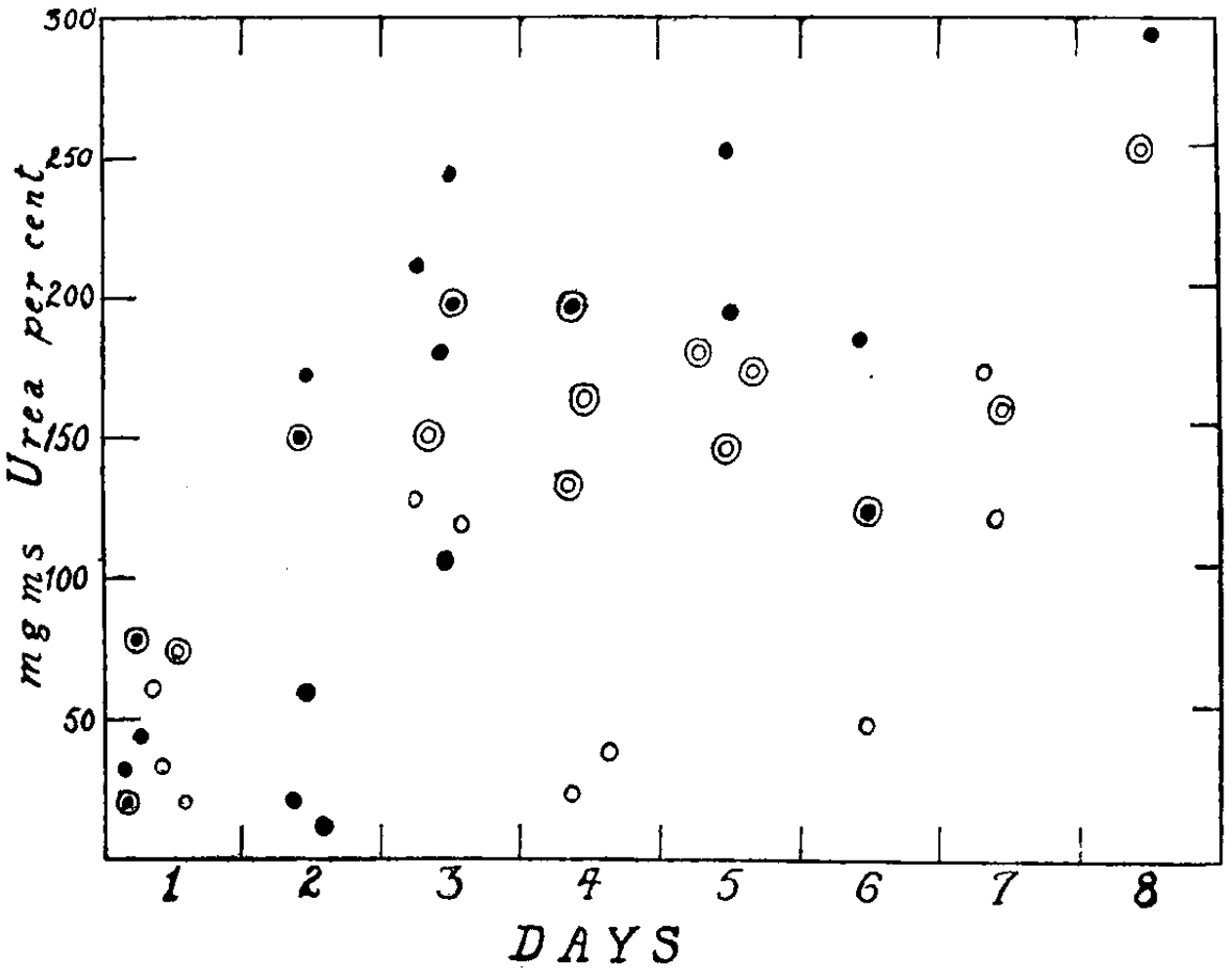


Figure 2. A scatter diagram showing the blood urea values of 39 acute cases of cholera on various days after the onset of the disease. Fatal cases are shown as black dots, those that recovered as open circles, and those who received *Betaxin* are shown with concentric circles.

the continued state of renal fatigue. It is evident therefore that since none of the conditions for normal kidney function prevails during the acute stages the use of diuretics which act by mobilising body fluid or by irritating the kidney is strongly contra-indicated. Increasing the renal circulation is obviously the first consideration in dealing with this condition and this is accomplished by saline infusion followed if necessary by hot loin packs or high warm enemata. Another

method of aiding urinary secretion is, after the circulation has been restored, to facilitate oxidative processes in the renal cells. In order to promote this we had recourse to the exhibition of Betaxin for the following reasons.

R. A. Peters (1934) and his co-workers at Oxford have shown that the consumption of oxygen by renal tissue in avitaminosis B_1 is lower than normal while its pyruvic acid content is raised, and that on the exhibition of B_1 the consumption of oxygen is raised to its normal value, and the pyruvic acid is reduced. We have already produced evidence by the pyruvic acid figures of the presence of avitaminosis B_1 in these acute cases, and on the strength of these figures many of these cases were treated with intravenous injections of *Betaxin*. All those cases in Figure 2 thus treated are indicated by a concentric circle surrounding the dot or circle. It will be seen that most of those cases which recovered after having a blood urea of over 100 mgs. per cent., were treated with *Betaxin*.

Against this it may be pointed out that conversely in a group of acute cases all with blood urea over 100 mgs. per cent., 16 were treated with *Betaxin* and only 9 recovered and 7 died. We may explain this as follows; in any group of the poor Chinese population such as the one chosen, there must be a definite percentage who have kidneys previously impaired by disease, and these cases under the strain of cholera, will develop a high blood urea due to this previous organic damage; added to these there must be a number of cases which in the acute stage develop an organic nephritis accompanied by renal changes; these cases constitute the group which exhibits no response to B_1 treatment, since B_1 is only of use in those cases where the kidney tissue, while otherwise normal, is suffering suboxidation. This incidentally must be the explanation of why we found no albuminuria in the convalescent cases; those cases with damaged kidneys together with those who developed organic nephritis all succumbed during the acute stage, leaving only those with intact kidneys having any chance to weather the storm, and to be included in the convalescent group.

This beneficial effect of vitamin B_1 administration on kidney function may be demonstrated in another way as shown in Table IV.

In this table we have data concerning 22 acute cases in most of which the urea and pyruvic acid were estimated on the same sample of venous blood. Looking first at the 12 cases that were not treated with *Betaxin* we notice that all the four cases that recovered, had, at the time when their blood contained over 100 mgs. per cent. of urea, low pyruvic acid values, indicating that they were then not suffering from avitaminosis B_1. Of the 8 fatal cases, 3 pyruvic acid values were unfortunately not determined, 3 had high values and 2 were relatively normal.

TABLE IV.

Acute Cholera Cases With Blood Urea of Over 100 mgms.%

Result	TREATED WITH BETAXIN				NOT TREATED WITH BETAXIN			
	No.	*Date*	*Urea*	*P.A.*	*No.*	*Date*	*Urea*	*P.A.*
FATAL	1231	13.10.37	194	0.80	1108	27. 9.37	189	2.27
		14.10.37	204	0.45*	1148	27. 9.37	194	2.27
		15.10.37	232	0.54	1169	27. 9.37	188	1.22
						28. 9.37	200	1.66
	1234	18.10.37	134	0.13*	1186	30. 9.37	44	0.20
		20.10.37	111	2.09 (abortion)		5.10.37	186	0.42
		21.10.37	109	0.18*	1192	4.10.37	172	—
	1256	22.10.37	82	1.67	1194	4.10.37	234	—
		23.10.37	150	0.97	1217	8.10.37	112	—
		25.10.37	117	0.70*	1230	18.10.37	300	0.67
		26.10.37	128	1.67				
RECOVERY	1197	4.10.37	150	—	1174	30. 9.37	121	0.27
		8.10.37	162	0.49	1177	30. 9.37	116	0.20
		9.10.37	102	0.26*		9.10.37	15	0.30
		14.10.37	22	0.53	1198	8.10.37	132	0.42
	1210	8.10.37	138	1.64	1228	15.10.37	170	0.26
		9.10.37	158	0.02*		21.10.37	26	1.28
		14.10.37	30	1.23				
		18.10.37	23	1.89				
		22.10.37	23	1.30				
	1226	14.10.37	250	0.70				
		18.10.37	152	0.33*				
		19.10.37	98	0.00*				
		25.10.37	22	0.96				
		28.10.37	33	1.16				
	1243	19.10.37	178	2.43				
		20.10.37	148	0.11*				
	1244	19.10.37	178	0.00*				
		22.10.37	160	0.73				
		19.10.37	83	0.73				
	1254	22.10.37	172	0.80				
		25.10.37	— Miscarriage					
		26.10.37	106	3.32				
		28.10.37	26	1.40*				
	1250	21.10.37	135	0.42*				

Showing the pyruvic acid (P.A.) in mgms. per 100 gms. of blood in acute cholera cases having blood urea values of 100 mgms. or over; * indicates pyruvic acid values taken from 12 to 24 hours after the administration of 5 mgms. of Betaxin intravenously. Zero readings indicate amounts too small for accurate measurement.

The ten cases which received *Betaxin* all show a fall in blood pyruvic acid which we are accustomed to find after such treatment in patients lacking in vitamin B_1, and in the 7 recovery cases the pyruvic acid fall was most marked.

The number of cases here given does not enable us to draw definite conclusions, but they do constitute evidence in favour of the theory that where there is no actual kidney damage there may yet be impaired kidney function due primarily to sub-oxidation of the kidney cells, and that where there is evidence of lack of vitamin B_1, administration of this substance intravenously may enable the kidney to tide over the danger period, provided always that the renal circulation is first restored.

The reason for the deficiency of B_1 we believe to be two fold. In the first place the daily diet of these patients is such that many of them must be incipient beri-berics just as some of them we know are in the sub-acute stage of this condition; during the tremendous loss of fluid in the acute stages of cholera, soluble stores of B_1 in the blood must also be lost, and on the restoration of the blood volume by infusions, the amount remaining along with all other plasma solutes must be greatly lowered in concentration. The result is that some develop clinical beri-beri while others show less dramatic effects of lack of vitamin B_1.

It is from this deduction of B_1 loss that we in our last paper considered it reasonable to suppose that the post-choleraic oedema may in part be due to similar loss as well as to excessive demands made on the hormone of the suprarenal cortex which plays an important part in the maintenance of the water balance of the body.

Blood Chlorides.

Both Rogers (1921) and Peters and Van Slyke (1931) quote Schmidt as having found a fall in blood chlorides in the acute stages of cholera. We examined the whole-blood chlorides of 34 convalescents and 33 acute cases and found no significant difference in the mean values of the two groups; in order to see whether there were any differences in the distribution of chlorides between cells and plasma, 18 convalescent cases and 21 acute cases were investigated, the whole blood and plasma chlorides being measured directly and the cell chlorides estimated from the observed cell and plasma volumes. All these results are set forth in Table V.

Our figures show that neither the acute nor the convalescent whole-blood or plasma chloride concentrations differ from normal; but that the cell chloride concentration in the acute cases is greater than that in the convalescent cases. That the acute figures are the abnormal ones is shown by the fact that the average cell/plasma chloride ratio in convalescent cases was 0.522 ± 0.023, the normals quoted by Peters

and Van Slyke being 0.43 to 0.53 (Wu) and 0.52 to 0.58 (Gram). The mean ratio in the acute cases was 0.652 ± 0.024 giving a significant difference between the two groups of 0.130 ± 0.033. Hence we conclude that the chloride concentration per volume of red cells is greater in acute cases than in convalescents and normals.

TABLE V.

Cases	*No.*	*Chlorides*	*Differences*
Convalescent	34	Whole Blood 471.47 ± 10.30	0.86 ± 14.76
Acute	33	,, ,, 470.61 ± 10.58	(Not significant)
		Complete Cases.	
Convalescent	18	Whole Blood 486.44 ± 11.52	1.25 ± 16.38
Acute	21	,, ,, 485.19 ± 11.65	(Not significant)
Convalescent	18	Plasma 586.67 ± 11.79	5.72 ± 15.86
Acute	21	,, 580.95 ± 10.61	(Not significant)
Convalescent	18	Cell 308.89 ± 12.17	62.54 ± 16.64
Acute	21	,, 371.43 ± 11.34	(Significant)

Mean chloride values expressed in mgs. of NaCl per 100 ccs. In the 34 convalescent and 33 acute cases only whole blood chlorides were investigated. In the complete cases, the means of whole blood, plasma and cell chlorides were estimated on the same 18 convalescent and 21 acute cases.

Since the total osmolar ionic concentration must be the same in plasma and the cells with which it is in equilibrium, the only method of arriving at the true significance of these chloride findings would be by measuring at least the total base and HCO_3 ions in plasma and serum in both acute and convalescent cases. In the absence of such data we can only conjecture that a raised chloride concentration per unit volume of cells accompanied by a normal plasma concentration could only be brought about by a chloride-water shift into the cells, resulting in a lowered protein concentration per unit cell volume.

It would thus appear that in the acute stage of cholera, the plasma loses water and chloride, not only to the bowel fluids but also to the blood cells themselves. We have further evidence of this water shift in the same 21 acute and 18 convalescent cases; the average cell volume of the former group was $46.62\% \pm 2.131$ while that of the convalescent group was $37.11\% \pm 1.718$, a significant difference of $9.51\% \pm 2.737$.

These results are just what one would expect following on the evidence given above concerning the lowered pH in acute cases, and the further the pH falls, the closer it approaches the iso-electric point of the haemoglobin and the more is base liberated and made available for the chlorine. This fixing by the chlorine of the base liberated

from the haemoglobin must be one of the most serious interferences with normal blood function found in cholera.

Here it might be of value to collect together in one table all the comparative data on acute and convalescent cases referred to in this discussion.

TABLE VI.

	MEAN VALUES FOUND IN CASES		*Difference*	*Remarks*
	Acute	*Convalescent*		
Chlorides (whole blood)	485.19 ± 11.65 (21)	486.44 ± 11.52 (18)	1.25 ± 16.38	Not significant
,, (plasma)	580.95 ± 10.61 (21)	586.67 ± 11.79 (18)	5.72 ± 15.86	,, ,,
,, (cell)	371.43 ± 11.34 (21)	308.89 ± 12.17 (18)	62.54 ± 16.64	Significant
,, c/p ratio	0.652 ± 0.024 (21)	0.522 ± 0.023 (18)	0.130 ± 0.033	,,
Cell Volume	46.62 ± 2.131 (21)	37.11% ± 1.718 (18)	9.51% ± 2.737	,,
pH	7.120 ± 0.034 (21)	7.444 ± 0.032 (17)	0.324 ± 0.047	,,
N. P. N.	115.2 ± 8.1 (21)	40.0 ± 3.3 (20)	75.2 ± 8.7	,,
UREA	130.3 ± 11.5 (39)	23.0 ± 1.1 (54)	107.3 ± 11.5	,,

Setting out the comparative blood analyses in acute and convalescent cholera cases referred to in the text. The figures in brackets indicate the number of cases.

Before leaving the blood chemistry it should again be emphasised that although these figures are stated to be obtained from the acute cases, they were not untreated cases; most of them had received varying amounts of normal saline, Roger's solution and bicarbonate, and hence our results cannot be taken as failing to substantiate Schmidt's chloride findings which, we gather, were made on acute untreated cases.

In the only case we investigated before infusion we found whole blood chloride 412, plasma chloride 567, and cell chloride 337 mgs. per cent.; 10 minutes after intravenous infusion of 1 pint of bicarbonate and 3 pints of Roger's solution the values were 506, 644 and 412 respectively.

Sedimentaion Rates.

The sedimentation of the blood of 34 acute and 17 convalescent cases was examined using Wintrobe tubes and for details concerning the results tabulated below or presented in Figures 3-7, the description of the method by Ride (1936) should be consulted. A brief explanation of these terms is as follows: the Aggregation Time is the time taken for the blood corpuscles to form their maximum aggregates while sedimenting; the Sedimentation Time is the time such aggregates would take to fall from the plasma meniscus to the level of the true

corpuscle volume; the Aggregate Sedimentation Rate is the maximum rate at which the aggregates fall.

In the convalescent cases it was found that the sedimentation rates were greatly increased, the average rate for the 17 cases being 41.53 mms. ±3.10. These rates which have not been standardised according to either temperature or cell volume, were from 8 males and 9 females, the average of the former 36.13 mms. ±4.54 and of the latter 46.33 mms. ±4.45. The difference, 10.20 ±5.66 is not significant, and would be even smaller if we omitted two pregnant cases and one of abscess of the shoulder, which conditions we know increase the sedimentation rate.

The consideration of the mean rate in acute cases is even less satisfactory because most of these cases were of necessity complicated by frequent intravenous infusions, and hence calculation of average rates is of no value whatsoever. There are certain points however which emerge from these investigations and we have set out some of the results in Table VII and in graph form in Figures 3, 4, 5, 6 and 7 to examplify these points.

In the first place untreated cases of acute cholera have very slow sedimentation rates; see Figure 3, Case No. 1245, and Figure 7, Case No. 1260. In Case No. 1245 the corpuscle meniscus fell only 3.5 mms. in 2 hours. In the second place when cases were shown clinically to require further infusion they invariably showed slow sedimentation rates; see Figures 3, 4, 6 and 7, cases No. 1234, 1245, 1256 and 1260. In the third place intravenous infusion invariably raised the sedimentation rate and the data in 5th, 6th and 7th columns of Table VII show why. The aggregation time is in each case greatly shortened by infusion and hence the stage of accelerated sedimentation is shorter and the stage of uniform sedimentation is reached sooner. Added to this the sedimentation time is also reduced, in spite of the fact that the lowered cell concentration in infused cases means that the corpuscle meniscus has further to fall; hence the reduced sedimentation time can only be due to an increased aggregate sedimentation rate which our data show does actually occur. Our method of recording the sedimentaion rates therefore discloses the fact that the raised sedimentation rate after infusion is due to two factors, a decreased aggregation time and an increased aggregate sedimentation rate.

Fahraeus (1929) has explained that the velocity with which spherical particles sink through a fluid is directly proportional to the square of the radius of the sinking particles, to the difference in specific gravity between the particles and the fluid, and inversely proportional to the absolute viscosity. We have no evidence of change in specific gravity difference between cells and plasma. That the viscosity is increased in acute untreated cases we can infer from the difficulty experienced in withdrawing venous blood through the needle into a syringe; but

TABLE VII.

Case.	*Result.*	*Date.*	*Remarks.*	*S.R.*	*A.T.*	*S.T.*	*A.S.R.*	*Fig.*
		Oct. 37						
1230	Died	15th	After 4 days of infusion.	0.54	7′	687′	0.64	3
		18th	One day before death.	1.80	9′	171′	2.22	
1234	Died	20th	Before infusion.	0.50	61′	196′	1.90	4
		21st	15 hours after infusion.	2.54	15′	114′	3.44	
1245	Rec.	19th	On admission, before infusion.	0.00	62′	750′	0.36	3
1254	Rec.	22nd	After 4 days treatment.	0.80	31′	159′	1.65	5
		26th	Convalescent.	6.30	6′	21′	20.10	
		28th	,,	5.98	7′	22′	18.18	
1256	Died	23rd	Before infusion.	0.16	51′	260′	0.88	6
		,,	After 1 pint bicarbonate and 3 pints of Roger's solution.	3.54	16′	43′	5.00	
		25th	After 1¾ pints of Roger's solution.	3.54	8′	64′	5.64	
		26th	During infusion.	1.00	14′	228′	1.62	
		,,	After 1 pint bicarbonate and 1 pint of Roger's solution.	2.26	6′	65′	5.21	
1260	Died	25th	On admission.	0.14	43′	372′	0.50	7
		,,	After 1 pint Sodium bicarbonate and 1 pint of Roger's solution.	1.24	40′	67′	3.50	
		,,	After 2 further pints of Roger's solution.	1.44	30′	83′	3.08	
		,,	24 hours after previous infusion.	0.80	31′	171′	1.68	

Table VII showing some of the sedimentation tests on certain of the cases during treatment. S.R. = Sedimentation Rate expressed in cms. per hour; A.T. = Aggregation Time in minutes; S.T. = Sedimentation Time in minutes; A.S.R. = Aggregate Sedimentation Rates in cms. per hour. For details see text.

whether that is sufficient to account for the change in the sedimentation rate of the aggregates, or whether there is also an increase in the size of the aggregates, cannot be settled until we have more information concerning the factors which control size of aggregates.

The dimunition in aggregation time must be due to either increased rate of aggregate formation or to diminished size of the ultimate aggregates formed. Hence infusion may on the one hand cause either increased rate of aggregate formation or diminution in size of aggregates formed, or on the other hand may result in increased size of aggregates or decreased viscosity. We are thus left with two possibilities, increased rate of aggregate formation and increased viscosity, and of these two the latter would seem to be the more important for the increased aggregate sedimentation rate contributes far more to the increased sedimentation rate than does the decrease in aggregation time. Whatever be the nature of this change it is a reversible one because as more fluid is withdrawn from the blood by continued diarrhoea, the slow sedimentation again reappears. We do not yet know enough about the factors which affect the rate of aggregate formation to justify further discussion of this point and in the absence of data on plasma proteins or fibrinogen the order of the change in the sedimentation rate of the aggregates must remain unestablished.

DISCUSSION.

A detailed discussion of treatment of cholera lies outside the scope of this paper, and this aspect of the 1937 Hong Kong epidemic will be dealt with much better by those who were directly responsible for the treatment; nevertheless the foregoing work is valueless unless we try and deduce some valid conclusions concerning treatment from the data given.

Treatment is of two kinds, that directed against the causative organism and that aimed at correcting the biochemical imbalance of the body fluids, consequent on the invasion of the gut by the vibrios. The true scientific approach would be to deal with the vibrios first and then treat the abnormal conditions they have caused later; but in cholera these conditions are so abnormal, so acute and so dramatic, that their treatment may legitimately take pride of place.

Our attempts at the former method of treatment were few in number and abortive but they are worth mentioning. Rogers states that .02—.05% HCl destroys cholera vibrios in a few minutes especially if pepsin be present, but in the presence of albumin .1—.2% solution is required and hence we endeavoured to render the contents of the intestine acid by continuous administration through a duodenal tube of acid solutions; in order to prevent the neutralization of these solution by the alkaline juices of the duodenum we buffered the solution strongly with sodium hydrogen phosphate. For our first attempt we chose three females whose clinical condition appeared hopeless; two died, one recovered. The course of the disease in the last case did

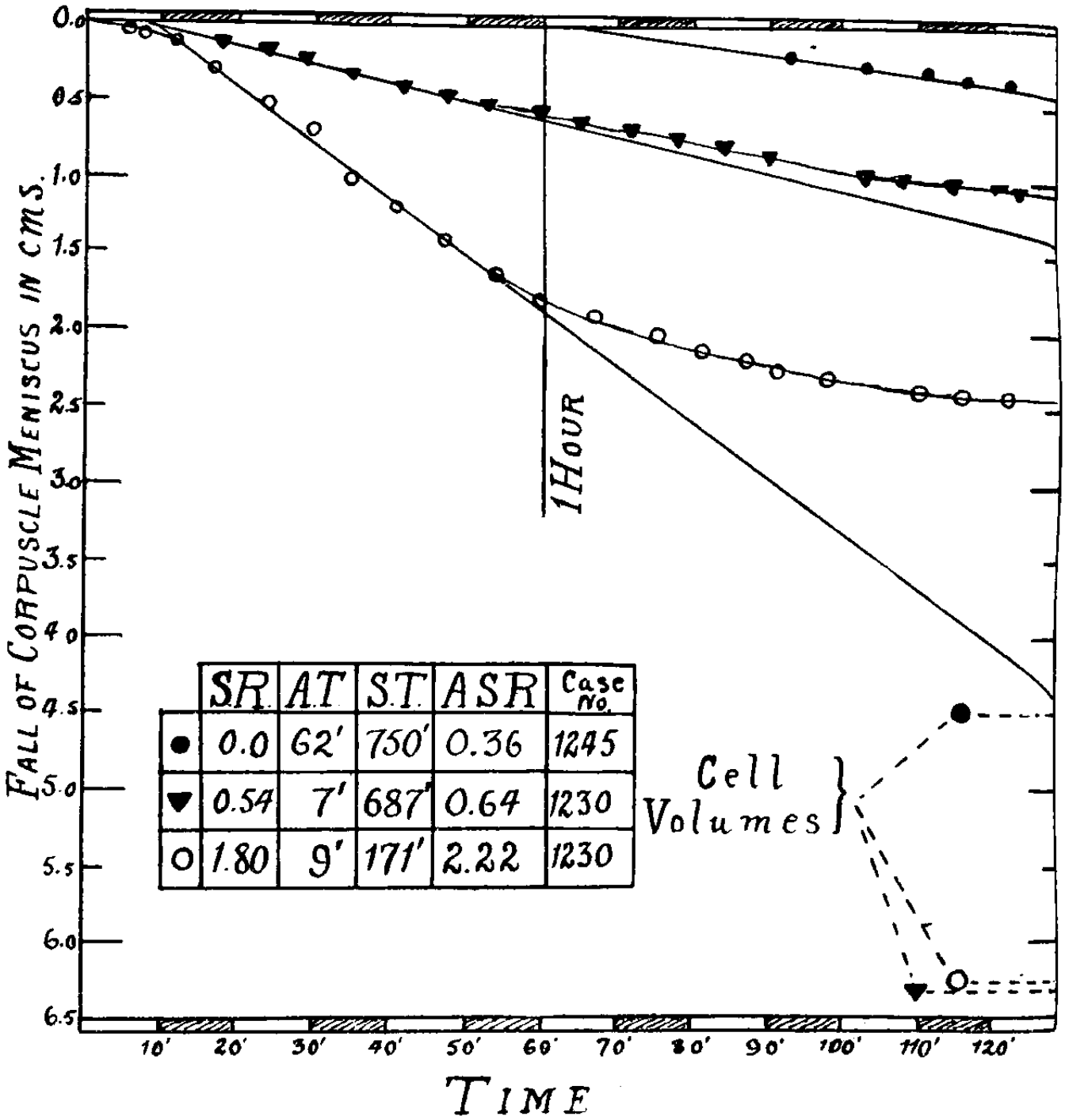


Figure 3. Sedimentation curves showing slow sedimentation of untreated cholera blood (Case No. 1245), and the small effect of repeated infusions in fatal cases (Case No. 1230).

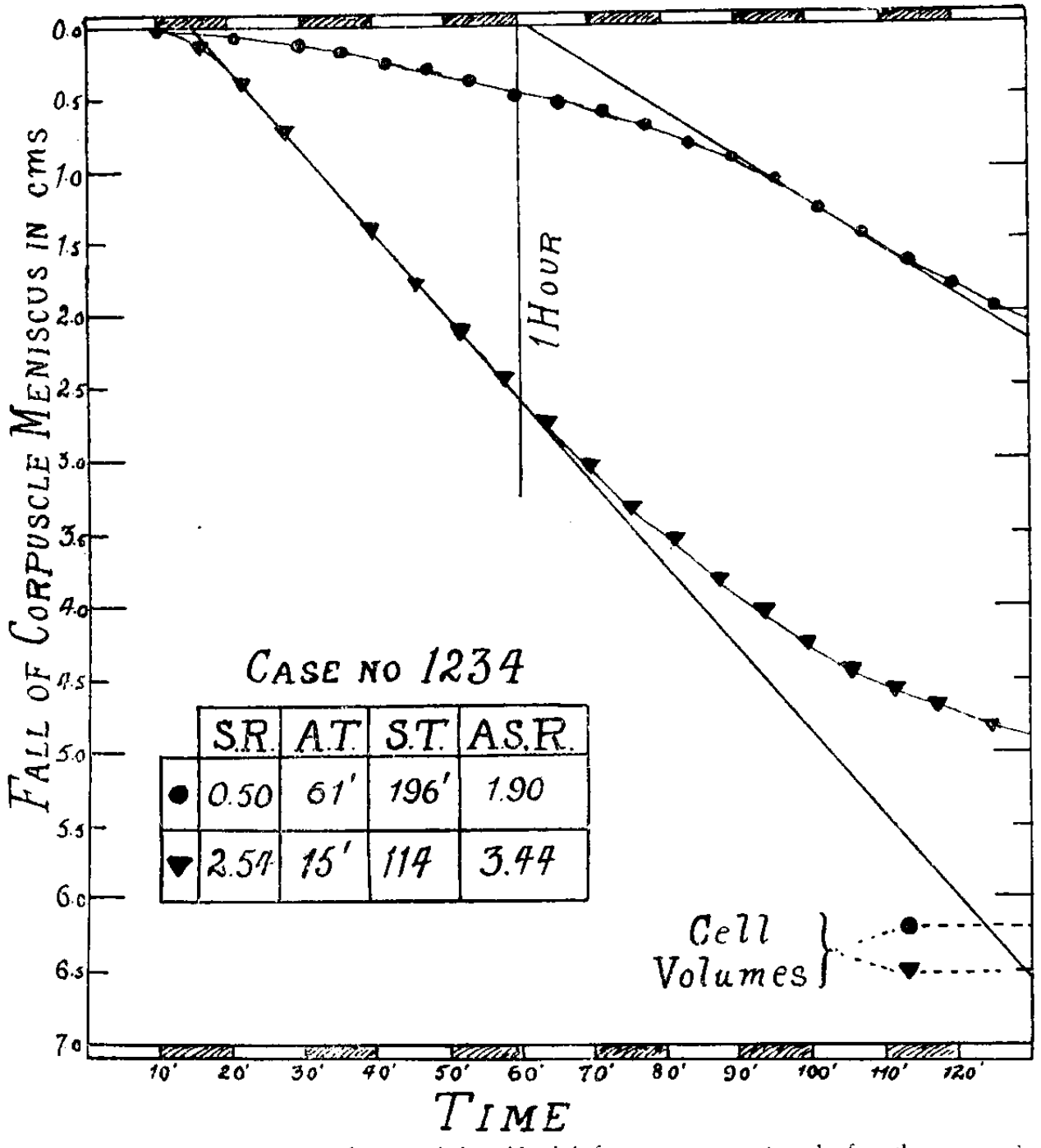


Figure 4. Sedimentation curves of acute cholera blood before (upper curve) and after (lower curve) intravenous infusion.

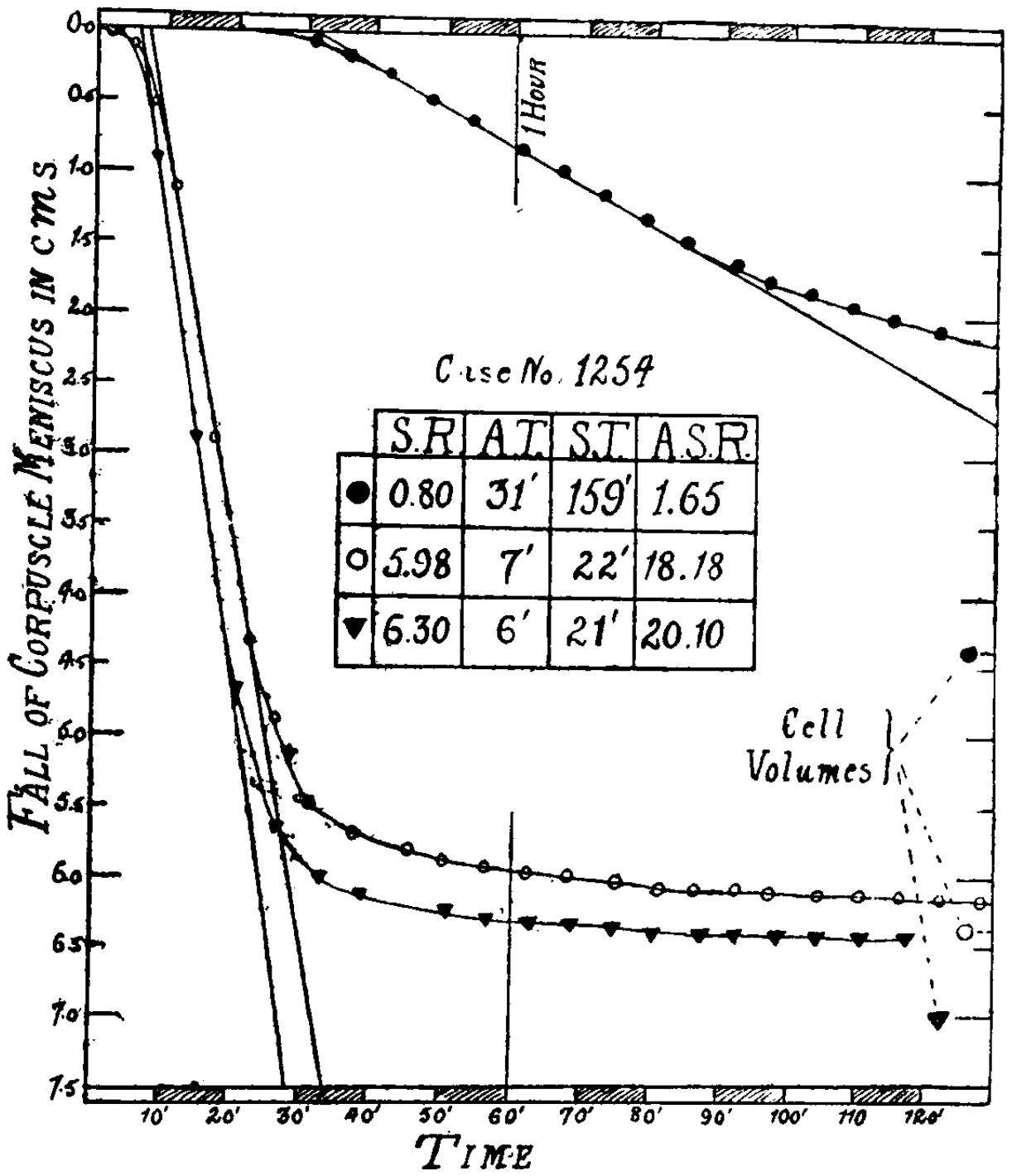


Figure 5. Sedimentation curves of blood from a cholera patient showing the changes between the acute (upper curve) and convalescent (lower curves) stages.

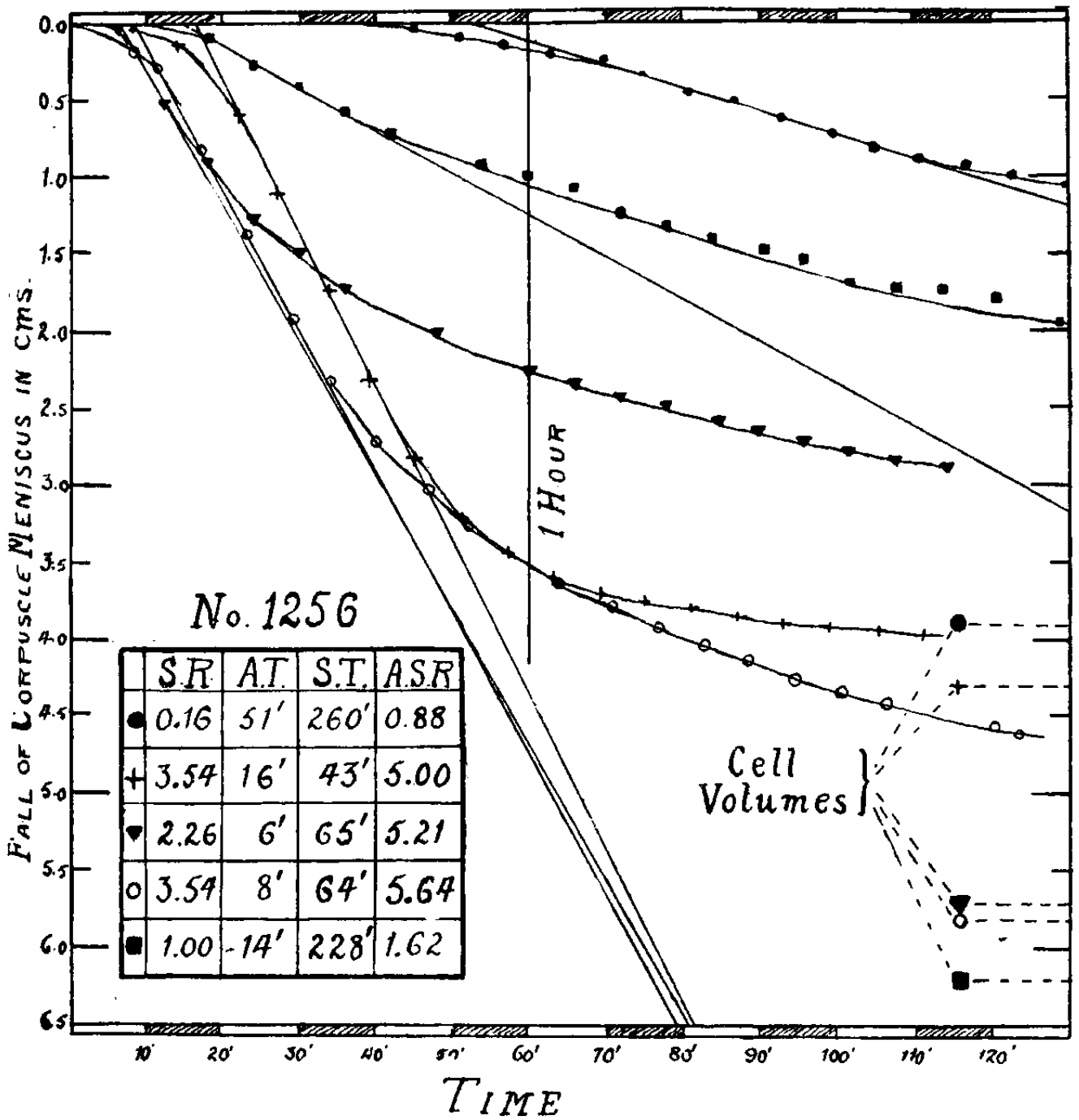


Figure 6. Sedimentation curves of acute cholera blood showing the effect of intravenous infusions. For details, see Table VII.

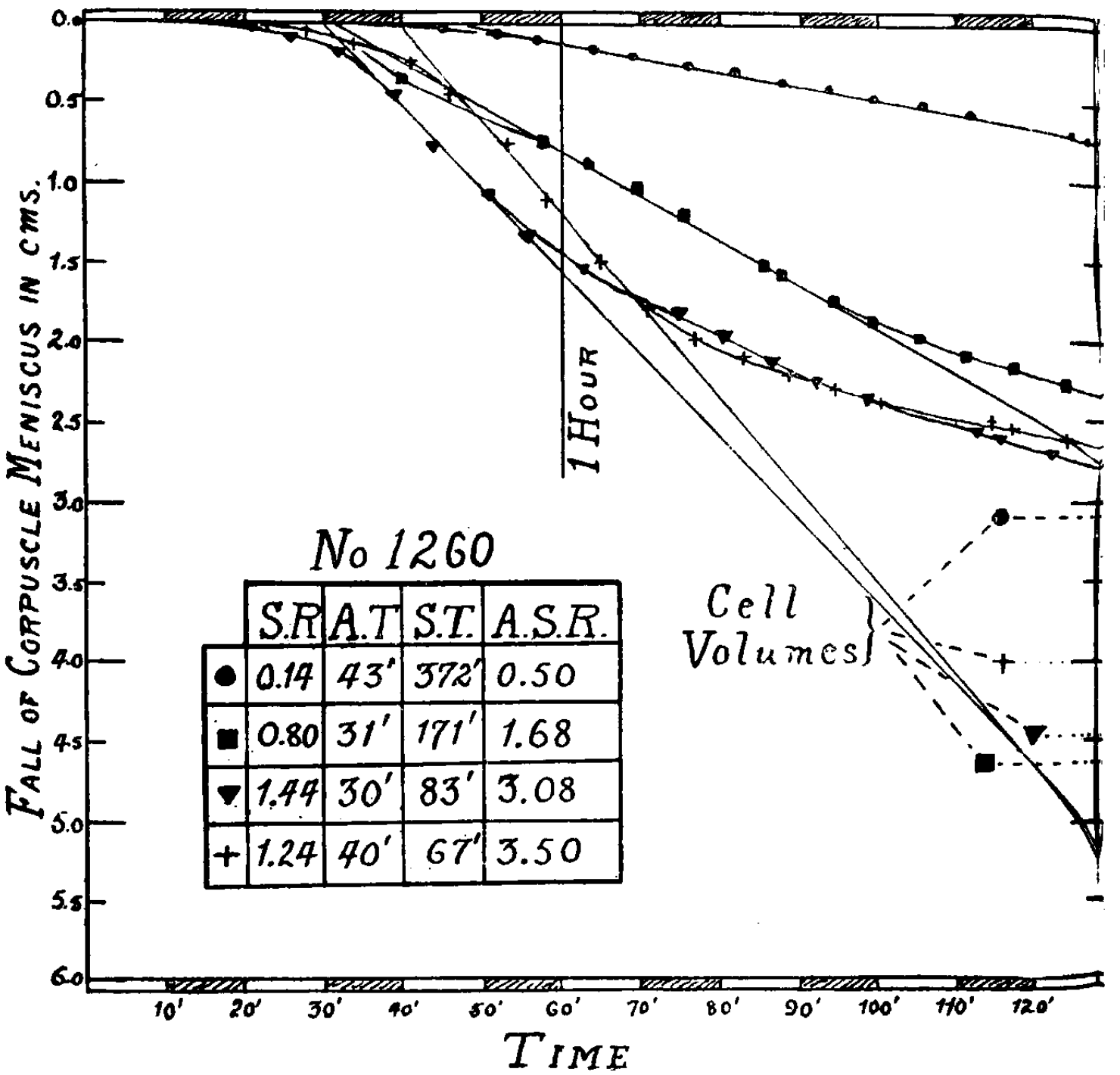


Figure 7. Sedimentation curves of acute cholera blood showing the effect of intravenous infusions, for details of which see Table VII.

not differ in any way from that of the cases which recovered with the ordinary routine treatment and hence the recovery could hardly have been claimed to be due to the new treatment. It seemed reasonable however to persevere with the method and later on some early acute cases were treated similarly; in these we tried to overcome the discomfort and the tendency to vomit the tube up, by cocainising the nose and back of the throat and passing the tube by the nasal route. This was a distinct improvement. Later we added hydrogen peroxide to the buffered acid; but we had to discontinue the method owing to a definite and in some case alarming increase in respiration, shown by patients within half an hour of starting the administration. We explained this by the fact that these acute cases were being treated simultaneously with intravenous infusions, and the consequent beneficial effect of these infusions on the alimentary circulation promoted absorption of the acid which aggravated the condition of acidosis we have shown exists in these acute cases. These experiments were of value though for two reasons. They showed that it was possible to pass acids into the duodenum and that the chemical imbalance of the body fluids was of such a high order that it demanded priority of treatment over all else. It does seem possible however that once the blood volume is restored and the initial acidosis counteracted, the attack may well be curtailed by subsequent continuous administration of a disinfectant acid solution through a duodenal tube.

We have been discussing the algid condition as though it were certain that it is due solely to a biochemical imbalance of the blood; this leaves out of account toxaemia as a possible cause. The presence of toxins has been proved bacteriologically; clinically there is the evidence of the fever in those cases with cold cyanosed extremities; where mouth temperatures do not disclose pyrexia, rectal temperatures often will do so; that toxins are present in the gut is also shown by the pyrexial response which so frequently follows saline infusions; this response is almost certainly due to the increased toxin absorption facilitated by the improved alimentary circulation after infusion. The toxins, though potent produce short-lived effects, for the clinical symptoms so frequently found in other more prolonged toxaemias are not common in cholera; added to this we have abundant evidence that unless the biochemical imbalance of the blood is treated, chances of recovery are very meagre indeed.

Before considering the biochemical treatment, let us summarise our evidence of biochemical imbalance and discuss its cause. In acute cases we have demonstrated a fall in plasma pH, a rise in both non-protein nitrogen and urea, an increase in cell volume and cell chlorides, while the whole blood and plasma chlorides remain normal. In discussing these findings we must also take into account the following clinical observations; the low arterial and venous blood pressures; the cyanosis and cold skin and extremities indicating constricted arterioles

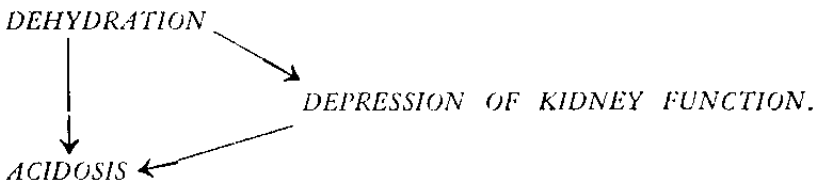
and dilated capillaries and the consequent stagnant anoxia of the tissues; the marked loss of fluids together with minerals and electrolytes in vomit and stools; on top of all this we must emphasise the dramatic suddenness of this fluid loss, giving the compensating mechanism of the body little time to react to the new conditions.

The exact chemical nature of the fluid lost should be ascertained but there is no doubt it contains both metallic and acid radicles, and from the indirect evidence of our observations on convalescent cases, plasma proteins also. We have seen how the preponderance of basic radicles in diarrhoea stools accounts for the early fall in blood pH. The uncompensated water loss with retention of corpuscles renders the blood more viscous: this together with the fall in arterial blood pressure decreases the rate of flow through the capillaries; if this rate of flow through the short and comparatively straight capillaries of the skin is enough to set up a state of stagnant anoxia there, the flow through the tortuous and lengthy capillaries in the kidney glomeruli must be greatly reduced. Even if the glomerular flow were not in many cases blocked, the volume of blood passing through per minute must be so reduced as to cause almost complete cessation of glomerular-filtrate formation; reabsorption of as much water as the tubules are capable of from this small filtrate must further reduce the amount of urine secreted, and thus is removed the one method the body has of getting rid of its non-volatile acids. Thus the excessive dehydration, first by alkali loss and then by acid retention, causes a fall in pH long before there can be any morphological changes in the kidney. Added to this, tissue dehydration increases protein katabolism, yielding further acid radicles which are added to the already increased store in the blood.

The early stage of acute cholera therefore provides an excellent example of what Fishberg (1937) calls prerenal azotaemia, an azotaemia resulting from a severe depression of renal function not due to morphological changes in the kidneys or obstruction of the urinary passages, but to extra-renal factors. Our conception of this condition in cholera bears out Fishberg's line of reasoning exactly, namely that the extra-renal factor causing the azotaemia is primarily, not hypochloraemia or low arterial blood pressures, not toxins or altered pH, but decreased renal blood flow.

In our view therefore, dehydration initiates the fall in pH and at the same time causes the interference with kidney function which increases the severity of the acidosis: hence the real position in acute cholera is not, as Rogers states, that acidosis is the cause of the kidney failure but rather that the factors which prevent the kidney from performing its function in a normal quantitative manner are the causes of the acidosis. Nor can we ascribe to his view that the symptoms of the disease can be fully accounted for by the powerful toxins enter-

ing the circulation through the congested mucous membrane of the small intestine. They are much better accounted for by the excessive and rapid dehydration, which acts according to the following scheme.



Our treatment of acute cholera must be aimed therefore not at correcting the symptoms of acidosis or depression of kidney function, but at the cause of these symptoms, namely the dehydration. We shall see later in which directions this basic treatment should be modified, but let us first consider the rest of our chemical evidence. The depletion of serum base, the loss of water and the alteration of acid-base balance all result in the imbalance of permeable ions—especially chlorides—in plasma and cells, thus interfering with the CO_2 carrying power of the blood; but an even more important effect of the fall in blood pH is that on the functions of haemoglobin. The effect on its oxygen-carrying power is obvious, and we have already referred to the fact that the nearer the pH approaches the isoelectric point of haemoglobin the more will potassium be liberated and be taken up by the chlorine which we have shown passes into the cells. This fixing of the potassium by the chlorine ions must further decrease the CO_2 carrying power of the blood, and contribute to the tissue anoxia already described as being due to physical causes. This anoxia must affect the kidney cells and make it even more difficult for them to carry out their functions against the already highly adverse conditions, and thus is set up the inevitable viscous circle leading to complete cessation of kidney function with its consequent uraemia, extreme acidosis, coma and death.

TREATMENT.

In the light of the above data and arguments, on what lines should the treatment of acute cholera be based? At present we are going through a stage of heroic biochemical interference comparable with that of surgical interference in its most devastating period, excepting that in the one case tonsils, appendices and colons were sacrificed whereas in the other the long suffering body has to act as unwilling host to hordes of bicarbonate and chloride molecules packed in hypertonic solutions. Undoubtedly in the hands of some workers the hypertonic technique has produced excellent results, but it is doubtful whether these beneficial results are the universal experience of all workers who have tried both hyper and iso-tonic saline infusions. It may be that this empirical hypertonic treatment will eventually be based on scientific findings but at present we know of no such basis and our work does not provide any; until we have ascertained the chemical nature of the fluid loss,

it would be better and more scientific to attempt to make good the dehydration loss by normal saline infusions; until we are certain what will do the most good, it would be better to use that which we know will produce the least harm and that undoubtedly is normal saline. This further fact would not be lost sight of that in most other cases where infusions are required, the kidneys can rapidly make any adjustments necessitated by a sudden influx of hypertonic saline, but in cholera that is asking a bit too much of the already failing kidney. In fact it may be another proverbial straw. Furthermore hypertonic saline in cases of moderate dehydration is rapidly counteracted by the diluting effect of the blood and the tissue fluid which would be drawn into the circulation, but in acute cholera where the blood volume is already low and the available tissue fluid nil, this dilution cannot take place; we have taken samples of blood from a number of patients after such an infusion of hypertonic saline and have found definite haemolysis, which must have added a little more work for the kidneys. It is also worth mentioning here that there is some evidence that hypertonic saline infusions may themselves raise the body temperature. This is based on the work of Rolly and Christiansen (1914) quoted by Barbour (1921) in which these writers found that intravenous injections of 3% but not of normal saline always increased the body temperature in rabbits. This effect of hypertonic infusions may well be a contributory factor to the hyperpyrexia already mentioned. According to our experience therefore, and until further work has provided to the contrary, it seems advisable that the dehydration should be counteracted by intravenous infusions of normal saline at body temperature, or in pyrexial cases at a lower temperature.

Lord Lister was convinced that "to introduce an unskilled hand into such a piece of Divine Mechanism as the human body is a fearful responsibility"; how much more in these enlightened days might we be expected to realise that the indiscriminate introduction of hypertonic solutions into the delicate ionic balance of the blood fluids is an unjustified procedure fraught with grave responsibilities.

If our reasoning be correct restoration of the blood volume should restore kidney function in those cases where there are no organic kidney changes, and prevent any further fall in plasma pH, but it will not raise the already lowered pH, hence bicarbonate infusion is also indicated and since the fall in pH is partly due to base loss in the stools, bicarbonate as well as saline will be required as long as there is any fluid loss.

Maintenance of an efficient kidney function is thus the most important requisite of treatment in acute cholera, and hence it is imperative that a record of urine volume should be carefully kept in every case. Note should be made, especially in the case of females, whether urine has been passed with the stools. In large epidemics where it is impossible to carry out many investigations on all patients,

blood specific gravity tests may be dispensed with but urine charts should be carefully kept. Fall in urinary output and increase in symptoms of acidosis are more certain and delicate tests for the need of further transfusion than blood specific gravity observations. If kidney function is still at fault after the blood volume is kept normal, then any method that will assist the failing kidneys should be employed. Diuretics are of no use, but warm packs to the loins or hot enemas may have a beneficial effect on the renal circulation and in those cases where renal activity is being retarded by lack of vitamin B1, this should be administered intravenously.

It is only when kidney circulation and function have been restored that further attempts to combat the organisms and their toxins by the duodenal tube method described above are justified.

CONCLUSIONS.

1. In the early stages of cholera there is a definite acidosis of the non-gaseous type due initially to disproportionate loss of base in the stools, and later to retention of non-volatile acid radicles; this retention follows the depression of renal function due to sluggish kidney circulation.
2. Fatal cases tended to have higher blood pyruvic acid contents than those that recovered.
3. Many of the high pyruvic acid cases responded well to treatment with Betaxin administered intravenously.
4. Those with low blood pyruvic acid fared better in the acute stage than those with high values, and of these latter, those treated with Betaxin had a better chance of recovery.
5. The rise in blood urea and non-protein nitrogen is due to lowered blood volume, increased protein katabolism and to depressed renal function. It is only those cases which exhibit no actual renal damage which stand any chance of recovery, and these during convalescence show all the signs of renal fatigue.
6. In the acute stage there is a shift of chlorides and water into the red cells, this chloride shift and the lowered pH interfering with the function of the haemoglobin of the red cells.
7. Sedimentation rates are greatly reduced in the acute stage and are restored by infusions. These changes are mainly due to altered blood viscosity.
8. The factor of paramount importance in early treatment is restoration of renal circulation and function. This can best be done by intravenous infusions of normal saline together with bicarbonate to restore blood base. Saline or irritant diuretics are contra-indicated. Adjuvant treatment in the form of B1 therapy or hot packs is indicated in certain cases.

9. It is only after the restoration of an efficient kidney function that other methods of combating the disease should be employed.

10. The clinical observations of most importance during the acute stages are those concerning renal function and the keeping of urine charts right from admission is essential in all cases.

SUMMARY.

The blood chemistry, including chlorides, urea, pyruvic acid, non-protein nitrogen, pH, cell volumes and sedimentation rates, in cases of acute cholera is discussed.

The symptoms of cholera are explained according to these findings and treatment discussed.

ACKNOWLEDGMENTS.

We again wish to record our thanks to the Hon. Director of Medical Services, Hong Kong, for permission to carry out this work in Government hospitals; to Drs. G. I. Shaw and P. B. Wilkinson and the nursing staff for help and advice; to the Nutrition Research Committee for financial assistance in the purchase of reagents; to the Ella Sachs Plotz Foundation of Boston U.S.A. for financial assistance in the purchase of the densitometer used in many of the blood and urine determinations; and to Messrs. Bayer whose local agents—China Export-Import—& Bank—Co. very generously donated the *Betaxin* which was used throughout this work.

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AN OVARIAN TERATOMA CAUSING DILATATION OF THE URETERS.

by

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A degree of dilatation sufficient to show up on excretion urography of the pelvis and ureters of pregnant women, after the stage where the uterus has risen out of the pelvis minor, is such a constant finding that it is now regarded as being physiological (Baker & Lewis, 1935). That it is more marked on the right side is, so far, an invariable finding. The other changes in association wih this dilatation are elongation of the ureter and lateral displacement. Figure A is a uroselectan urograph taken of a woman who was six and a half months pregnant. It shows quite clearly the dilatation of the ureters, which are visible on each side from the pelvis of the kidneys to the level of the sacroiliac joints, where the psoas muscles make an eminence over which the ureters pass. Dilatation of the ureters up to similar points on each side in their whole lengths above these points, suggests some degree of obstruction. Peristaltic waves passing along normal ureters cause parts to show up, and others not to be visible. A ureter showing up in its whole length is good evidence of a partial block at its bladder end. The picture also shows marked looping of the right ureter with possibly some lateral displacement above the loop. There is clubbing of the calyces, more marked on the right than the left. The main cavities of the pelvis are not very much, if at all, dilated. They are, however, well distended. The loop may be explained satisfactorily by considering it as being due to elongation.

The common sense explanation of this dilatation would seem to be that it is the result of pressure of the growing uterus on the ureters as they pass over the psoas muscles and external iliac vessels. (Not the pelvic brim, as has been suggested, which would imply a bony edge. The psoas muscles overhang the brim to a marked extent and form a cushion between the ureters and the bone).

Reasons for the very striking differences of the degrees in dilatation between the right and left ureters have been given by Baird (1932) who points out that the left ureter runs behind the sigmoid colon and its mesentery, and also that the external iliac artery lies more posteriorly on the left side, so the ureter crosses it at less of an angle. Thus, the ureter is protected by what is tantamount to a pad at this region and, as well, is not bent over a prominent ridge of artery.

Loss of tone of the muscular wall of the ureter is an explanation (Lee & Mengert 1934) which has been offered for the dilatation. Lee and Mengert following draining the ureters with large catheters for

24 hours, which large catheters, 8-10 F, they had no difficulty in passing, were sceptical that obstruction of any sort caused the dilatation and remark: "It seems to us that the condition is the result of some cause inherent in the pregnant state and probably is not yet solved." They also record two cases of ovarian cyst, one of tubo-ovarian abscess, carcinoma of the ovary, dermoid cyst, and uterine fibroids in which no signs were found; but they do not give any indication of the size and shape or position of these swellings. Whereas Baker and Lewis, in a series of 16 cases selected to give tumours comparable to the pregnant uterus, found that 16 showed dilatation of the right ureter and six a dilated left ureter, 15 showed dilatation of the right kidney pelvis and 10 showed also dilatation of the left.

In an outstandingly excellent paper Hundley and a team (Hundley *et al.* 1935) describe their investigations into the ureteric changes which take place during pregnancy. They show very clearly that there are softening changes in the wall of the ureter. To quote them "The abdominal spindle was always flaccid and ribbon like with definite loss of tone." The lower end of the ureter was quite firm and rigid and there was hypertrophy of Waldeyer's sheath—a muscular envelope in the last inch or so of the ureter. They found clear evidence of reduction in size of the pelvis after ureteral drainage for 72 hours.

Histologically they found hypertrophy of the musculature, oedema and increased vascularity. In the abdominal portion of the ureter there was thinning of the wall and small collections of round cells were found in the tunica propria and adventitia. The superficial cells of the mucosa were flattened. They were fortunate in getting a case of chorion epithelioma of the testicle in which very similar changes were found in the ureters but there was no dilatation.

They put forward the conclusion that there is a softening process in the ureter which yields to the obstruction caused by a semi-cystic uterus which would not be hard enough to cause compression of an unchanged ureter.

My excuse for describing the following case of a teratoma of the ovary is that it produced in striking degree a tumour comparable to a 6½ months pregnant uterus.

A prominence projecting downwards into the pelvis minor corresponded very closely with the cervical end of the uterus. With this tumour there was dilatation of both ureters, both pelvis and both sets of calyces, while the ureters on palpation did not feel flaccid.

Case:

Chinese female—age 14 years.

Admitted to University Clinic 28.3.38.

Previous illness—None.

Complaint: For seven months has been having slight pain in the right side of the abdomen. For 2 months has noticed swelling of the abdomen.

Menstrual history: She has had scanty and occasional periods starting first when she was about eleven years old, but she has had no bleeding for the last seven months. There has been no pain with these menstrual losses.

Vaginal discharge—Nil.

Micturition—Nil abnormal.

No pathological findings in the urine.

Bowels: Regular.

Examination: Shows a somewhat anaemic and undernourished but otherwise healthy looking girl. Haemoglobin 62%.

Abdominal Examination: Shows a rounded cystic swelling coming up from the pelvis to about two fingers breadth above the umbilicus. A thrill can be elicited and a faint "souffle" can be heard low down on both sides of the tumour. The tumour is slightly more prominent to the left of the midline than the right. See Fig. B.

Vaginal Examination: Not done.

Rectal Examination: The cervix was found to be pointing backwards and to the left. On moving the cervix, the tumour did not move.

X-ray pictures were taken after intravenous uroselectan was given and made quite clear the following points:
(See Fig. C).

(1) Filling and dilation of both ureters as far as the sacroiliac joints. (Compare with Fig. A).

(2) Both kidney pelvis dilated, the right being slightly but definitely larger than the left. This was more apparent in the series following this particular picture.

(3) "Clubbing" of all the calyces.

(4) There are no signs of elongation nor of lateral displacement.

At operation a teratomatous cyst replacing the right ovary was found. It had one complete twist in the pedicle but it was not strangulated. There were no adhesions so it was easy to lift the tumour up from its bed which it had made by displacing upwards the small intestines. Thus, its posterior wall was in contact with the lower lumbar vertebrae and the psoas muscles on each side. It was not possible to ascertain how much the sigmoid colon was acting as a pad.

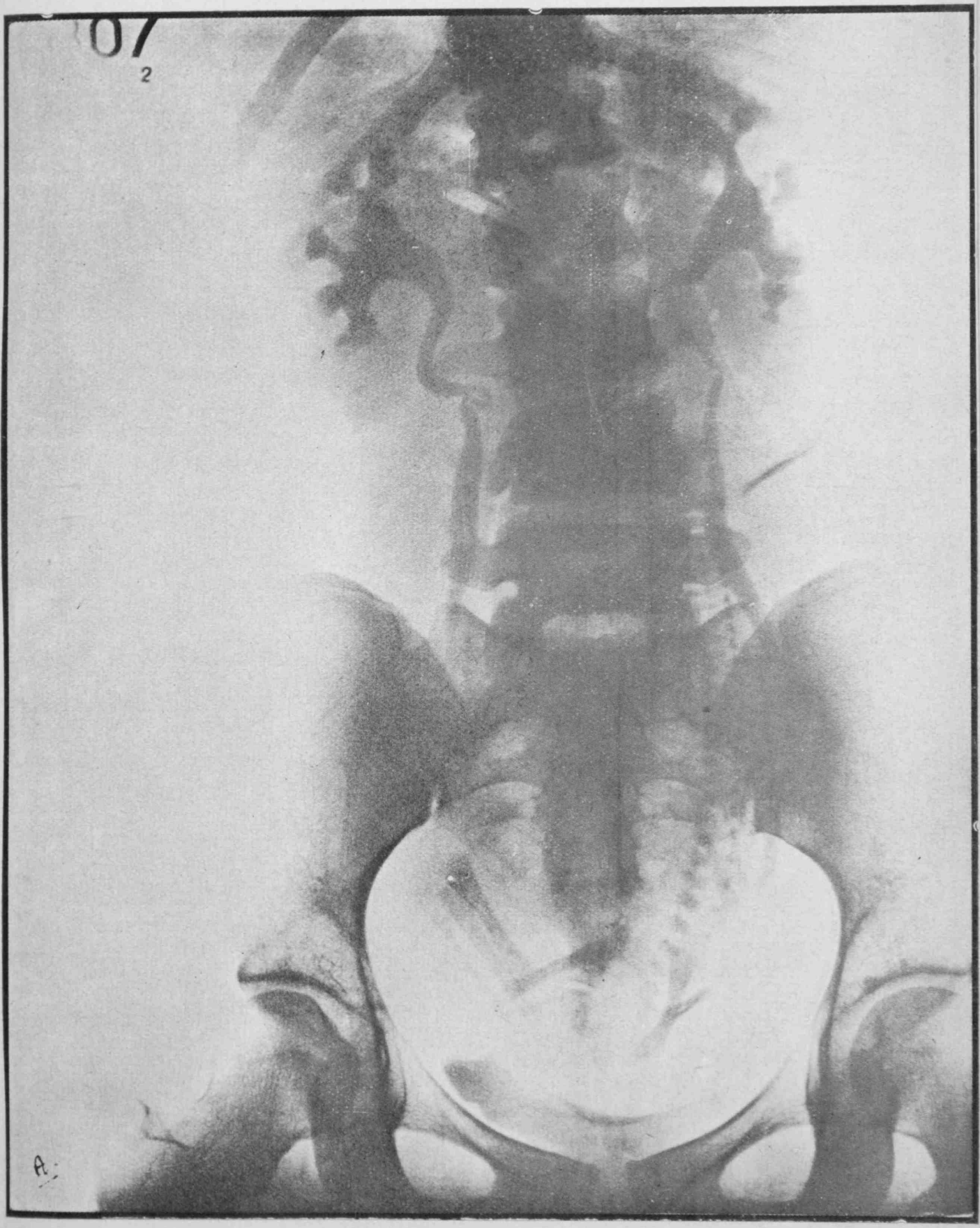
There was a bulge of the cyst fitting snugly into the pelvis minor. The bulge can be seen well in the photographs. (Figs. E & D).

The ureters could be identified by palpation in this bed but could not be seen. They felt of normal consistency, i.e., "cordlike" with nothing of the ribbon flaccidity of pregnancy ureters.

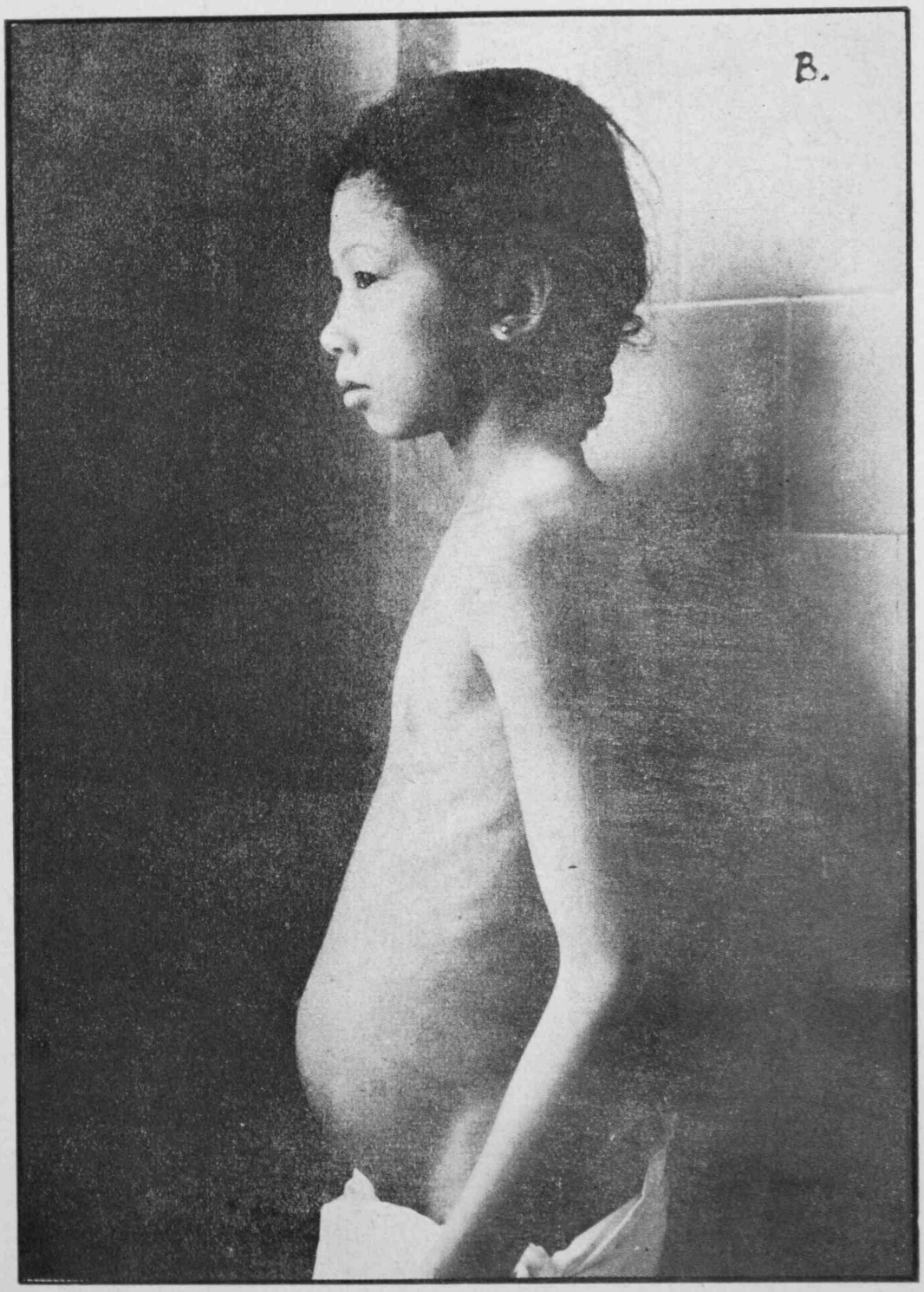
The peritoneum in the neighbourhood of the cyst pedicle and on the parietal peritoneum which came in contact with the cyst was studded with small white papules. Section of one of these papules was reported as showing vascular fibrous tissue.

The cyst was easily removed and convalescence was uninterrupted.

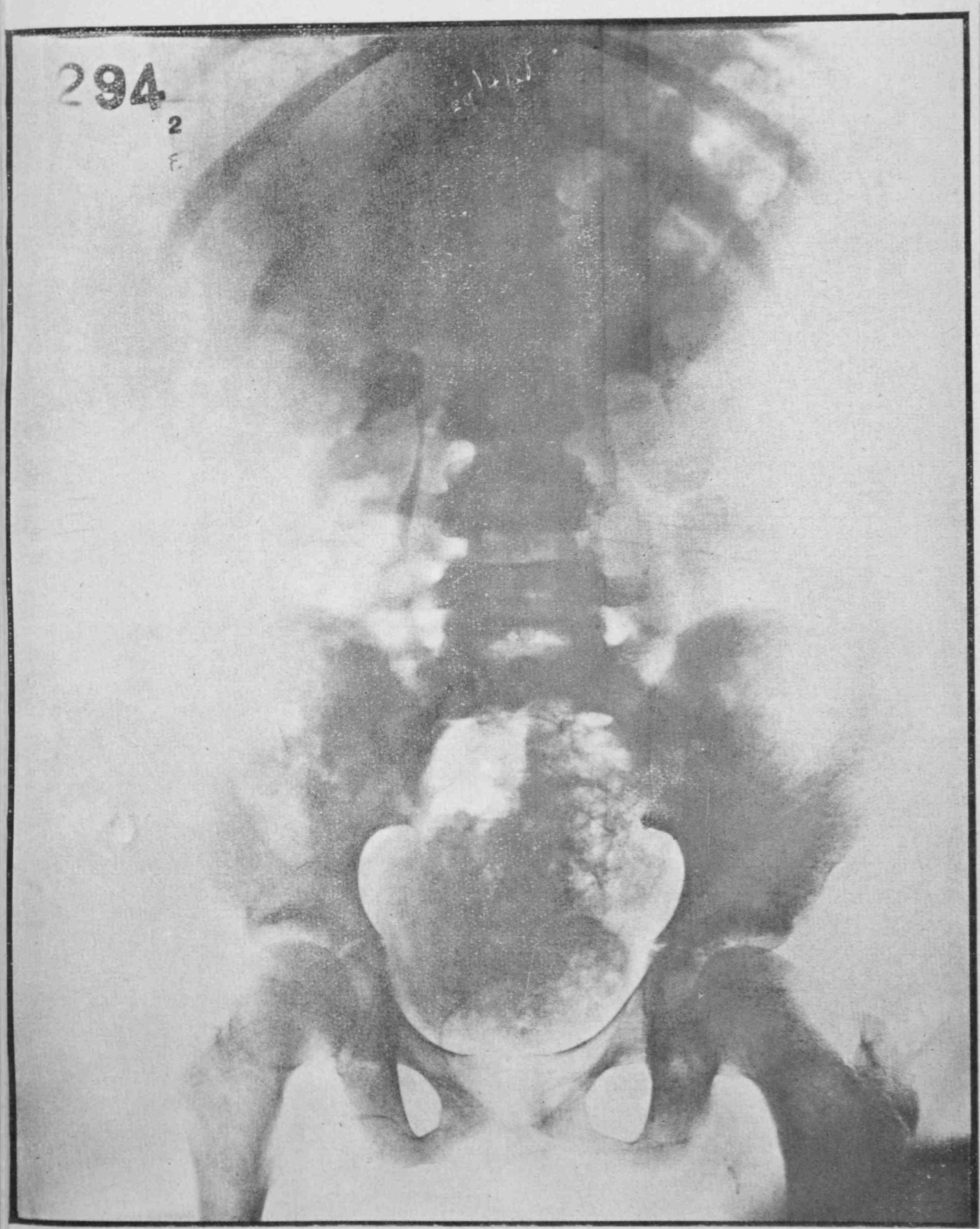
Ten days after the operation a second urography was done and showed a return of the kidney pelvis and ureters to normal limits. (See Fig. F).



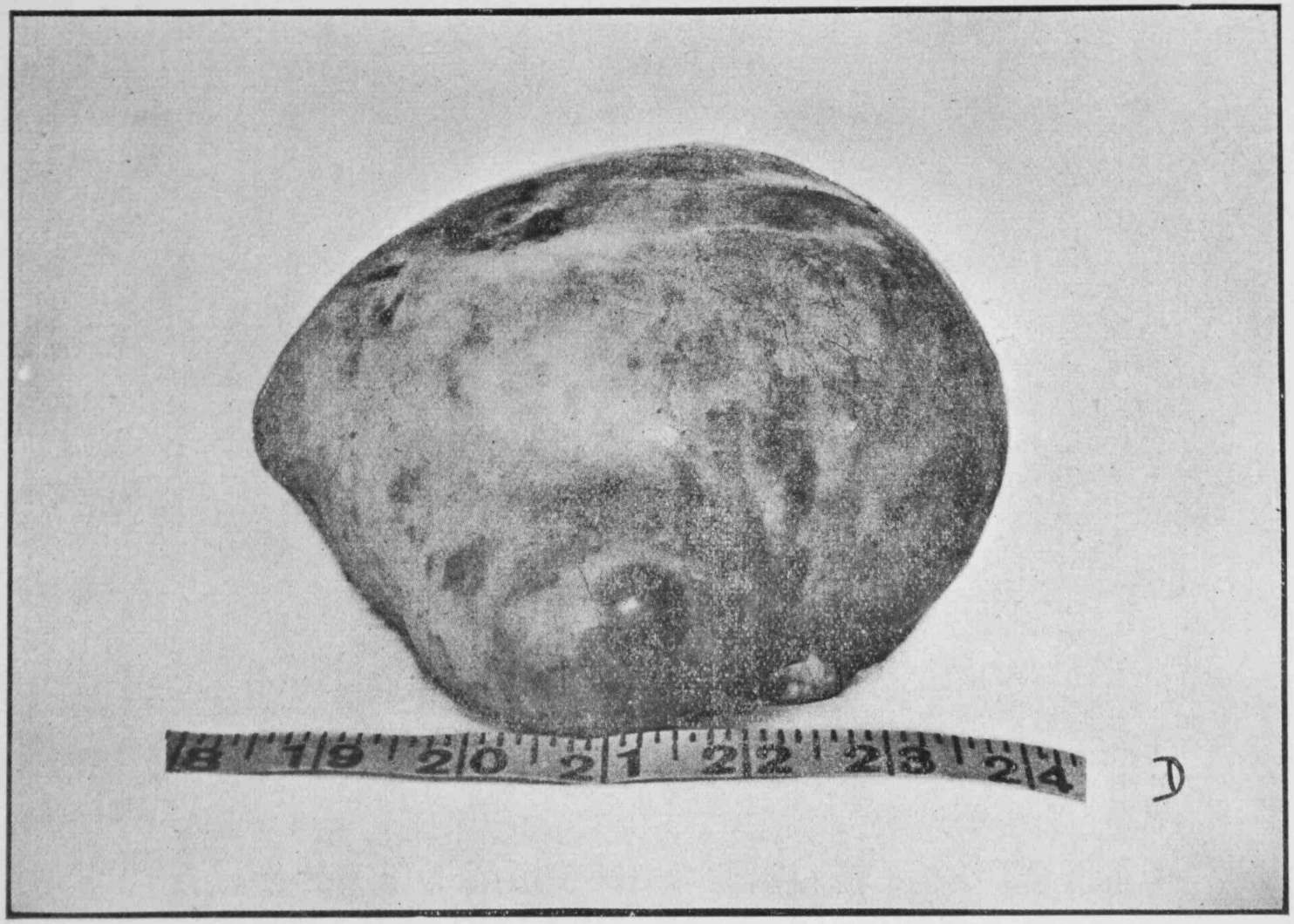
A. Uroselectan miograph taken of a woman 6½ months pregnant. (Breech presentation).



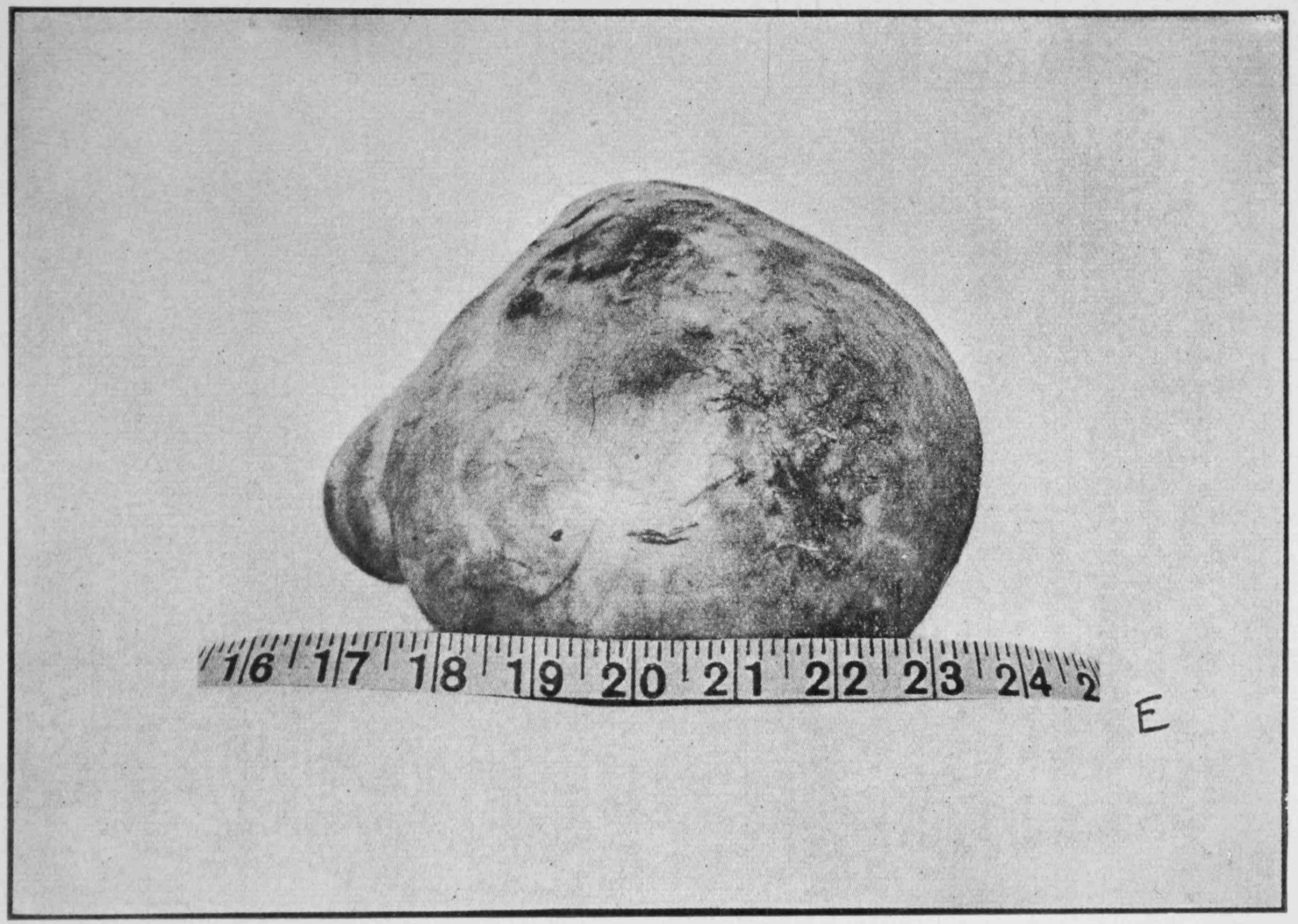
B. Photograph showing abdominal enlargement similar to that due to pregnancy.



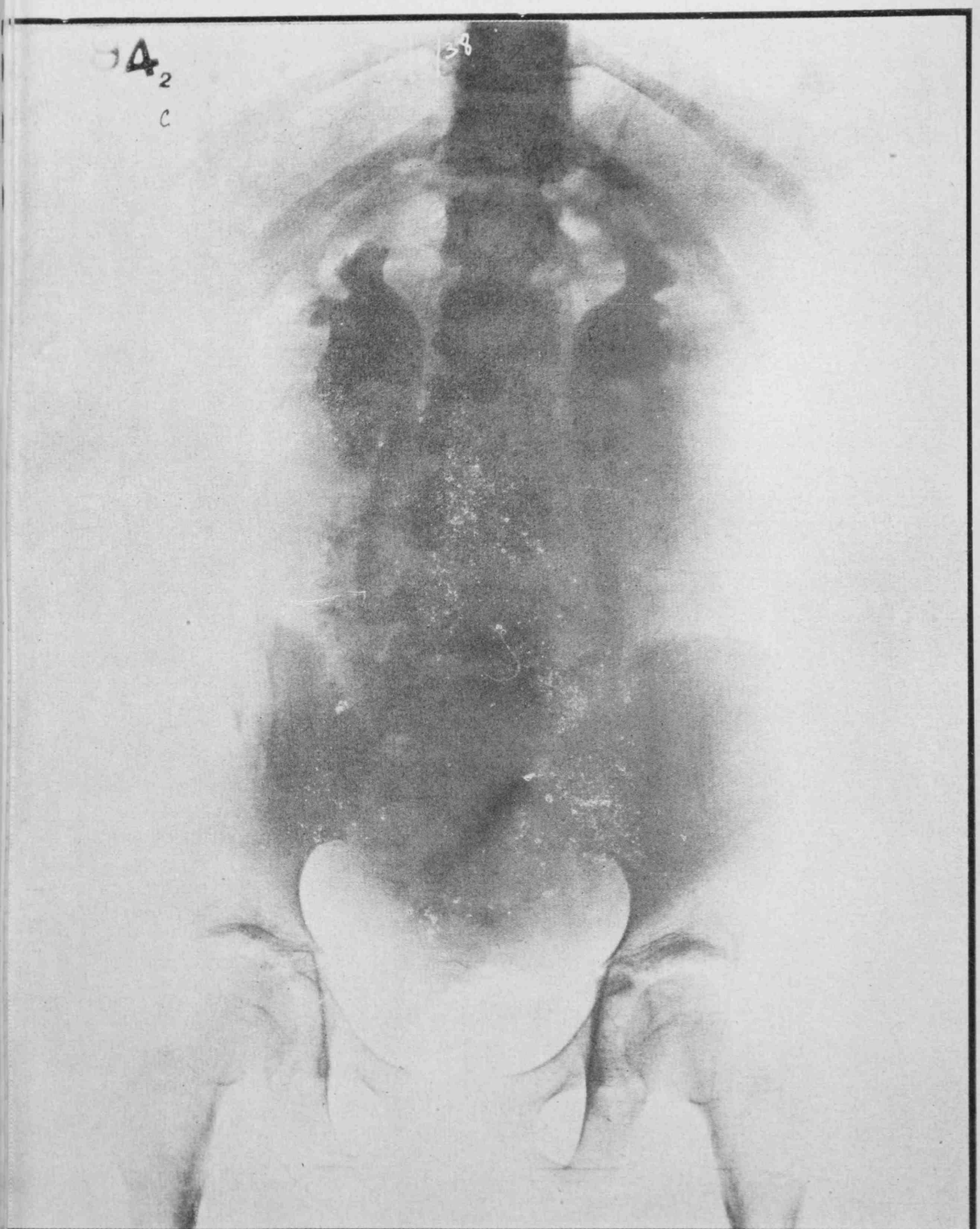
C. Uroselectan urograph taken 10 days after removal of the cyst.



D. The cyst after removal showing the bulge which fitted into the inlet of the pelvis minor.



E. Lateral view of the cyst showing the bulge.



F. Uroselectan urograph take before removal of the cyst.

Conclusion.

A teratomatous cyst in a young virgin is shown to have caused distension of the ureters, kidney pelvis and calyces very similar to those seen in association with pregnancy.

Differences noticed were the absence of elongation and lateral displacement of the ureters, while on palpation they did not feel flaccid.

My thanks are due to Dr. P. S. Selwyn-Clarke, Director of Medical Services, for permission to publish this case and to Doctors Quek and Ooi for their helps and care in getting the photographs, also to Doctors Pringle and Farr for the excellent X-ray pictures.

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THE "BLEEDERS" OF ST. HELENA.

by

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Haemophilia is an hereditary disease of males, characterised by a tendency to uncontrollable haemorrhage. The haemorrhage usually arises from a trifling injury or wound, which would in the ordinary person cause little or no bleeding. It is said that the haemorrhage may sometimes occur spontaneously.

As haemophilia is an uncommon disease, it seems worth while to put on record the facts which have been ascertained about the St. Helenian cases. There are two families on the island to-day which number "bleeders" among their males. The affected members of these families are well aware of their tendency to uncontrollable haemorrhage, and they have all proved most willing to give information about themselves and their family tree. There are several males in each family who suffer from the disease. In the Wade branch of the family only one of the sons has escaped this hereditary taint; that is to say, 82% or five out of six of III,11's sons have inherited the disease. In the Williams branch of the family, the percentage incidence of the disease is the same. II,5 had six sons; five of them were "bleeders," and two of them died of the disease in early manhood. III,10 died at the age of 20 from haemorrhage from a foot wound. III,3 died at the age of 20 from uncontrollable haemorrhage from the bladder and urethra, following on retention of urine. The exact nature of the bladder disease cannot now be ascertained, but the story current among the surviving brothers is that haemorrhage supervened on the passage of a catheter, persisted uncontrollably for some days and finally caused death.

The well-known sex-linked mode of inheritance is exemplified in the appended genealogical tree. On studying this tree it will be seen that the male bleeders now living on the island are descendants of either II,5 or her niece III,11. It is of interest to note that whereas II.5 transmitted the disease direct to her male offspring, her sister II,11 transmitted through her daughter III.11 to her grandsons. This accounts for the fact that the Wades are a much younger group of men than the Williamses. It is also noteworthy that the two families are sharply contrasted in build and general physique, the Wades all being thin, moderately tall, clear skinned men, wheas the Williamses are stocky, thick set men with slightly darker coarser skins than their cousins.

Careful cross-examination of the affected members of both families has failed to reveal evidence of the existence of a genuine female "bleeder," though the families believe firmly that such females do

occur. True, one of IV12's daughters died at the age of 13 of haemorrhage following tonsillectomy, but it seems more probable that the child died as the result of the operation than from haemophilia. Deaths following an operation for the removal of tonsils are not infrequently recorded; a geniune and well authenticated case of haemophilia in a female has, I believe, yet to be recorded. But the theoretical possibility of the disease occurring in the female, which is admitted by all; is much more likely to become an actuality in St. Helena than elsewhere for reasons which are given later on.

Another point which the trees bring out clearly is the fertility of "bleeder" families. I,2 had 13 children, II,1, her daughter, had 11 children, and III,11, her grand-daughter, had 12 children. This is a point which favours the diagnosis of haemophilia, as it has been known for many years that such families show this excessive fertility. It is also worth pointing out that the high percentage incidence of affected sons in these two families is highly suggestive, by itself, of the diagnosis. It is probable that there is genuine haemophilia in a family if 50 % or more of the sons of one generation show a tendency to uncontrollable haemorrhage. In both these families the percentage incidence of the disease on the sons is over 80%.

Unfortunately it has not been possible to trace the family tree further back than I,2—I,1, and the surviving recollections of this couple are very shadowy and indistinct. I, 2 to-day is merely *nominis umbra*. She is reported to have been a very "white" woman, and it is, of course, quite possible that she may originally have been of European or American descent. If this is not so, it is a little difficult to understand how the disease made its appearance in St. Helena, and it is a disease of the temperate zones, and nearly all the reported cases are of English, German or American origin. The disease is sometimes said to appear spontaneously in healthy stock; that is, in stock with no evidence of inheritance of the defect on either side.

In all cases which have come under observation, the haemorrhagic tendency is said to have manifested itself early in life. A brief history of each case is appended here, to show the age at which the complaint was first noticed, and the type of incident which caused the haemorrhage.

V. W., aet. 52. III, 4.

When 9 years of age he cut a toe and "bled for about a week." While he was at school he pulled a loose tooth out with his fingers, and "bled for some days after." When he was 20 he had two teeth extracted and haemorrhage persisted for a fortnight. He can remember that the sockets had finally to be plugged with dressings soaked in turpentine. At the age of 25 he cut a finger, as a result of which he spent seventeen days in hospital being treated for persistent bleeding. He is married and has 7

children, none of whom show haemorrhagic tendencies. One of his daughters got married in 1935, and has already reproduced her kind.

C. W., aet. 45. III, 9.

When he was a child of 10 one of his teeth was broken in an accident. He went to the hospital and the tooth was extracted by an orderly. He bled profusely, and can remember being plugged and finally "losing consciousness." He was wounded in the left temple when 35, and "bled for several days after this." Throughout his life he has been troubled by recurrent attacks of epistaxis. He states that he must have had at least a dozen attacks of severe nose bleeding. As a rule the bleeding comes on spontaneously, the left nostril only bleeds, and the attack does not last more than 2 or 3 hours. He generally has aching pains in the occiput and back of the neck, radiating down between the scapulae, for 12-24 hours before an attack of nose bleeding. His last attack of nose bleeding began early one morning, and he was seen at 10.00 a.m. On examination the mucous membrane covering the mddle turbinate was found to be oozing blood from several points. Stypven was not available so the nostril was lightly plugged with gauze soaked in adrenaline, 1 in 1,000. This proved ineffective, but the exhibition of horse serum at 1.10 p.m., appeared to control the haemorrhage. 10 c.c. were given intramuscularly, and one hour later bleeding ceased. He states that this is the longest attack he has known.

A. W., aet. 40. III, 5.

When a child of 7 he stubbed his toe on a stone. The wound "bled for several days" and he had to be admitted to hospital. At the age of 35 a splinter of stone struck him on the forehead while he was at work. He bled for 5 days, and had to be admitted to hospital. He has never had a tooth extracted because of his tendency to excessive haemorrhage, nor has he been troubled with epistaxis. He is a married man and has four young children, 3 boys and 1 girl, none of whom have shown any tendency to uncontrollable bleeding.

C. W., aet. 31. IV. 6.

At the age of 4 he cut his toe and had to be taken to hospital daily "for some days" as the wound oozed continuously. When he was 9 years old he cut his right foot and the wound bled for 4 days. He had a tooth extracted while he was at school, and had to be admitted to hospital where considerable difficulty was experienced in checking the haemorrhage. In 1926 he slipped on the rocks while fishing, thereby cutting his right foot. The wound oozed for a week and he finally had to go into hospital where

he was kept for 2 weeks. In 1933 he had an upper left molar extracted, and again he had to be admitted to hospital. In the first case the dentist was unaware that the man was a bleeder.

Some stypven was procured early in 1936. This man very courageously volunteered to have its styptic properties tested on him. He was given calcium lactate grs. xxx three times daily for 3 days beforehand. He had his left upper wisdom tooth extracted under local anaesthesia on August the 8th, 1936. He oozed continuously throughout the night of the 8th. At 9.30 a.m., on the 9th, his mouth was cleared of clot, and a gauze plug soaked in stypven solution was lightly packed into the socket. Oozing was immediately checked, and unfortunately the relief experienced by the patient was so great that within ten minutes of the exhibition of the drug he had fallen asleep. This caused the plug to become dislodged. A plate for the upper jaw was made during the morning, and the wound was redressed with stypven at 1.00 p.m., on the 9th, and the plate was inserted to keep it in position. This proved to be efficacious in controlling the haemorrhage until 2.30 p.m., on the 10th when he dislodged the plate by coughing in his sleep. Haemorrhage was fairly profuse after this, and the supply of stypven was exhausted. A gauze pad soaked in haemoplastin was applied at 10.00 p.m., and completely failed to control the oozing. On waking next morning, the man's mouth was full of loose clot. This was cleared out and a plug soaked in whole blood was packed firmly into the socket. The plate was reapplied, 20 c.c. of horse serum were given intramuscularly, and from that time on no further oozing occurred. Haemoplastin given both intramuscularly and intravenously exerted no influence on the oozing. I have to thank my colleague Dr. Johnston for making the plate and giving the blood used in this case.

H. W'., aet. 26. IV. 7.

When he was 9 years old he cut his forehead, and some difficulty was experienced in controlling the haemorrhage. He is vague about the details of this incident. At 12 years of age he cut his right knee and bled for four hours, but did not have to go to hospital. When he was 16 he cut his thumb; the wound bled from 9.00 a.m. to 6.00 p.m. and then became dry. It bled again for 4 hours next morning, but after that dried up. He pulled his right first lower molar out himself when he was 16. The socket oozed from noon on Saturday to the following Monday night. He did not go to hospital, and, in fact, scarcely considers himself a bleeder when compared with his brothers Charles and Fred.

H. W²., *aet. 24. IV, 8.*

His earliest recollection of a wound causing troublesome bleeding is a scalp wound which he got when a boy of 14. This oozed on and off for 4 days. At 23 years of age his lower gum was split in a fight, and he had to spend 9 days in hospital as the bleeding could not be checked. In the same year, 1935, he had a tooth pulled out, and the socket oozed for 3 or 4 days. The bleeding in this instance was controlled by packing with carbolised resin.

F. W., *aet. 19. IV, 9.*

When a child of 4, he stubbed his toe and cut it. Bleeding was troublesome but he did not have to go into hospital. Later on in his 4th year he fell downstairs and cut his head. Haemorrhage was difficult to control and he had to be admitted to hospital. A tooth was extracted when he was a school boy age 10. Bleeding was persistent, and he finally had the gum edges stitched together over the socket. He states that on this occasion he was in hospital for two months. He cut his foot when 16 years old, and the wound "oozed for a bit" but he did not seek medical aid. In 1936 he had a severe attack of nose bleeding. He had had three previous attacks. On every occasion haemorrhage occurred from the left nostril. He is the only bleeder in the Wade family who has suffered from troublesome epistaxis.

A. F., *aet. 41. IV, 12.*

He had a tooth extracted when he was 10 years old. He bled for a week from the socket, was admitted to hospital and remembers turpentine being uesd as a styptic. Another tooth was extracted when he was 22. This caused oozing which lasted for a fortnight, but was finally controlled by the local application of alum. When he was 30 he cut his left thumb with a broken bottle, but had practically no oozing from this wound. Neither he nor any of his half brothers have even been circumcised. IV 12's elder brother IV, 11 who died this year of cerebro-spinal specific disease, was known to me and was not a bleeder.

DISCUSSION.

Haemophilia is due to the transmission of a sex-linked recessive character, and a study of these family trees shows cleary the sex-linked mode of inheritance characteristic of the disease. The high percentage incidence of bleeders in each generation of the affected families, and the fertility of the family as a whole are also points in favour of the diagnosis. It is a curious fact that no St. Helenian bleeder, as far as can be ascertained, has ever suffered from haemorrhage into a joint, one of the commonest accidents of the disease. The tendency has manifested itself, in all the cases examined, early

obtained to show that it lessens with advancing age. There is some in life, and it seems to persist into middle age. No evidence has been evidence to show that bleeders do pass through phases when the tendency is not as marked as at other times, and in the Wade family the two brothers, IV, 6 and IV, 9 are held to be, and rightly so, the two most " dangerous " members of the family.

It is still uncertain whether the female can exhibit true haemophilia. Theoretically it is, of course, quite possible that a female should suffer from the disease, but the combination of chromosomes necessary to produce such a woman is very unlikely to occur in the average community; that is to say, the chances that a female transmitter of the disease should marry a male suffering from it are remote. In St. Helena, on the other hand, it is more than possible that such a marriage might occur. The St. Helenian community of 4,000 odd people is to all intents and purposes an unchanging one. New blood is rarely brought into the island and there is, and must have been for many years past, a certain degree of inbreeding. A glance at the St. Helenian tree will show how easily such a marriage might occur in this community, and there is therefore reason to hope that St. Helena may in time produce a genuine female haemophiliac. Mention has already been made of the fact that the two families believe that certain of their female children of the present generation are " bleeders," but the necessary linkage had not occurred in these marriages so the statements must be accepted with reserve. Two of the surviving daughters of IV,12 have been observed to bleed more than the normal child would after trifling injuries, but none of the females in these families has suffered from haemorrhagic purpura (Hess, 1916), as far as can be ascertained. The following diagrams show readily how a haemophiliac female might come into being. In them the affected sex chromosome is represented by x, the male sex chromosome by Y.

I. xX = XY

xX xY XX XY

A female transmitter married to a normal male may produce transmitting females, normal females, haemophiliac males and normal males. Half the sons and half the daughters are apt to be normal.

II. XX = xY

Xx XY Xx XY

A normal female married to a haemophiliac male may produce transmitting females and normal males. All the daughters may transmit, all the sons are normal.

III. Xx = xY

Xx XY xx xY

A female transmitter married to a haemophiliac male might produce transmitting females, normal males, haemophiliac females and haemophiliac males. This linkage is quite a possibility in St. Helena, and if one assumes that a haemophiliac female has been born of such a marriage, the fourth diagram becomes:—

IV. xx = XY

xX xY xX xY

A female haemophiliac married to a normal male might produce female transmitters and male haemophiliacs. Mating which is an infinitesimal possibility in the average continental community is a probability to be guarded against in so self-contained and isolated a community as the St. Helenian one. It is possible, however, that a double quantity of the defect in an ovum may inhibit development of the embryo, for such lethal factors are known, and this may be the reason why female haemophiliacs have not been reported.

Although the male does not transmit the disease to any of his children as an evident one, the possibility of his transmitting it to a grandson through his daughter has been raised. It is conceded that another sex-linked defect, colour blindness, may be so transmitted despite the fact that it is normally found in the male only, but most observers have denied such a possibility in haemophilia, a denial which has been elevated to the dignity of a law. Nasse's law is supported by the St. Helenian tree.

It will be noticed that the children of the female transmitters are predominantly male, the ratio male: female being 4:3 in the second generation, 3:2 in the third and 2:1 in the fourth. The percentage incidence of the disease in the affected sons of the 3rd and 4th generations is high, being 82% in each case. No figures can be given to show the percentage of transmitters' daughters who passed the disease on, as many members of the family had gone to South Africa in youth, a fact which increased the difficulty of obtaining accurate information. In fact, it is only fair to point out that only two of the eight sons were seen, the other six having left the island many years before.

It will be seen from the condensed histories of the eight bleeders who were examined that haemorrhage occurred most often after dental extractions, skin wounds of various kinds coming next in frequency as a cause. Recurrent epistaxis was noted in two of the cases and

bleeding from a mucous membrane was recorded in one. III, 10 died of haemorrhage following a wound of the foot, III, 3 as a result of bleeding either from the bladder or the kidney or both.

With the exception of stypven, whose action was most effective in the case of IV, 6, no local applications were found to be of perceptible value in checking oozing. Indeed, apart from the removal of ill-retracted clot to permit inspection of the bleeding point, the less the local interference, the better. Normal horse serum given intramuscularly in a dose of 10 c.c. did appear to have some effect in checking bleeding in one case. Haemoplastin applied locally or given intramuscularly or intravenously was conspicuous for its uselessness. The application of whole normal blood to the bleeding point has a physiological rationale and checked the haemorrhage following IV, 6's dental extraction. The platelets in haemophilia have been shown to be abnormally resistant to hypertonic saline (Birch 1932) and presumably whole blood hastens clotting in these cases by adding thrombokinase from its rapidly disintegrated platelets to the haemophiliac blood.

St. Helena is completely devoid of resources which would enable laboratory investigations to be carried out, so that neither the coagulation time nor the platelet resistance could be estimated.

SUMMARY.

1. The 8 bleeders now living on St. Helena have been investigated.
2. Their family tree has been worked out as far as possible.
3. The sex-linked mode of inheritance of their defect is demonstrated.
4. Reasons are adduced to show that they are in all probability suffering from true haemophilia.
5. The possibility of haemophilia occurring in the female in St. Helena is discussed.

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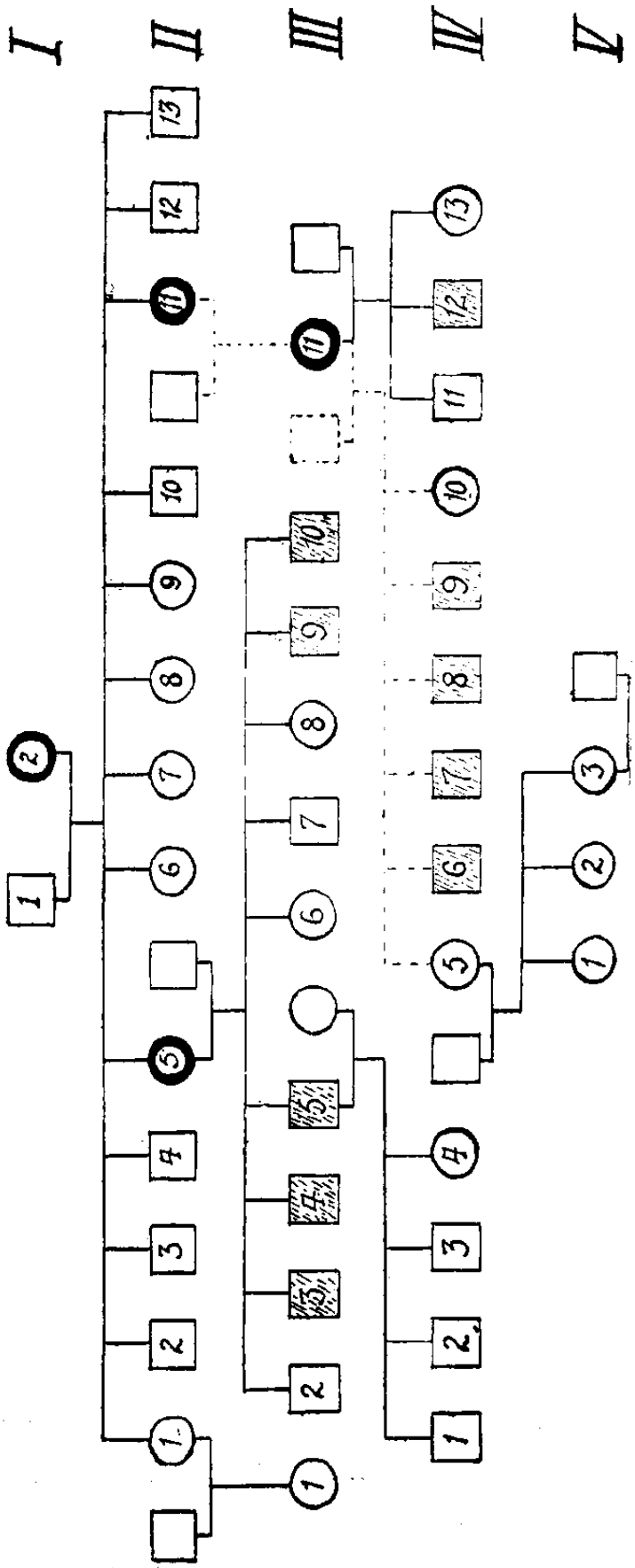

The genealogical tree of the St. Helenian bleeders, as far as it can be traced back to-day. The affected males are shown in shaded squares and the transmitting females in heavy black circles. It is curious that Rose John (1, 2) apparently did not transmit the tendency to any of her own children, but only to her grandchildren on the Williams side, to her great-grandchildren on the Wade side. At any rate no record persists of any of her sons having been bleeders.

THE PYRUVIC ACID CONTENT OF BLOOD IN CLINICAL BERI-BERI.

by

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The purpose of this article is to record additional evidence of the increased blood pyruvic acid content in fulminating beri-beri. An attempt to correlate the vascular syndromes produced by the injection of adrenaline with the pyruvic acid curve is made on some of the cases. The significance of this curve will be discussed in the latter part of this paper.

According to the recent conception of Myerhoff and Keissling (1933), pyruvic acid is one of its intermediate products of carbohydrate metabolism. In the absence or decrease of vitamin B_1, carbohydrate is incompletely metabolised and as a consequence pyruvic acid accumulates in the blood. Peters and Thompson (1934), and Thompson (1934) have shown that during respiration of B_1-avitaminous tissues (brain and kidney) in vitro, there is a marked accumulation of pyruvic acid and low oxygen uptake. The addition of a minute amount of crystaline vitamin B_1 causes an increase of the oxygen uptake and the removal of this intermediate product. This is in striking contrast to lactic acid whose removal is not influenced by vitamin B_1 (Meiklejohn, 1933). The phenomena are consistent with the view that vitamin B_1 has a specific and direct action on the oxidation of pyruvic acid and probably also on the resynthesis to glycogen. Thompson and Johnson in 1935 found a marked increase of pyruvic acid in the blood of B_1-avitaminous pigeons and rats; while Platt and Lu (1936) have demonstrated a similar increase in the blood in human beri-beri.

Blood Pyruvic Acid.

Two methods are used for quantitative estimation of blood pyruvic acid: one is by its property of binding bisulphites, possessed in common by all the aldehydes and most of the ketones (Tolleman). The total amount of bisulphite binding substances (B.B.S.) is then expressed in terms of pyruvic acid. The other is by colourimetric estimation of pyruvic hydrazone formed with 2-4 dinitrophenylhydrazine hydrochloride (Peters and Thompson, 1934).

Thompson and Johnson in 1935 believed that the increase in B.B.S. of B_1-avitaminous pigeon's blood is due entirely to pyruvic acid. But Johnson in his later work (1936) pointed out that the substance respnosible for the increased B.B.S. might not be entirely due to pyruvic acid.

TABLE I.

Hosp. Case No.	Blood of fulminating beri-beri.			Remarks.
	B.B.S. mg/100g.	P.A. mg/100g.	non-pyruvic acid. B.B.S.	
2602	—	1.92	—	During acute stage and fever above 103°F.
2236	11.2	1.71	9.49	
,,	12.1	1.42	10.68	
3456	13.2	5.77	7.43	During acute stage.
,,	12.2	4.27	7.93	
,,	13.2	5.10	8.10	
,,	13.6	5.40	8.20	
,,	12.6	5.10	7.50	
,,	8.6	1.16	7.44	After the acute stage.
2525	10.2	4.08	6.12	During acute stage.
,,	9.1	3.60	6.12	
,,	10.1	3.32	6.78	
,,	6.2	1.87	4.33	5-10 hours after 5 mgs. of *Betabion*: symptoms still acute.
,,	6.4	1.71	4.69	
,,	7.4	1.20	6.20	
,,	5.0	0.94	4.06	After the acute stage.
2631	11.2	5.52	5.68	Case failed to respond to *Betabion*. Pyruvic acid and B.B.S. remained high.
,,	11.2	5.76	5.44	
,,	12.2	4.26	7.94	

Amount of pyruvic acid (P.A.) in the total bisulphite binding substances (B.B.S.) in the blood of fulminating beri-beri.

Table I shows the relationship of pyruvic acid to total B.B.S. in the blood of fulminating beri-beri. Estimation of pyruvic acid and B.B.S. was made on the same sample of blood drawn at various intervals during and after the acute phase. The result gives evidence that the increase in the B.B.S. is not entirely due to pyruvic acid, for more than half of the B.B.S. consists of non-pyruvic acid substances.

This finding differs from that found in experimental animals in which the increase of B.B.S. is accounted for by the increase of pyruvic acid (*vide* Thompson and Johnson, 1935, Table III). It is probable that the different factors which contribute to the production of clinical beri-beri may account for this difference.

Another point of interest to be noted from this table is that in some cases pyruvic acid may play only a small part in the increase of B.B.S. (*vide* case 2236). For example, cases of fulminating beri-beri complicated with fever above 103°F. contained very marked increase of B.B.S., while the increase of pyruvic acid is insignificant, being less than 2 mg/100g.

The Normal Blood Pyruvic Acid Level as estimated by Hydrazone Method.

Johnson (1935) gave the normal level as being not more than 0.9 mg. of pyruvic acid in 100 g. of pigeon's blood.

Platt (1936) investigating the blood of a number of healthy Chinese students at baso-metabolic state gave a value of 0.5 mg/100g. and Edwards' value from three healthy young men (blood taken just before exercise) had a range of 0.1 to 0.18 mm. per 1,000 cmm. blood (i.e., 0.6 to 1.8 mg/100g.). Immediately after rigorous exercise it shot up to 3 or 4 mg/100g. blood, and in less than an hour returned to its resting value.

Six out-patients, being free from all signs of nutritional deficiency were taken as normal and they showed blood pyruvic acid values ranging from 0.45 to 0.7 mg. with an average of 0.54 ± 0.03 mgs. per 100 g.

This wide range of normal blood pyruvic acid level is probably accounted for by the different metabolic state of the individual when blood was taken. In our cases we consider a blood pyruvic acid value of 0.7 mgs. per 100 g. of blood to be the upper limit of normality.

The Blood Pyruvic Acid Level of Non-fulminating Beri-beri patients.

The blood pyruvic acid of 82 cases of polyneuritis with evidence of nutritional origin has been estimated. Fifty-two of these cases came from various hospitals in Hong Kong and thirty from the Henry Lester Chinese Hospital in Shanghai; seven of the thirty cases were fulminating beri-beri.

TABLE II.

Group of Cases.	No. of Cases.	Range of P.A. Values. mg/100g.	Mean Value.	Differences in Group Means.	
Normal	6	0.45 — 0.7	0.54 ± 0.03	normal and non-fulminating beri-beri.	Remarks.
Non-fulminating beri-beri	23	0.5 — 2.4	1.203 ± 0.022	0.663 ± 0.04	Significant
Fulminating beri-beri	7	1.7 — 5.77	3.593 ± 0.560	non-fulminating and fulminating beri-beri. 2.390 ± 0.561	Significant

Blood was taken either at the Out-patient Department or on admission.
P.A. = pyruvic acid.

I now propose to discuss the effect of injection of crystaline vitamin B_1 preparations (*Betaxin* and *Betabion*) on the blood pyruvic acid of these 30 cases from the H.L.C.H. They were patients under my observation for pyruvic acid value which was examined on admission, repeated 24 hours later and then every third day or week according to the condition of the patients. The value obtained after a night's rest was often lower than that taken on admission; and subsequent examinations showed a slight fluctuation within 2 mgs.

Prof. Ride has very kindly worked out the mean values and the difference in the means of the normal and of the different types of beri-beri recorded in Tables II and III. I wish also to express my deep appreciation for the comment he made on them.

In Table II the mean values for the different groups were: $0.54 \pm .03$ for 6 normal cases, $1.203 \pm .022$ for 23 non-fulminating beri-beri, and $3.593 \pm .560$ for 7 fulminating beri-beri. On comparing the means of the normal group with the non-fulminating and the latter with the fulminating revealed a difference of $0.663 \pm .04$ and $2.390 \pm .561$ respectively and the difference between each group was significant being more than three times the standard error.

TABLE III.

Blood pyruvic acid on admission mg/100g.	Blood pyruvic acid 24 hours after rest mgs/100g.	Differences in the two values, mg/100g.
0.80	0.75	—.05
0.80	*0.83	+ .03
0.80	*1.40	+ .51
0.97	0.94	— .03
1.05	0.90	— .15
1.21	1.07	— .14
1.22	0.88	— .34
1.85	0.92	— .93
1.93	0.97	—.96
2.40	0.88	— 1.52
Mean value of pyruvic acid on admission 1.312 ± 0.138.		
Mean value of pyruvic acid 24 hours after rest 0.989 ± 0.059.		
The difference in the two means 0.323 ± 0.150 (significant).		

The effect of rest alone on the blood pyruvic acid content of 10 non-fulminating beri-beri.
* The only 2 cases out of which showed a slight increase; (—) = decrease; (+) = increase.

Out of 10 cases set out in Table III only two showed a slight increase in the blood pyruvic acid while the other 8 revealed a varying decrease of 0.03 to 1.52 mg% in 24 hours with rest only. On admission the mean blood pyruvic acid content was $1.312 \pm .138$ mg%, 24 hours later it dropped to $0.989 \pm .059$, giving a significant difference of $0.323 \pm .150$. This difference in the acid level, before and after

admission, served to show that when a patient had been kept for some time in the hospital his blood often gave only a slight increase and not infrequently within normal limit of 0.7% of pyruvic acid. The improvement of beri-beri symptoms noticed in 24 hours with rest alone was not so rapid as the improvement of pyruvic acid in approaching to normal level. Hence the value of pyruvic acid observed amongst the in-patients often bore no relationship with the degree of symptoms present. For this reason and as would be suggested in the later part of this paper the correlationship of blood pyruvic acid with the state of B_1 deficiency of a patient could be better shown by the curve of adrenaline test.

With regard to the two cases in Table III showing an increase in the difference of the two values they might be due to anxiety or fear or sleeplessness. They were patients of the coolie class who had never been in hospital before.

The normal diet of the hospital was below the International Standard Requirement of 300 I.U. of B_1 per diem for a person of 70 Kg. body weight (Johnson and Edwards, 1937). It contained 150 to 200 I.U. and had a caloric value of 2,500 to 3,000 chiefly derived from rice. Under such diet with complete rest in bed, some of the patients showed signs of improvement of symptoms while others became worse with increasing evidence of interstitial oedema and a rise in blood pyruvic acid level.

Daily weighing of patients at a definite hour of the day and measuring the twenty-four hour fluid intake and output often revealed increased retention of tissue fluid which, otherwise escaped detection by the usual method of examination, i.e., pitting on pressure at the ankle and dorsum of the foot.

Intramuscular or intravenous injection of 5 mgs. of *Betabion* to these cases brought down the pyruvic acid to normal level and was followed by improvement of symptoms such as an increase in the output of urine; an improvement of the appetite; deminution of oedema, palpitation, numbness of finger-tips while pain in the calf muscles was much relieved; the pulse rate slowed down sometimes to 50 or 60 beats per minute. In contrast to this, injection of 5 mgs. of *Betabion* did not give such dramatic effect to the contracted muscles of the so-called dry beri-beri. The recovery of such muscles was slow and needed other measures beside replacing the B_1 deficiency. Daily massage, passive and active movement to the muscles were part of the treatment of dry beri-beri.

The Blood Pyruvic Acid Level of the Rapidly Developing Fulminating Types of Beri-beri.

In two cases, the increasing values of the blood pyruvic acid were found to correspond with the increased severity of beri-beri symptoms.

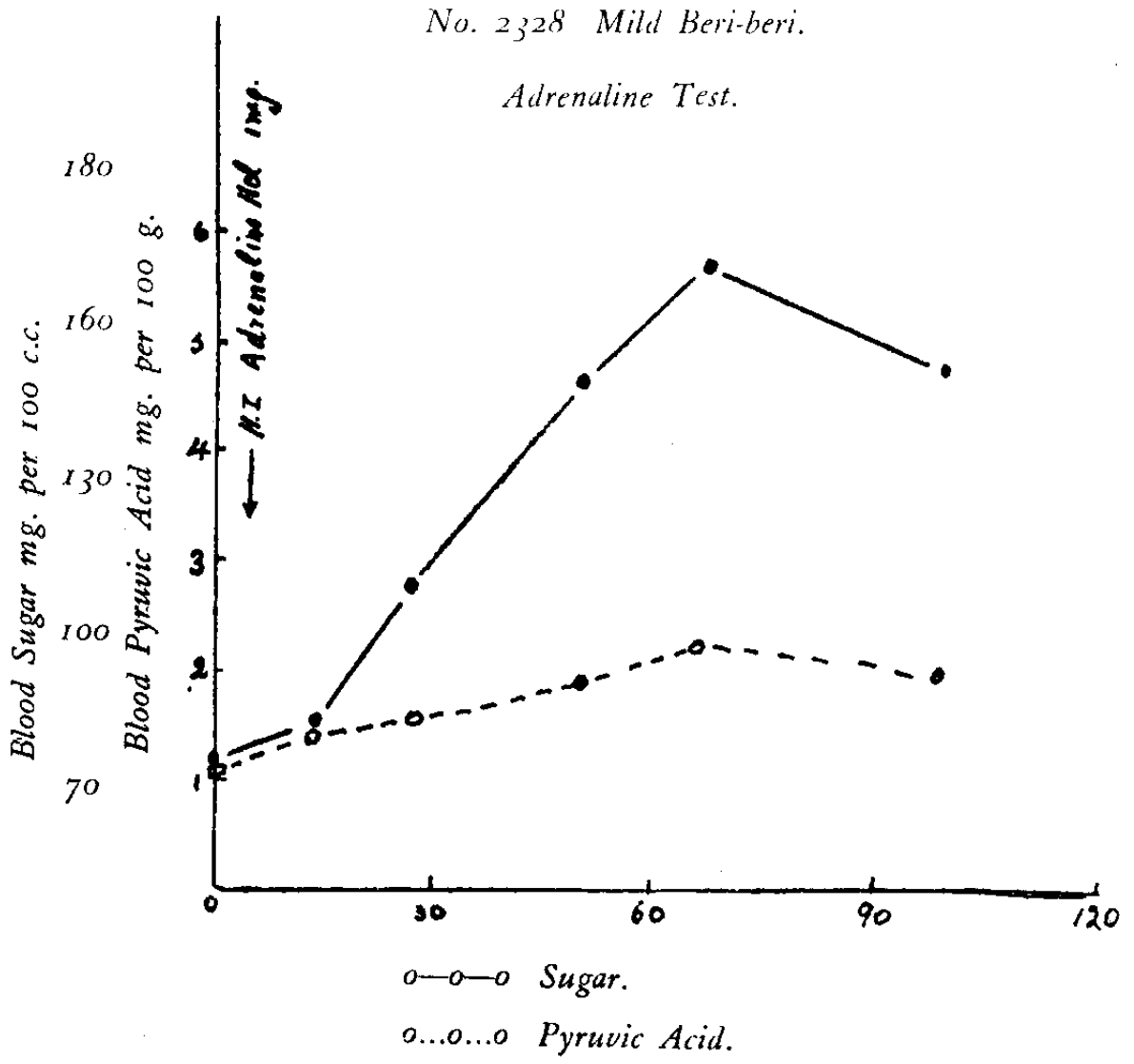
These two patients were rapidly developing into the acute type. One was an out-patient, case 2525, diagnosed as mild type of beri-beri; he was a male, aged 32, coolie and complained of oedema of feet for 5 months, dyspnoea and palpitation on exertion for 2 months; he showed visible pulsation over the precordial and epigastric regions; knee jerks were absent and calf muscles were slightly tender to deep pressure; he complained of anorexia for one week, and had a blood pyruvic acid value of 0.9 mg/100g. He was treated with one drachm dose of dry yeast, three times a day. Two days later he came to out-patients and complained of dyspnoea and palpitation even during rest. The blood pyruvic acid had risen to 1.2 mg/100g. Unfortunately he could not be admitted owing to lack of accommodation, but he was advised to stop working. He failed to follow the advice for economic reasons. A week later he was brought into the hospital in a very restless state of fulminating beri-beri, and the blood pyruvic acid before treatment was 4.08 mg/100g. He was immediately given 5 mgs. of *Betabion* by the intravenous route. In 15 hours his blood pyruvic acid had come down to 0.9 mg/100g.

The other case was (574 T.Y.H.) beri-beri in a primipera at full term pregnancy at Tsan Yuk Hospital, Hong Kong. Before delivery her blood pyruvic acid was found to be 1.36 mg/100g. There was marked oedema of lower limbs and loss of knee jerks. The urine was clear. On the 9th day of puerperium following normal delivery she suddenly became intensely dyspnoeic with symptoms of circulatory failure. The pulse rate was 138 per minute, the temperature 99.8°F., the blood pressure 156/116 mm. Hg., and the blood pyruvic acid 2.8 mg/100g. Examination of her urine showed presence of albumin and granular casts. She was first treated with H.I. Digitalin 1/80 gr. and H.I. Coramine 1.7 c.c. 4 hourly for two days without improvement. Her urinary excretion became less and less in amount until she was passing only 6 ozs. of urine in 24 hours. The cardiac stimulants were then stopped and in their stead only *Betaxin* (4 mgs.) was given intravenously and repeated 12 hours later. The next day she showed marked improvement: the pulse rate came down to 100 per minute; she was less dyspnoeic and passed 29 ozs. of urine. Her blood pyruvic acid had come down to 1.9 mg/100g. Except for a slight occurrence of oedema of the lungs during the convalescent period she made uneventful recovery and was discharged 1½ months later. In all she had 12 mgs. of *Betaxin*. Before she was discharged from the hospital, her blood pyruvic acid was 0.9 mg/100g., the urine was free from albumin, and her knee jerk on one side showed signs of recovery, that is, tapping the left patella tendon produced contraction of the extensor thigh muscles. The blood pyruvic acid of her baby gave a value of 0.9 mg/100g.

Some Observations of the Effect of Subcutaneous Injection of 1 mg. of Adrenaline Hydrochloride on the Pyruvic Acid Level of Non-fulminating types of Beri-beri.

Thirteen cases that had a normal or slightly raised resting blood pyruvic acid, were tested for adrenaline reaction of Aalsmeer. The blood pyruvic acid values at various intervals of 15 and 30 minutes after the injection of 1 mg. of adrenaline hydrochloride hypodermically were estimated and then presented in the form of a curve.

Chart I.



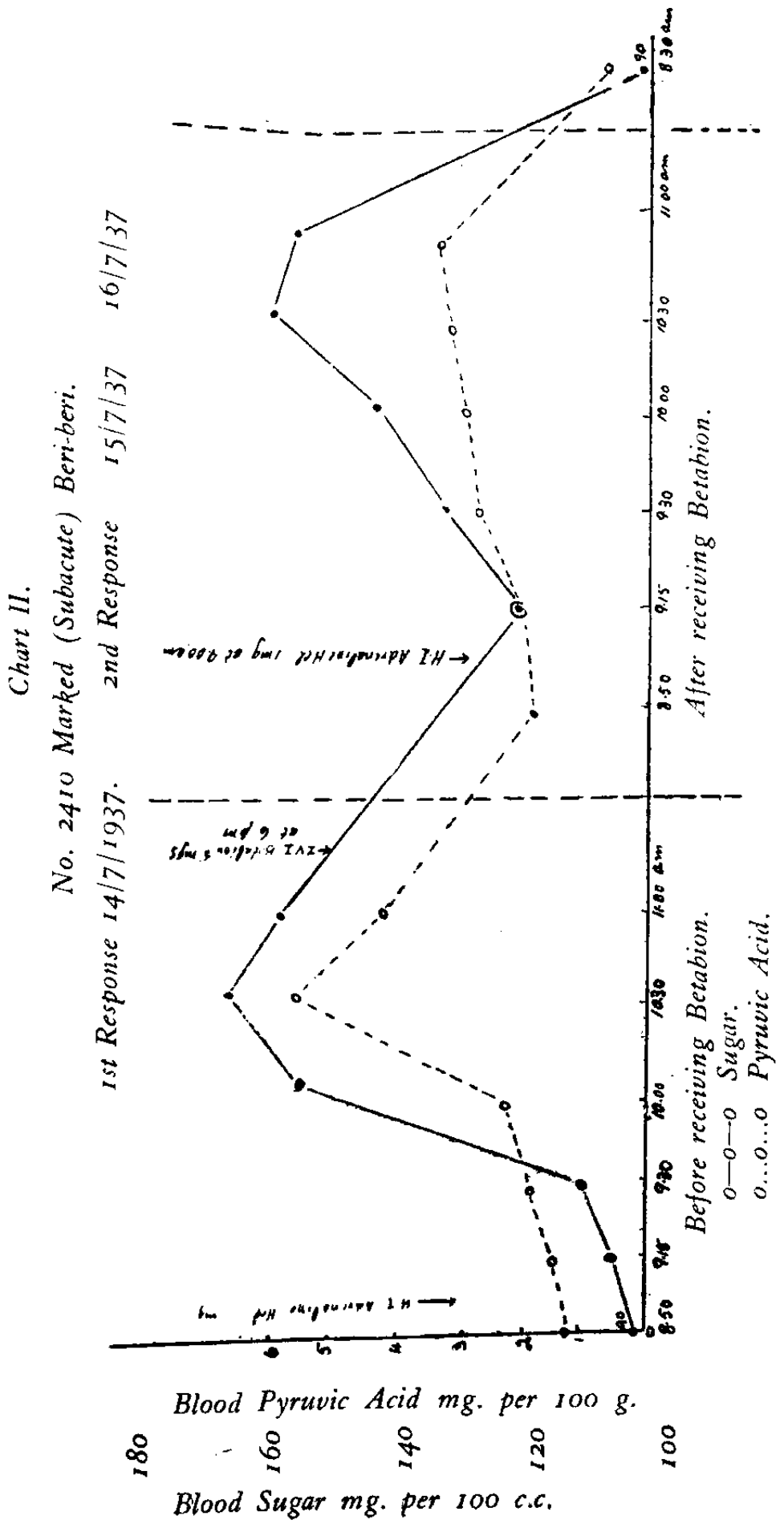


Chart II.
No. 2410 Marked (Subacute) Beri-beri.
1st Response 14/7/1937. 2nd Response 15/7/37 16/7/37
After receiving Betabion.
Before receiving Betabion.
o—o—o Sugar.
o...o...o Pyruvic Acid.
Blood Pyruvic Acid mg. per 100 g.
180
160
140
120
100
Blood Sugar mg. per 100 c.c.

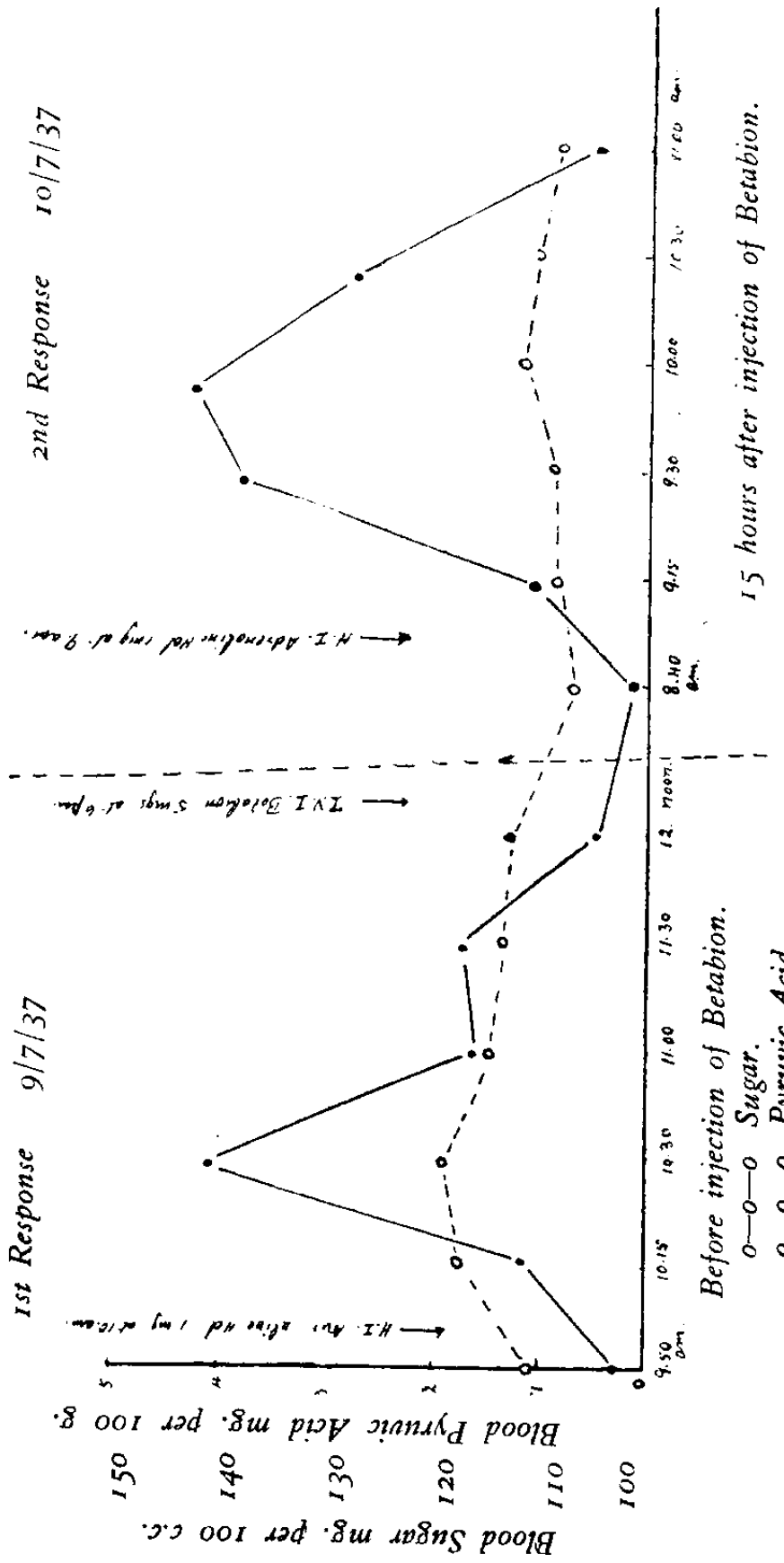


Chart III.
No. 1681 Convalescent Stage of Acute Beri-beri.
Adrenaline Test.
1st Response 9/7/37
2nd Response 10/7/37
Blood Sugar mg. per 100 c.c.
Blood Pyruvic Acid mg. per 100 g.
150
140
130
120
110
100
9.30 a.m.
10.15
10.30
11.00
11.30
12. noon
8.40 a.m.
9.15
9.30
10.00
10.30
11.00 a.m.
Before injection of Betabion.
o—o—o Sugar.
o...o...o Pyruvic Acid.
15 hours after injection of Betabion.

Aalsmeer states that the action of adrenaline is due primarily on the heart itself and also to its dilating effect upon the peripheral blood vessels. The sum total of the difference is called the "Gradient" expressing the fact that the rapidity of development of the fall of final sound pressure and unstable wave front are the most important factors concerned in these vascular syndromes. Minor symptoms also appear such as increased arterial and venous pressure at the neck, wide spread pulsation at the precordial and epigastric regions, accentuation of heart sounds or murmurs and palpitation which at times caused great discomfort to the patients.

Examination of such curves showed that adrenaline induced a marked rise of pyruvic acid to 2 mgs. or more according to the severity of depletion of vitamin B_1 reserve of the body. The rise began within 15 minutes and the peak was reached in 1 to 1½ hours. The return to its original value was not reached in two hours. The height of the rise and the late return of the curve to original level seemed to be the characteristic part of the curve. The height of the peak also gave significant comparison with that of the mild, marked and convalescent case of fulminating beri-beri (see chart I to III). The degree of B_1 deficiency was divided in the manner as reported in *The Caduceus* 1937 (Lim 1937). In repeating the test on cases 2410 and 1681, 15 hours after I.V.I. of 5 mgs. of *Betabion* they produced different types of curves. The curves were flatter, and the pyruvic acid value obtained 24 hours later was less than that before the test.

The vascular syndromes as observed by Aalsmeer were also affected in the same manner. The 5-minute blood pressure changes of case 1681 and 2410 for a period of half an hour were recorded in Table IV. On examining this table and comparing it with the pyruvic acid curves in chart II and III, the following features were noted:—

(1) That the fall of final sound (F. S.) was delayed or prevented by previous injection of 5 mgs. of *Betabion*.

(2) That the vascular syndromes were somewhat related to the vitamin B_1 reserve of the body.

(3) That there was a close correlation between the vitamin B_1 reserve of the body and the accumulation of pyruvic acid, and probably also with other internal secretions of ductless glands, such as pancreas, suprarenals, thyroid, etc., as shown by the rise of blood sugar and the appearance of vascular syndromes.

(4) That information with regard to the vitamin B_1 reserve of the body could be better obtained from the study of the pyruvic acid curve. The B_1 deficiency of case 1681 (convalescent stage of acute beri-beri) had been corrected by previous treatment

TABLE IV.

No. Case	Date & Time.	Systolic pressure mm. Hg.	Diastolic pressure mm. Hg.	Final sound mm. Hg.	Pulse rate per min.	Respiratory rate per min.	Remarks.
1681	9/7/1939		1st Response.				
con-vales-cent beri-beri	9.45 a.m.	122	78	48	84	18	Patient in the convalescent stage of acute beri-beri. Adrenaline injected at 10.00 a.m. Vascular syndromes appeared within 1 minute of injection of adrenaline. Patient complained of severe palpitation at 10.15 a.m. Arterial sound appeared over the following superfial arteries:—femoral, popliteal, dorsalis pedis, brachial, facial and temporal. At 6 p.m. the brachial arterial sound was still present, but disappeared within 2 hours of injection of Betabion 5 mgs.
	10.05 ,,	128	60	20	84	20	
	10.10 ,,	124	48	0	80	23	
	10.15 ,,	128	?38	0	80	24	
	10.20 ,,	128	?38	0	92	24	
	10.25 ,,	128	?38	0	96	24	
	10.30 ,,	128	?38	0	96	24	
	10/7/1937		2nd Response.				Patient received 5 mgs. of Betabion (15 hours) before the test ((i.e., given at 6 p.m. 9/7/1937). Adrenaline injected at 9.00 a.m. Vascular syndromes appeared within 1 minute of injection and were not so severe as in the first response. Final sound showed a gradual fall to zero pressure —a delay of ¼ hour as compared with the first response. Brachial arterial sound disappeared within 3 hours after the test (absent at 12.30 p.m.).
	8.40 a.m.	128	62	50	64	20	
	9.05 ,,	130	58	48	68	22	
	9.10 ,,	130	58	42	68	23	
	9.15 ,,	130	54	40	70	22	
	9.20 ,,	138	56	26	72	22	
	9.25 ,,	138	52	0	72	23	
	9.30 ,,	138	56	0	74	25	

The vascular response to hypodermic injection of 1 mg. adrenaline hydrochloride before and after Betabion: 1st response before injection of Betabion; 2nd response 15 hours after I.V.I. of 5 mgs. of Betabion. (?) = doubtful.

TABLE IV.—(*Continued*)

No. Case	Date & Time.	Systolic pressure mm. Hg.	Diastolic pressure mm. Hg.	Final sound mm. Hg.	Pulse rate per min.	Respiratory rate per min.	Remarks.
2410	13/7/1937		1st Response.				Had mild vascular syndromes.
Marked beri-beri	8.50 a.m.	118	80	50	80	21	Slow fall of final sound to zero pressure; taking 30 minutes from the time of injection of adrenaline.
	9.05 ,,	118	70	30	82	21	
	9.10 ,,	114	60	28	82	22	Arterial sound appeared over the femoral poplitial and brachial arteries.
	9.15 ,,	114	68	20	84	23	
	9.20 ,,	114	64	20	86	24	The brachial arterial sound disappeared 2 hours later (i.e., absent at 12.30 p.m.).
	9.25 ,,	114	64	10	90	24	
	9.30 ,,	112	62	0	92	24	
	14/7/1937		2nd Response.				Patient received 5 mgs. of Betabion (15 hours) before the test (i.e., at 6 p.m. 12/7/1937).
	8.40 a.m.	134	96	80	52	20	Adrenaline given at 9.00 a.m.
	9.05 ,,	162	94	80	56	22	Note the final sound did not fall to zero pressure and the slow pulse rate was due to the effect of previous injection of Betabion.
	9.10 ,,	138	86	64	58	24	
	9.15 ,,	130	84	64	62	23	
	9.20 ,,	134	84	64	66	24	
	9.25 ,,	132	82	64	66	23	
	9.30 ,,	132	82	64	66	23	

given during the acute stage, but his vascular tone was still weak. The adrenaline test performed on him gave a low blood pyruvic acid curve with marked vascular syndromes; case 2410 was a case of subscute beri-beri and had never been treated before. He produced the opposite result of the test—a high pyruvic acid curve with milder vascular syndromes—showing that though he had a lower vitamin B_1 reserve his vascular tone was much better than that of case 1681.

This finding is consistent with the fact that the vascular syndromes are dependent upon the tone of the arterial wall, the pyruvic acid upon the carbohydrate metabolism. Hence the involvement or improvement of the vessel depends on a time factor, while the accumulation of pyruvic acid, on the immediate state of the vitamin B_1 reserve of the body. Further more the arterial sound which has been given much prominence by Aalsmeer is not always present in fulminating beri-beri and the prognosis of the case does not depend on the absence or presence of this physical sign alone.

The Blood Pyruvic Acid and B.B.S. Levels in Fulminating Beri-beri.

As shown in table I a very considerable increase in pyruvic acid and B.B.S. similar to the amount obtained in experimental animals was found only in the blood of afebrile cases of fulminating beri-beri. Probably as stated by Platt and Lu the latter represented the nearest approach to the pure experimental form of B_1-deficiency. But when the fulminating form was accompanied with fever of 103° F. or above, only the B.B.S. were significantly increased, while the pyruvic acid was usually less than 2 mg./100 g.

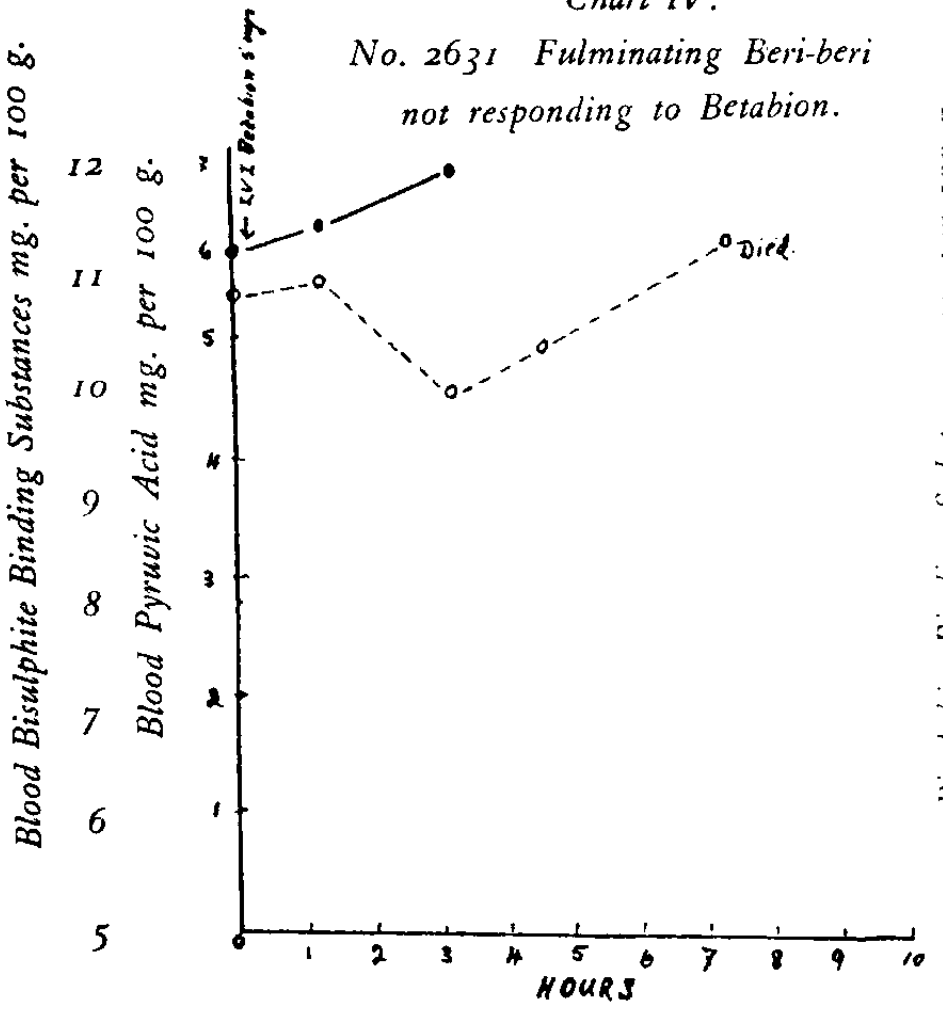
The order of treatment for the fulminating beri-beri was as follows:—Lumbar puncture; venesection, 300 to 500 c.c. of blood being drawn from the mid-cubital or external jugular vein and followed immediately by intravenous injection of 5 mgs. of *Betabion*. Hourly samples of blood were then drawn for estimation of B.B.S. and pyruvic acid, until the acute phase had passed off.

Two of the seven cases of fulminating beri-beri that failed to respond to 5 mgs. of *Betabion* continued to maintain high levels of B.B.S. and pyruvic acid. They remained intensely dyspnoeic to the end. (See chart IV).

In those that recovered, the levels of B.B.S. and pyruvic acid began to fall steadily within 5 hours of injection of 5 mgs. of *Betabion*, reaching the normal level in 15 to 20 hours (see chart V and Table I case 2525). In patients where adrenaline was used to maintain the circulation, the B.B.S. and pyruvic acid levels went up again, until the effect of adrenaline had passed off. Then the values steadily came down to normal level in 20 hours.

Chart IV.

No. 2631 Fulminating Beri-beri not responding to Betabion.

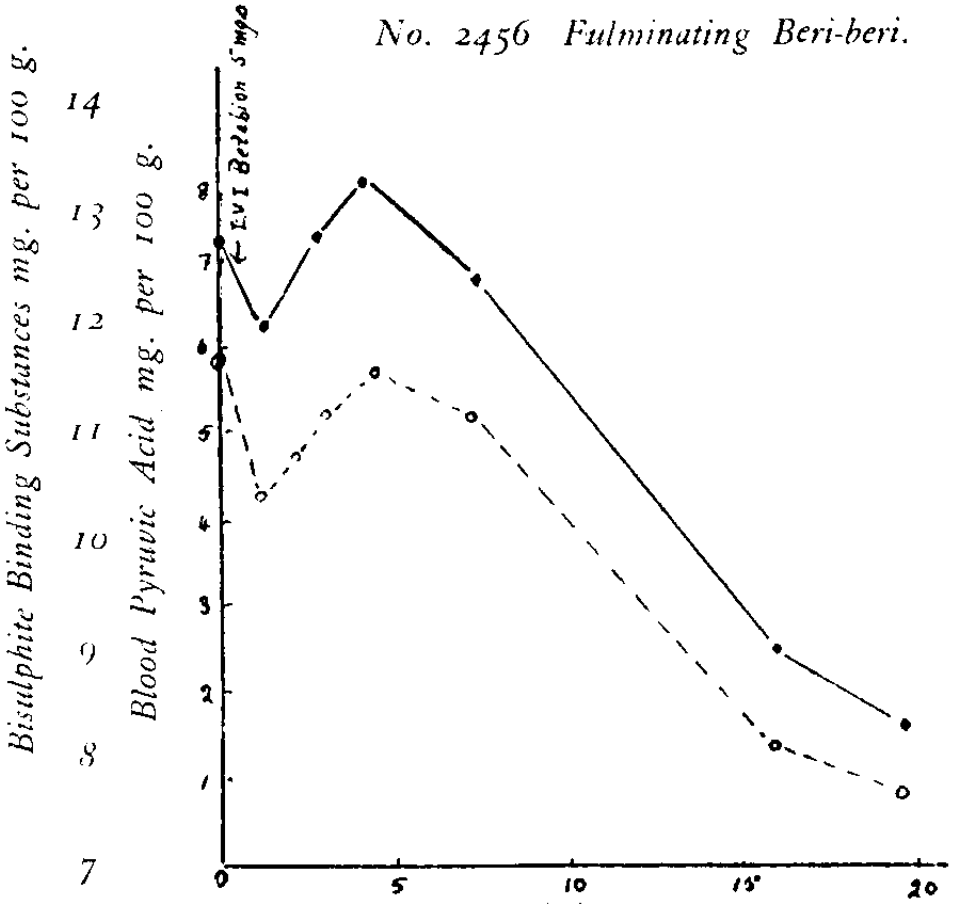


HOURS.

Patient died 7 hours after admission.
The blood pyruvic acid remained at high level to the end.
o—o—o Bisulphite Binding Substances.
o...o...o Pyruvic Acid.

Chart V.

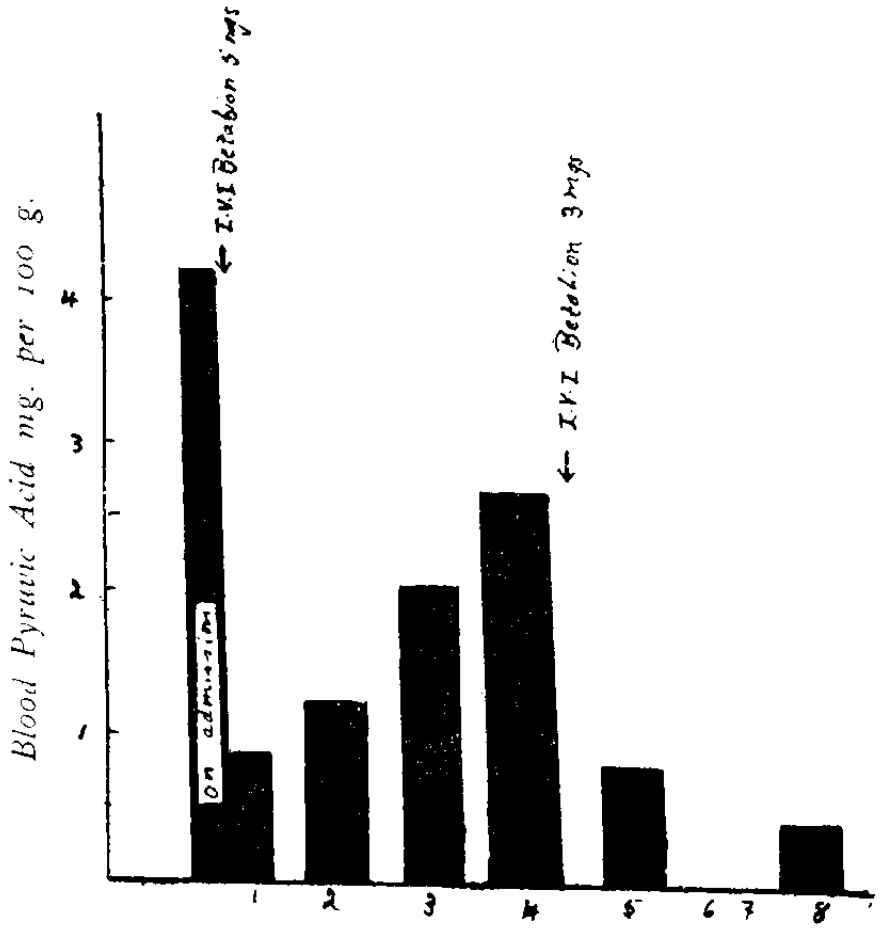
No. 2456 Fulminating Beri-beri.



5 mg. of Betabion given on admission.
Blood pyruvic acid and B.B.S. values came down to normal level in 20 hours.
o—o—o Bisulphite Binding Substances.
o...o...o Pyruvic Acid.

Chart VI.

No. 2525 Fulminating Beri-beri.



The first injection of Betabion reduced the blood pyruvic acid to normal level; the second injection kept the pyruvic acid low for 4 days.

Remission of acute symptoms was also noticed as early as 8 to 10 hours after injection of *Betabion*. Respiratory distress which was the main cause of restlessness became less and vomitting and retching were much relieved. Like a woman immediately after labour, the patient became very drowsy, pulse rate dropped by 10 to 20 beats per minute, the tension and volume of pulse improved while the systolic and diastolic pressure were raised. If not complicated by other diseases, there was no danger of relapse once the acute stage had passed off. In two to five days later, the pyruvic acid began to rise again until another dose of 3 to 5 mgs. of B_1 was given (see chart VI, case 2525). The second injection usually caused bradycardio. The excretion of urine was found to be markedly increased after every injection of *Betabion*.

During the first few days following the acute phase, patients usually experienced extreme weakness of limbs. The calf muscles which were tense during the acute stage now became flabby and markedly atonic. This apparent change of muscular tone was due to loss of interstitial fluid. Headache was a common complaint, most likely an after effect of lumbar puncture. Constipation and retention of urine often followed. Bradycardia for a few days was quite common; but at times it might last as long as 2 to 3 weeks.

A series of teleradiograms of case 1681 showed that the heart was extremely enlarged to the right and left. In 30 days the transverse diameter of the heart was shorter by 5.3 cms. With improvement of the heart, the vascular congestion of the lungs also cleared up. The teleradiograms of case 2260 showed another interesting point, the involvement of the phrenic nerve and/or the hypotonic state of the diaphragm. When the first picture was taken on the 13th July, 1937, the right half of the diaphragm was on a much higher level (9th rib posteriorly) than that of the left (10th rib posteriorly). On screening the movement of the diaphragm was seen to be very limited, about ½ inch during forced respiration and there was nothing to indicate of the presence of paralysis of the muscle as revealed by the absence of paradoxical movement. The second picture was taken three weeks later. The level of the diaphragm had come down to normal and the movement had markedly increased to 1¼ inches.

If the diet of the convalescent period immediately following the acute phase were cut down to rice, salted vegetables and salted eggs, signs of dry atrophic beri-beri would rapidly begin to appear. Due to increasing weakness of the extensor muscles of the extremities, wrist- and foot-drop would develop and the fingers would be flexed. In consequence, if left untreated, the development of contracture of fingers and other signs and symptoms of dry beri-beri would be only a matter of time.

To a neglected case of post partum beri-beri which had developed clawed hands, atrophy of calf muscles and foot-drop, 3 mg. dose of crystaline B_1 given intramuscularly for 5 days showed no perceptible improvement.

CAES REPORTS OF FULMINATING BERI-BERI.

Case 2260, a tailor, aged 19, was admitted into the hospital at 9.30 p.m. on 2nd July, 1937.

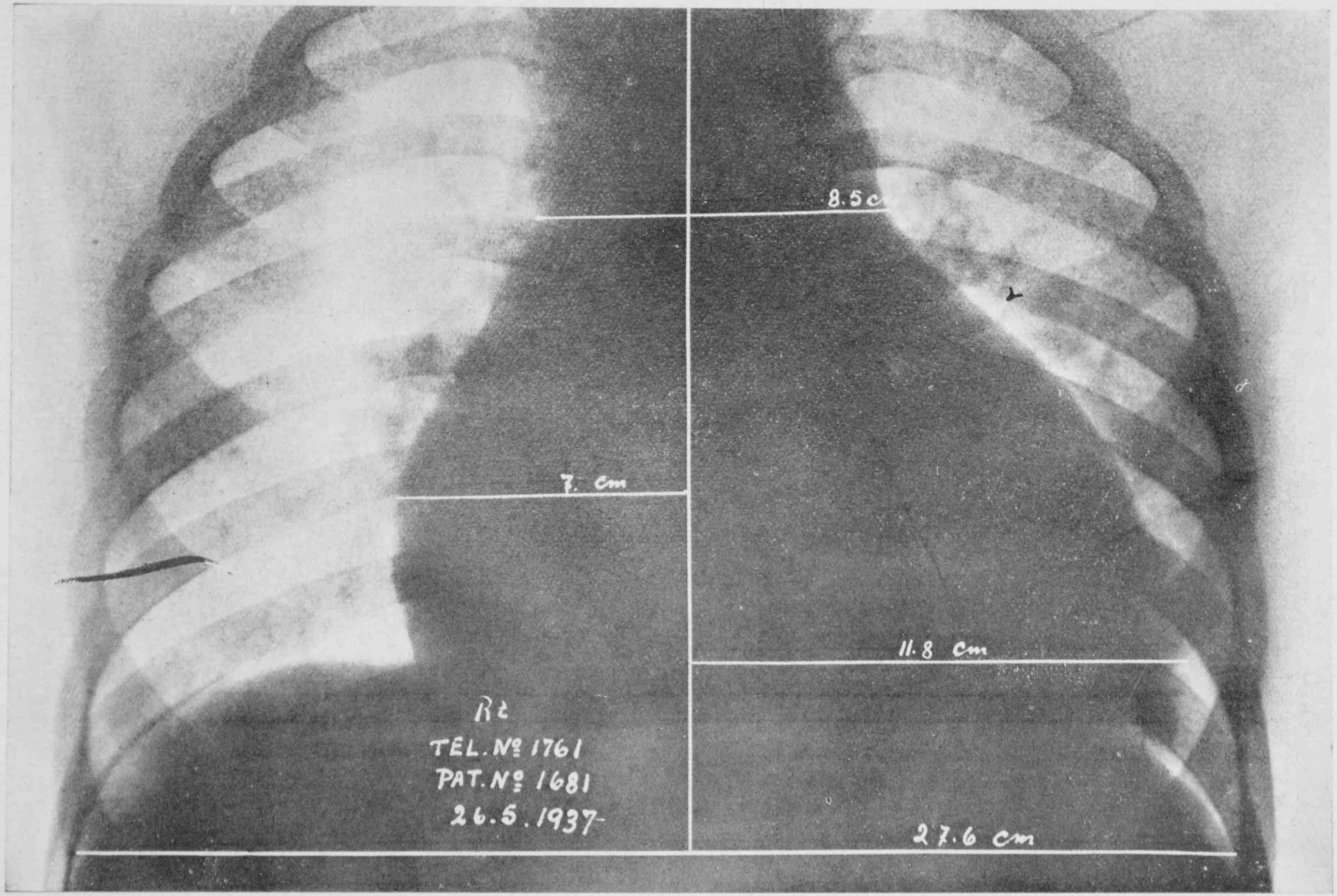
Chief complaint:—Intense dyspnoea for 9 hours.

Diagnosis:—Fulminating beri-beri associated with vitamin C deficiency.

Treatment:—I.M.I. 21 mgs. of Betabion; 5,500 mgs. vitamin C (in Redoxon tablets) by mouth and complete rest during convalescent period.

Result:—Recovery

History:—Three days before admission he had fever and twenty-four hours later he developed aphonia. At three o'clock in the evening on the day before admission he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7. cm
11.8 cm
Rt
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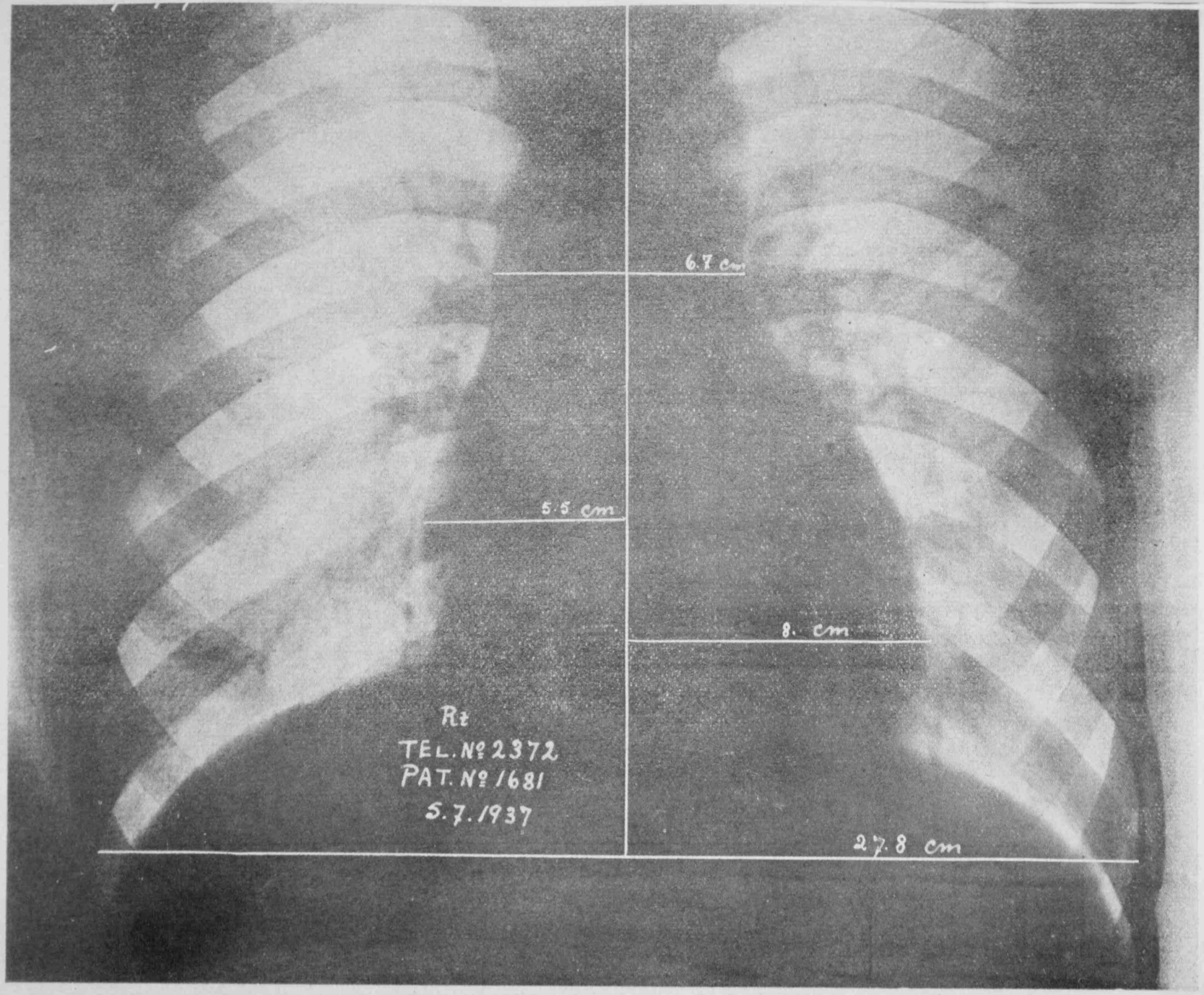
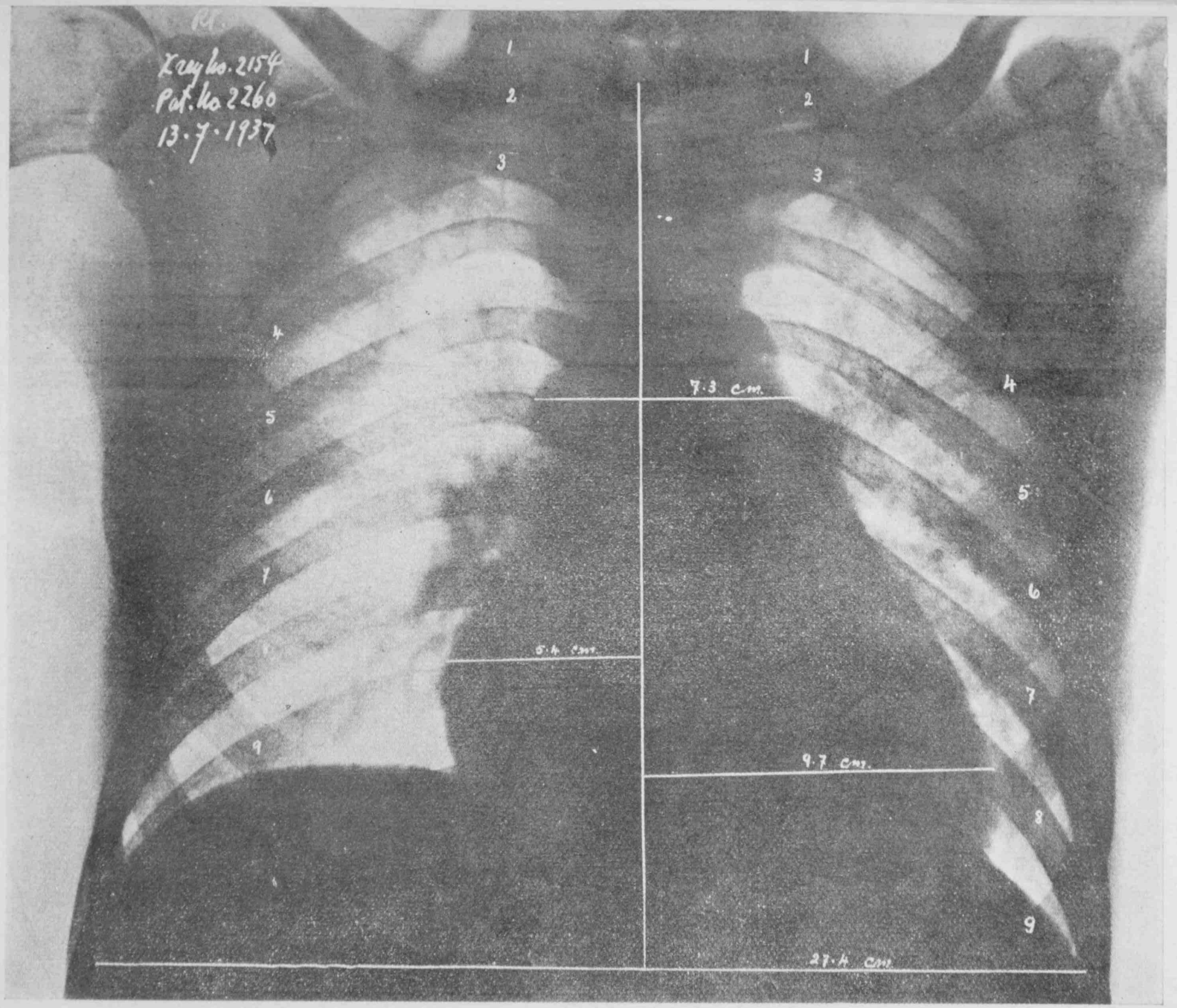
PAT. Nº 1681
26.5.1937
27.6 cm


6.7 cm
5.5 cm
8. cm
Rt
TEL. Nº 2372
PAT. Nº 1681
5.7.1937
27.8 cm


R.
X-ray No. 2154
Pat. No 2260
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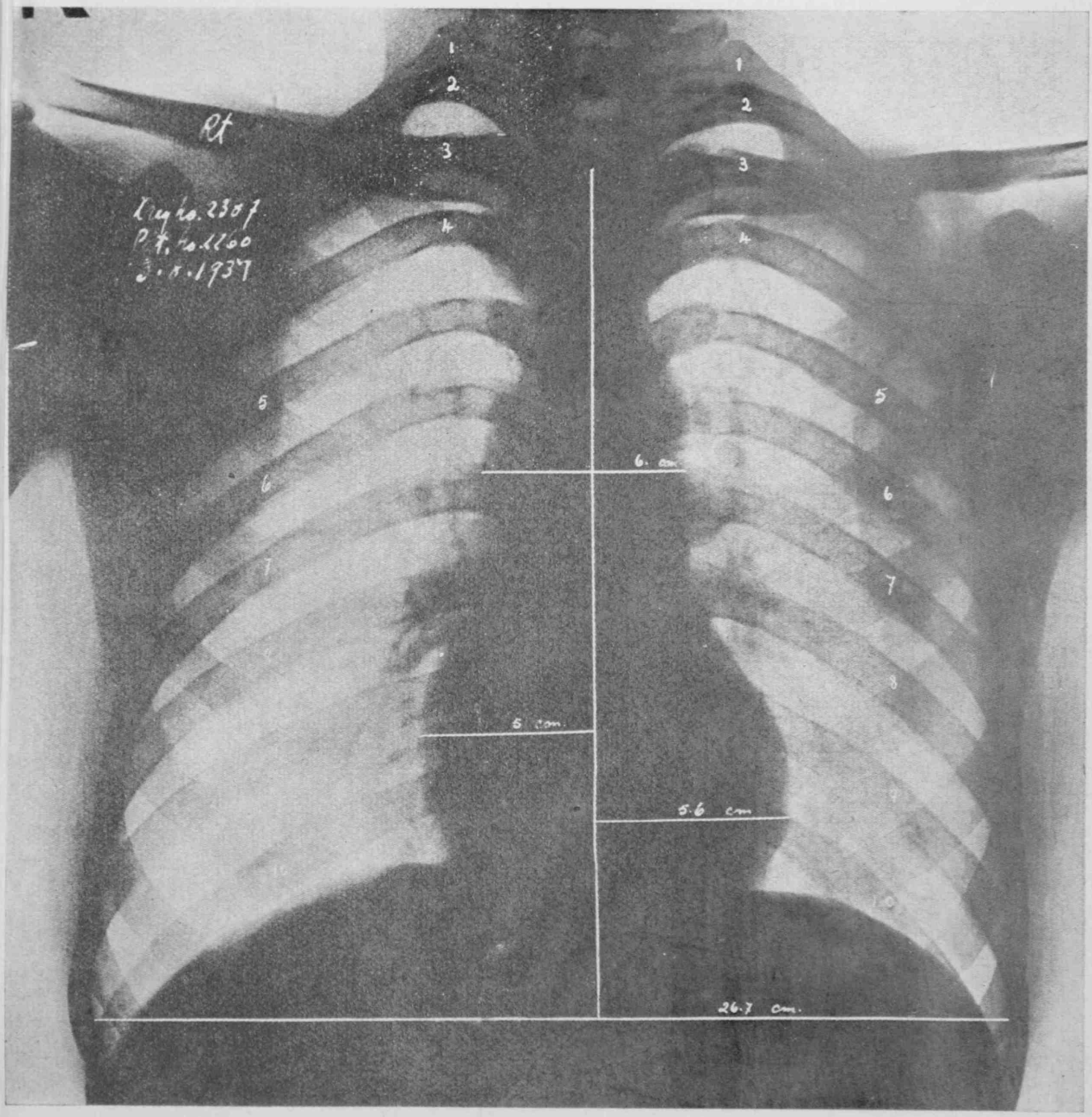
27·4 cm.


Rt
Lung. 2307
P.T. No. 2260
3.11.1937
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2
3
4
5
6
7
6. cm
5 cm
5.6 cm
26.7 cm.

suddenly become dyspnoeic. He had not taken any food for the previous twenty-four hours and had vomited about six times prior to admission.

Condition on Admission:—He was very restless, tossing himself from side to side, and pressing his chest every now and then to aid respiration. Due to paresis of the left vocal cord his cry assumed the character of a hoarse groan. The breathing was rapid and shallow, 40 per minute. He had a temperature of 101.6° F.; a pulse rate of 156 per minute; and blood pressure of 110/60, F.S. = O., i.e., arterial sound could be heard with the stethoscope applied on the brachial artery without any pressure. Soon after the blood pressure was taken, numerous haemorrhagic spots appeared on the forearm. The veins at the root of the neck were markedly engorged and cardiac pulsation was present over the entire precordial area and epigastrium.

Past illness:—He had fever and rigor three years ago and occasional epistaxis and bleeding from the gums. Each time he bled from the nose, he lost about one Chinese tea-cupful of blood, i.e., about 2 ozs. of blood. Two months after he had recovered from the fever, he developed elephantiasis of the lower limbs, involving the left more than the right limb. During the first two years the development of elephantiasis was said to be very slow, but had increased rapidly in the last 6 months.

Personal history:—He was not married and denied exposure to veneral diseases. Being an apprentice he received only food and lodging for his work. On inquiry, the diet appeared to be grossly deficient in the essential food elements. Four out of ten workers in the shop who had their meal together had oedema of the legs.

Physical examination:—His facial expression was very anxious. The gums were cyanosed, otherwise, normal. Strong pulsation was seen over the entire precordial area, the epigastrium and at the root of the neck. Systolic murmur was present in all the vulvular areas and pulmonary area. The abdomen was very tender. The liver was enlarged, extending 1 inch below the costal margin. The spleen was not palpable. The lymphatic glands in both groins were palpable. The skin of the legs was dry and hard and the hair on them was fine and scanty, being easily pulled off without causing pain. Pin point pigmentation (follicular keratosis) was present only on the lower limbs. There was unequal diminution of the air and bone conduction of the accoustic apparatus, more marked on the left than the right ear. The vibratory sense of the long bones of the body (tibia, fibula, radius and ulna) was also similarly affected. Formication and loss of cotton wool touch were present on the finger tips and on the legs from the knee downward. The capillary resistence test produced more than 20 petechiae in an area of 1 inch diameter drawn on the cubital fossa.

The capillary resistence test is carried out by applying a standard pressure of 50 mm. Hg on the arm for 15 minutes. At the end of which time the pressure is released. The number of petechiae appearing in an area of 1 inch diameter on the cubital fossa is then counted. Normally there should not be more than 5 petechiae, more than this number shows that the capillary wall is fragile, a condition present in vitamin C deficiency. This test has been widely used for the diagnosis of pre-clinical stage of scurvy. (Gothlin, 1931, and Falk, 1932.)

Laboratory examination:—The blood pyruvic acid on admission was 2.96 mg./100 g. Twenty-four hours after I.M.I. of 5 mgs. of Betabion, it came down to 0.88 mg. The cerebro-spinal fluid was removed slightly under pressure and on examination the B.B.S. and the pyruvic acid content were 5 and 1.37 mg./100 g. respectively.

Other laboratory findings were as follows:—

Cerebro-spinal Fluid: No organism found on staining, Pandy's test negative.

Blood: Wassermann's test doubtful; Kahn's test + + ; no microfilaria seen in 3 successive days examination of blood smears taken at noon, 10 p.m., and midnight; calcium 11.2 mgs. %; Non-protein nitrogen (N.P.N.) 27 mgs. %; total protein 8.1 gms. %; sugar 117.4 mgs. %; chloride (as NaCl) 472 mgs. % uric acid 3.3 mgs. %; urea 11.5 mgs. %; r.b.c. 4,008,000 per c. mm.; Hbl 12 g. %; colour index 0.87; w.b.c. 8,700 per c. mm.; differential count (200 cells counted): neutrophils 62%, eosinophils 12%, lymphocytes 23%, monocytes 3%; Coagulation Time 16 min. and 20 secs.; bleeding time 3 mins. and 45 secs.

Urine: Colour, light yellow; reaction, acid to litmus paper; specific gravity, 1.020; protein +; reducing sugar, nil; w.b.c., few; r.b.c., nil; epithelial cells, nil; granular casts, + +.

Faeces: Foul smelling, watery, and dark brown with occult blood, having the general appearance and consistency of "red bean congee," hookworm ova + +, Charcot Leyden crystals +.

Treatment and progress: Prior to I.M.I. of 5 mgs. of Betabion, patient had a lumber puncture and venesection of 300 c.c. blood. Twenty-four hours later, the acute symtoms of beri-beri were relieved; the pulse rate came down to 80 per minute, and the respiration 24 per minute. 500 mgs. of vitamin C (in Redoxon tablets) were then given by mouth for 9 successive days. It was stopped for 5 days and then continued again for another two days. The treatment for hookworm with oil chenopodium was delayed on purpose until the patient was free from symptoms of vitamin B_1 and C deficiency (28:7:1937).

The daily excretion of ascorbutic acid in urine showed gradual increase during administration of vitamin C, and rapidly decreased on stopping it. But at no time was the urine completely saturated with ascorbutic acid. The estimation of urinary excretion of ascorbutic acid was titrated against 2:6-dichlorophenolindophenol in acid solution. (Harris, 1935.)

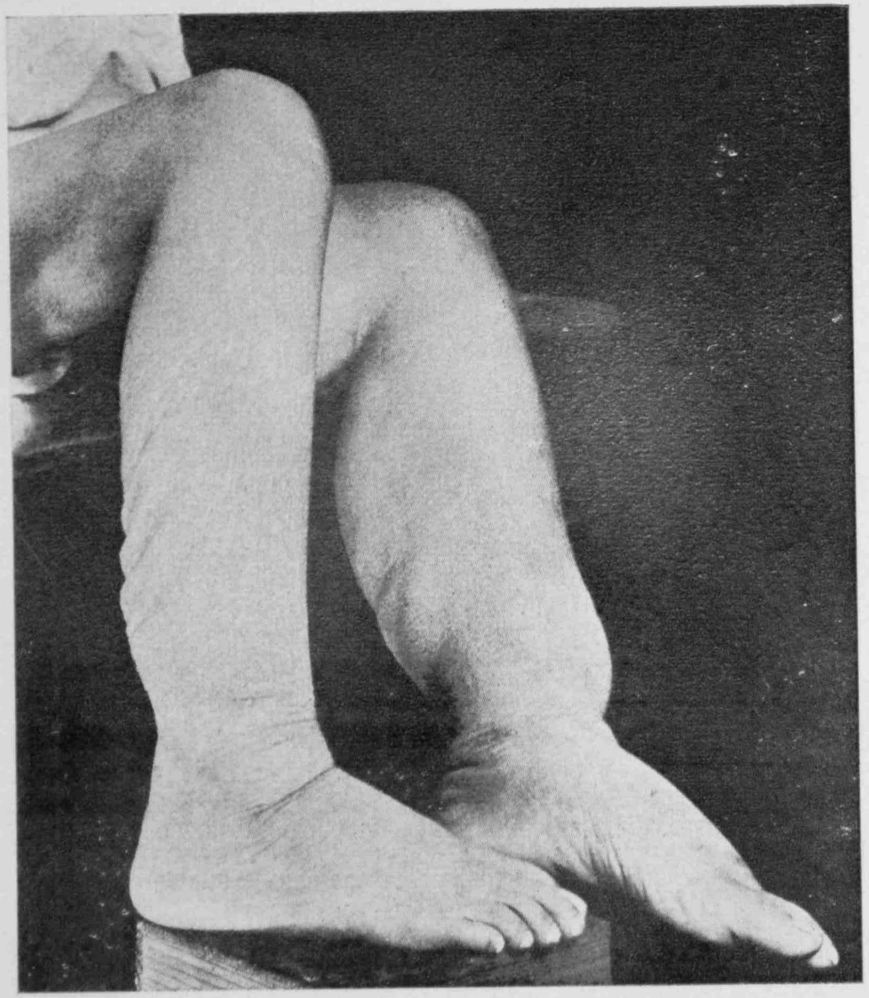
The effect of vitamin C on the daily excretion of ascorbutic acid.

Date July, 1937.	Dose of vit. C orally.	I.M.I. of Betabion	Mg.% of ascorbutic acid in urine.	24 hours fluid intake.	24 hours urine.
	mgs.	mgs.	mg.%.	c. c.	c. c.
2	—	5	—	520	600
3	—	—	trace	480	2,330
4	500	2	4.2	500	820
5	500	—	7.6	1,400	620
6	500	2	7.97	2,300	800
7	500	—	7.97	1,930	1,800
8	500	3	8.25	2,280	1,700
9	500	2	26.15	2,300	1,900
10	500	—	65.15	1,900	2,670
11	500	—	98.10	2,300	2,600
12	500	—	106.80	3,180	1,900
13	—	2	90.00	1,600	2,670
14	—	—	3.80	2,000	1,900
15	—	—	4.73	2,880	2,210
16	—	—	4.74	3,100	2,100
17	—	—	3.82	2,600	3,000
18	500	—	16.76	2,700	2,300
19	500	—	23.00	1,920	2,280
20	—	—	trace	2,000	2,120
26	—	5	—	—	—

At the end of the third week marked improvement was observed in the patient. The voice had come back to normal. Report of the E.N.T. examination was that the larynx was of infantile type and vocal cord moving well. The blood coagulation time was reduced to 4 minutes and 30 seconds. The abdomen was no longer painful on palpation and the blood in the stool was found only to be a trace when tested with benzidine. The capillary resistence test produced only three petechiae on the same area. The blood pressure had come up to 130/88, F.S. = 84 mm. Hg., that is, arterial sound absent. The skin of both legs was loose and wrinkled, not unlike the abdominal skin of a women after delivery (see photographs of the legs). The movement of the diaphragm showed definite improvement. When it was screened on 13th July, 1937, the movement was very limited and the patient could not hold his breath for more than a few seconds (approximately 5 to 10 seconds) due to loss of diaphragmatic tone

24:7:1937

Sitting position, right lateral view.



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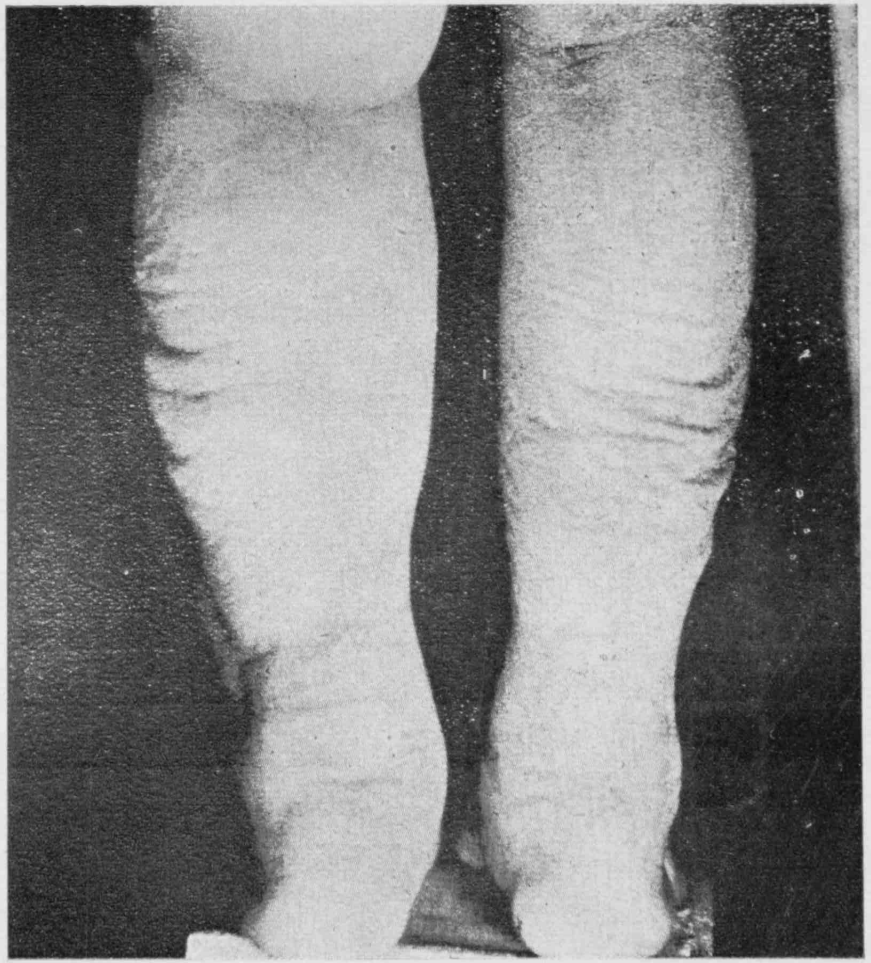
Standing position, posterior view.



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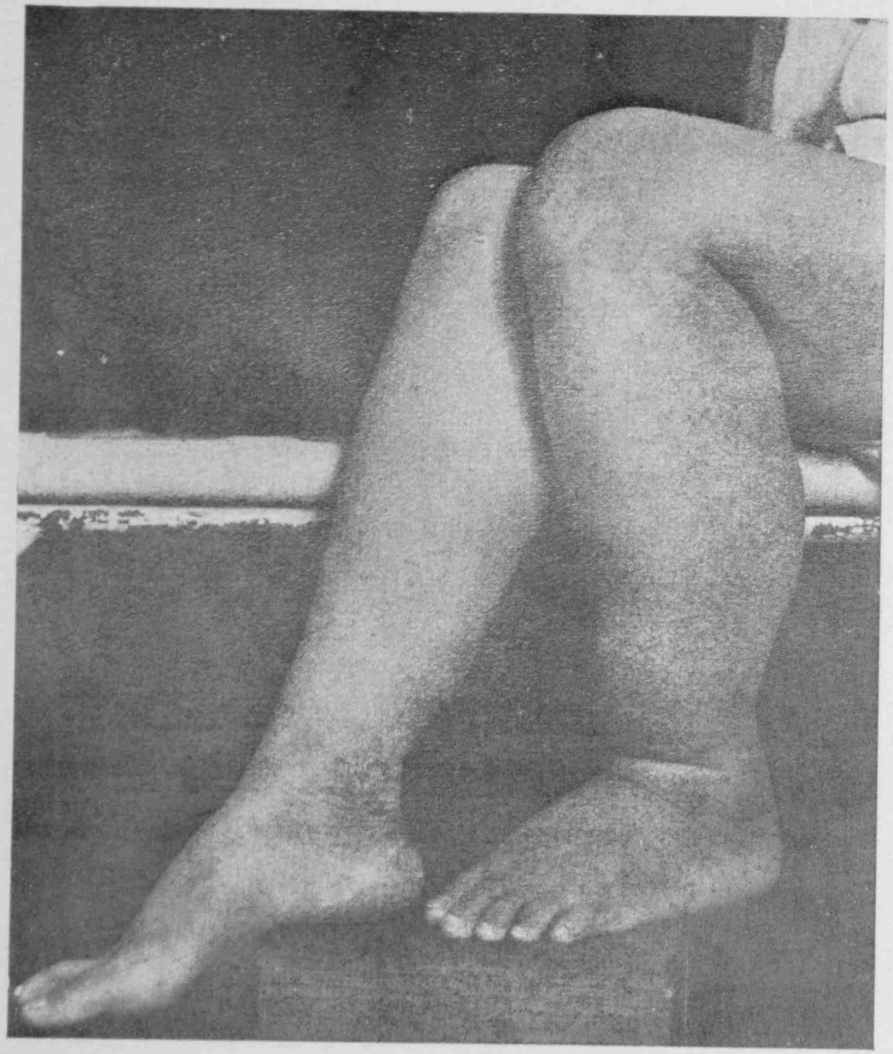
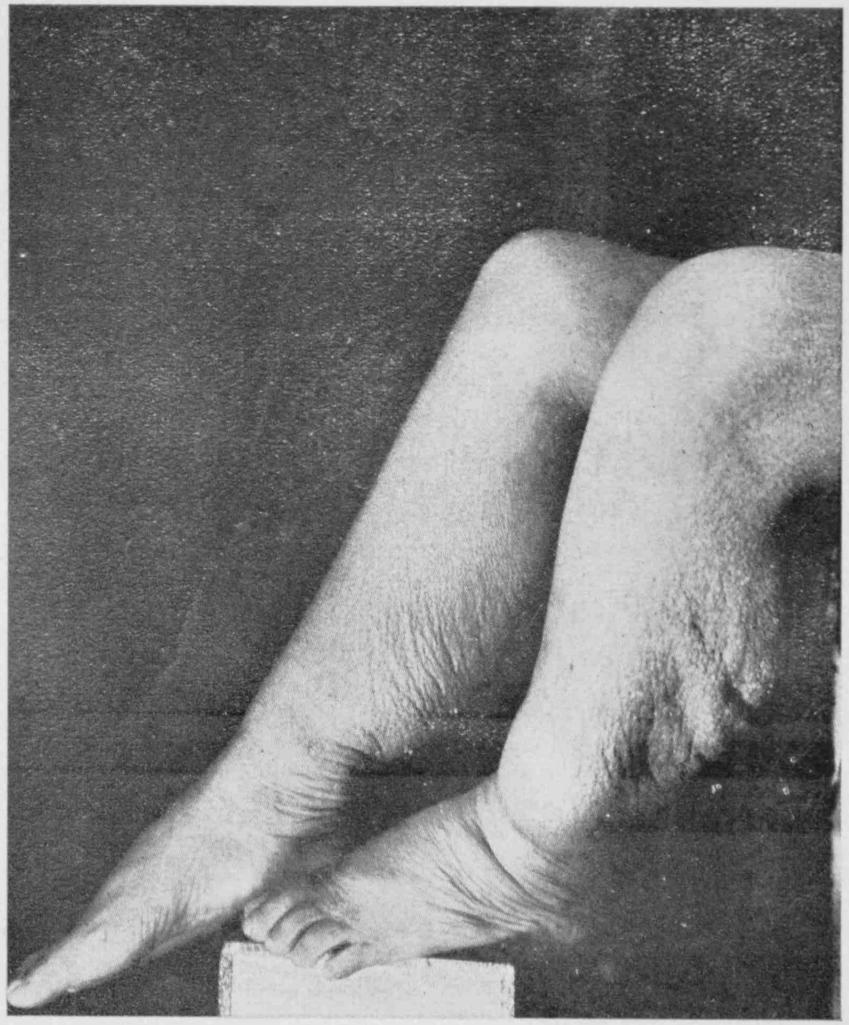
Sitting position, left lateral view.



Showing condition of the limb on the 5th day of treatment. Circumference around the calf, measured from a point 10 cm. from the lower border of patella bone: right calf 29.5 cm.; left calf 40 cm.

24:7:1937

Sitting position, left lateral view.



Showing condition of the limbs 21 days after treatment. Circumference of the calf measured from a point 10 cm. from the lower border of patella bone: right calf 21.6 cm.; left calf 36 cm. A reduction of 7.9 cm. and 4 cm. (In the right and left calves respectively) from previous measurements. Note wrinkling of the skin due to excessive dehydration of tissue fluid.

and the tumulteous movement of the enlarged heart. Three weejs later, the upward and downward movement of the diaphragm on forced breathing had improved from half an inch to one and a quarter inches. The level of the diaphragm had come down from 9th to the 10th posterior rib, and the transverse diameter of the heart was reduced by 4.5 cm (see X-Ray No. 2154 and 2387). The urine had become clear and free from urinary casts. He was discharged as recovered from B_1 and C deficiency after 2 months' stay in the hospital.

Comment: The improvement of elephantiasis of limbs in this patient suggests very strongly that vitamin B_1 and C are concerned with the proper maintenance of the water-balance of the tissue fluid, and that there is an element of unequal water-retention in the production of elephantiasis which, in the past, has been unreservedly attributed to lymphatic obstruction.

Case 2456, a sailor, aged 27, was admitted into the hospital at 1.20 p.m. on 15th July, 1937.

Chief complaint:—Severe respiratory and circulatory distress for 13 hours.

Diagnosis:—Fulminating beri-beri.

Treatment:—I.V.I., 7 mgs. of Betabion and complete rests.

Result:—Recovery.

History:—During the last 6 months he had palpitation, dyspnoea and oedema of legs. The oedema around the ankles and feet was more marked during the day. Sometimes he felt pain in the calf muscles while at work, and became easily tired. His appetite had been poor for the previous 6 days, consuming only one bowl (instead of the usual 2 or 3) of rice at each meal.

He said that the onset of the acute symptom was sudden. It happened during a dinner party at which alcohol was being freely taken at 1 a.m. (on day of admission) when he became dyspnoeic.

Condition on admission:—When first seen in the ward he was very restless and dyspnoeic. His fingernails and lips were cyanosed. The breathing was rapid—40 per minute. He complained of difficulty in breathing and tried to help the respiration with his hands. He could not keep still and was continually shouting and throwing himself about on the bed. His alae nasi were widely dilated and his mouth was parched. The veins at the root of the neck were markedly engorged and the strong and diffused pulsation over the entire precordial and epigastric areas gave evidence of severe cardiac failure.

Systolic murmur was present in all the vulvular areas, and the 2nd pulmonary chart sound was markedly accentuated. The pulse was weak and rapid, 154 per minute. The blood pressure could not be accurately estimated because of his extreme restless condition, ?100/?60 mm. Hg. The lungs were free from adventitious sounds and his mind was clear. When told that it would be better for him to keep still instead of being so restless, he replied that he could not help it. The constant presence of the sense of constriction around the chest prevented him from breathing freely and the violent movement of the heart gave him much discomfort and was at times painful.

In the family history or in the history of his past illnesses there was nothing of importance to record.

Diet:—On board the ship he had two heavy meals a day. For a group of 8 to 10 people the diet consisted of:—

1 bowl of vegetable soup containing a little fish or other meat as conveniently varied from day to day.

1 plate of leafy vegetables lightly fried in oil (6 ounces).

1 plate of fish or pork or other meat prepared differently from to day (4 ounces).

1 small plate of salted bean curd, or salted fish or salted eggs (4 to 5 eggs).

Rice of unlimited amount.

He said that in the ship on which he was working there were several members of the crew working in the engine room and on deck who had oedema of legs, and that he would not have been so seriously ill had he taken measures customarily advised, i.e., eating large quantities of boiled peanuts.

Physical examination:—The physical examination was delayed until the acute phase had passed off, i.e., 24 hours after treatment The lungs were clear. Radiological examination of the heart showed enlargement to the right and left. The liver was just palpable below the costal margin. Pitting oedema was slight on the ankles and dorsum of feet. The calf muscles were markedly tender to deep pressure. The knee, biceps, and triceps jerks off were absent. There were loss of cotton wool touch on the lateral aspect of both legs and hands.

Laboratory examination:—The blood B.B.S. and pyruvic acid values before treatment were 13.2 and 5.77 mgs./100g. respectively. Twenty-four hours after I.V.I. of 5 mgs. of Betabion, their values were B.B.S. 7.9 mgs. and pyruvic acid 0.84 mgs./100g.
Cerebro-Spinal Fluid: B.B.S.: 7.2 mgs./100g.

Pyruvic acid: 2.96 mgs./100g.

Blood: Wassermann's reaction + +; Kahn's test —; sugar 92 mgs. per 100 c.c.; N.P.N. 30.6 mgs.%; urea 8.6 mgs.%; uric acid 2.5 mgs.%; r.b.c. 5,074,000 per c.mm.; w.b.c. 10,700 per c.mm.; Hbl 19.3 g/100c.c.; colour index 1.0; differential count (200 cells counted); neutrophils 78%; eosinophils 3%; lymphocytes 16%; monocytes 3%.
Urine: Colour, lemon yellow; reaction, acid to litmus paper; specific gravity, 1,010; albumin +; sugar, nil; w.b.c., nil; r.b.c., nil; epithelial cells, +; granular casts, a few; hyaline and blood casts, nil.

Treatment:

15-7-1937,

At 1.20 p.m. (on admission) he was given 2 mgs. of Betabion intravenously and 40c.c. of blood were drawn from the midcubital vein. 20c.c. of cerebro-spinal fluid were removed slightly under pressure.

At 3.30 p.m. patient collapsed, breathing almost stopped, and pulse hardly felt at the wrist. Immediately he was given intracardiac injection of 1 mg. adrenaline hydrochloride, artificial respiration and venesection of 400c.c. of blood from the external jugular vein, and followed by 5 mgs. of Betabion into the same vein.

At 3.45 p.m. patient's breathing became deep and prolonged, 14 per minute. The pulse was perceptible at the wrist.

At 4.00 p.m. patient regained consciousness, but his mind was still dazed.

At 6.00 p.m. he complained of discomfort in the chest and pain at the back of his head. He was restless and dyspnoeic. The respiratory rate increased again to 36 per minute.

16-7-1937. There was no more dyspnoea, but patient still complained of headache and unlocalised pain in the abdomen from the epigastrium downwards. His bowels had not moved since admission. He felt drowsy and wished to be left alone. The blood pressure was 120/70 and F.S. 50 mm. Hg. The oedema of legs had completely subsided. The muscles of the lower limbs were weak and markedly atonic.

27-7-1937. He was found trying to create discontent among other patients in the wards and was immediately discharged. His condition had considerably improved; he was able to walk slowly when supported; appetite good; pulse rate 80 per minute; blood pressure 120/70 and F.S. 66 mm. Hg., and the blood pyruvic acid 0.58 mg./100g.

Comment: This case clearly shows that the first dose of 2 mgs. Betabion is definitely insufficient and that venesection 40 c.c. of blood as a mean of relieving the strain of the right side of the heart is

ineffective. The minimum dose, therefore, for fulminating beri-beri should be at least 5 mgs. of Betabion. A number of out-patient cases have received a 5 mg. dose of Betabion and showed no ill effect with the exception of one case who had a spell of gidiness for 10 minutes immediately after intravenous injection.

Intracardiac injection of adrenaline, venesection of 400 c.c. of blood and artificial respiration were responsible for the restoration and maintenance of respiratory and vascular circulation until Betabion had time to take effect (5-10 hours). Had these measures not been taken I doubt if patient would have recovered.

Case 2236, a school boy, aged 12, admitted to the hospital on 30th July, 1937.

Chief complaint:—Dyspnoea and restlessness for two days.

Diagnosis:—Fulminating beri-beri.

Treatment:—I.V.I. of Betabion 5 mgs.

Result:—Died of respiratory failure.

History:—The history was obtained from the father who said that his son had slight oedema of legs, palpitation, dyspnoea and weakness of limbs on slight exertion for 5 months. His appetite had been poor during the last four days. Two days before admission he suddenly became dysphnoeic while playing. The discomfort in the chest, caused by violent movement of the heart, became at times very painful, and gave him no peace at night. In the last 24 hours vomiting and retching were frequent, adding further to his discomfort. The vomit was not bile stained, and the amount was small.

Condition on Admission:—The oedema of legs was not noticeable on inspection, but showed pitting on pressure at the ankles and dorsum of feet. He was extremely restless, shouting and tossing himself about on the bed. The pulse rate could not be counted being very weak and rapid. The heart sound had a tic-tac rhythm. The respiration was shallow and rapid. The lips and finger nails were cyanosed. Quite suddenly he gave a struggle for want of air; and before anything could be done for him, he fell back unconscious. Except for inspiratory movements at long intervals the respiration had almost ceased. The pulse could no longer be felt at the wrist; and only examination with the stethoscope showed that the heart had not completely failed.

Treatment: 1 mg. of adrenaline hydrochloride was injected straight into the heart. Simultaneously artificial respiration was administered and venesection from the external jugular vein was carried out. Immediately after 400 c.c. of blood was withdrawn, 5 mgs. of Betabion were given by the intravenous route. The cerebrospinal fluid was clear and drawn under pressure.

Ten minutes later, patient's breathing became stetorous and convulsions occurred every 7 minutes. Each attack lasted for ½ minute spreading from below upwards. During the convulsions the legs were stretched, the back and head arched forward, the mouth tightly closed, the fists clenched and the upper extremities rigidly flexed.

He died two hours later without regaining consciousness.

The finding of the blood examination was as follows:—

	No organisms found.
C.S.P.:	B.B.S. 4.2 mg./100g.
	Pyruvic acid 1.0 mg./100g.
Blood:	B.B.S. 11.2 mgs./100g.
	Pyruvic acid 2.22 mgs./100g.
	Sugar 32 mgs./100 c.c.
	N.P.N. 72 mgs.%.
	Urea 14.2 mgs.%.

Comment: This is one of the few cases in record that have low blood sugar, slight increase of non-protein nitrogen and blood pyruvic acid. The only distinguishing feature from the point of view of biochemical change is the high B.B.S. and non-protein nitrogen.

Intracardiac injection of adrenaline, venesection and artificial respiration were responsible for the tempory recovery of respiratory and circulatory failure. Had these measures not been taken I think he would have died immediately on admission into the ward. But in this case he survived for 2 hours.

DISCUSSION.

Vitamin B_1 deficiency in experimental animals has been produced under standarised conditions. Other factors than vitamin B_1 deficiency and associated minor deficiencies of other vitamins have as yet not been thoroughly investigated.

In human beings these factors are many and variable. The composition of foods, the function of internal secretory glands, the intensity of muscular work, the association with pregnancy, the accompaniment of febrile diseases, and the time element in the development have an important influence on the clinical picture of beri-beri.

Association with other Vitamin Deficiencies.

A diet deficient in vitamin B_1 most probably is also deficient in other vitamins e.g., vitamin A, C, etc. Critical investigation of the diet in the lower class of Chinese people bears out this truth. The fault usually lies in the quality rather than the quantity of food consumed. Consequently pure vitamin B_1 deficiency in man is rare or not found at all. Pre-clinical manifestations of vitamin A, B_2 and C deficiencies are often found in beri-beri patients, such as dry pigmented and unhealthy skin, perléche (i.e., chronic ulceration at the angle of the mouth), and gross unsaturation of ascorbutic acid in the urine of typical beri-beri as have been observed by Platt and Yang in 1935.

Further the association of multiple vitamin deficiencies often modifies or aggravates the symptom-complex of B_1 avitaminosis. Case 2269 is a typical example of acute beri-beri associated with vitamin C deficiency. It shows that if both vitamins B_1 and C are lacking in the diet, the symptoms of B_1 deficiency appear first, and then later, those of vitamin C deficiency; but if the acute sypmtoms of B_1 deficiency have developed, symptoms of vitamin C deficiency would be masked together. Not until the appearance of numerous petechiae, as demonstrated by the capillary resistence test and the absence of ascorbutic acid in the 24 hours urine was the association of vitamin C in the particular patient (case 2260) found out.

Association of Hypofunction of Liver.

Literature on B_1 deficiency produces abundant proof that the liver undergoes atrophy which is to some extent masked by passive venous congestion. The histological picture gives at times evidence of necrosis, cloudy swelling and fatty degeneration of liver cells. In the findings of some workers on experimental animals, the glycogen content showed a marked fall. Case 2236 had a blood sugar of 36 mgs./100 c.c., thus giving strong evidence of severe depletion of liver glycogen which sometimes occur in the last stage of acute beri-beri.

Association of Fever in Fulminating Beri-beri.

It is well to remember that the presence of sepsis in mild diabetes precipitates the onset of coma. Likewise, sepsis precipitates the onset of fulminating beri-beri and is highly fatal. The pyruvic acid is usually below 2 mgs. but with a marked increase of B.B.S. of 10 mgs. or more per 100g. blood.

In the past Platt experienced failure in effecting a cure on cases complicated with fever (Annual Report, Henry Lester Institute, 1936). The occurrence of hypoglycaemia sometimes met with in the last stages of beri-beri led me to modify the treatment of one case of febrile fulminating beri-beri, and the result obtained was most encouraging.

Case 2602 was a school boy, aged 17, and had history of oedema of legs on and off for 6 months and palpitation on exertion. Twenty four hours before the acute onset he felt slightly indisposed. In the same evening he became dyspnoeic. On admission into the hospital his pulse was 144 per minute; rectal temperature 105.6°F., breathing 40 per minute. He was restless; and he had many attacks of vomitting but no vomit was brought up. Blood pressure was 120/70. F.S.=0 mg. Hg. Septic sores and slight inflammation on both legs were noticed. Probably this might have accounted for the rise of temperature. Culture made from the pus produced colonies of staphylococci. The blood pyruvic acid was 1.92 mg. per 100g.

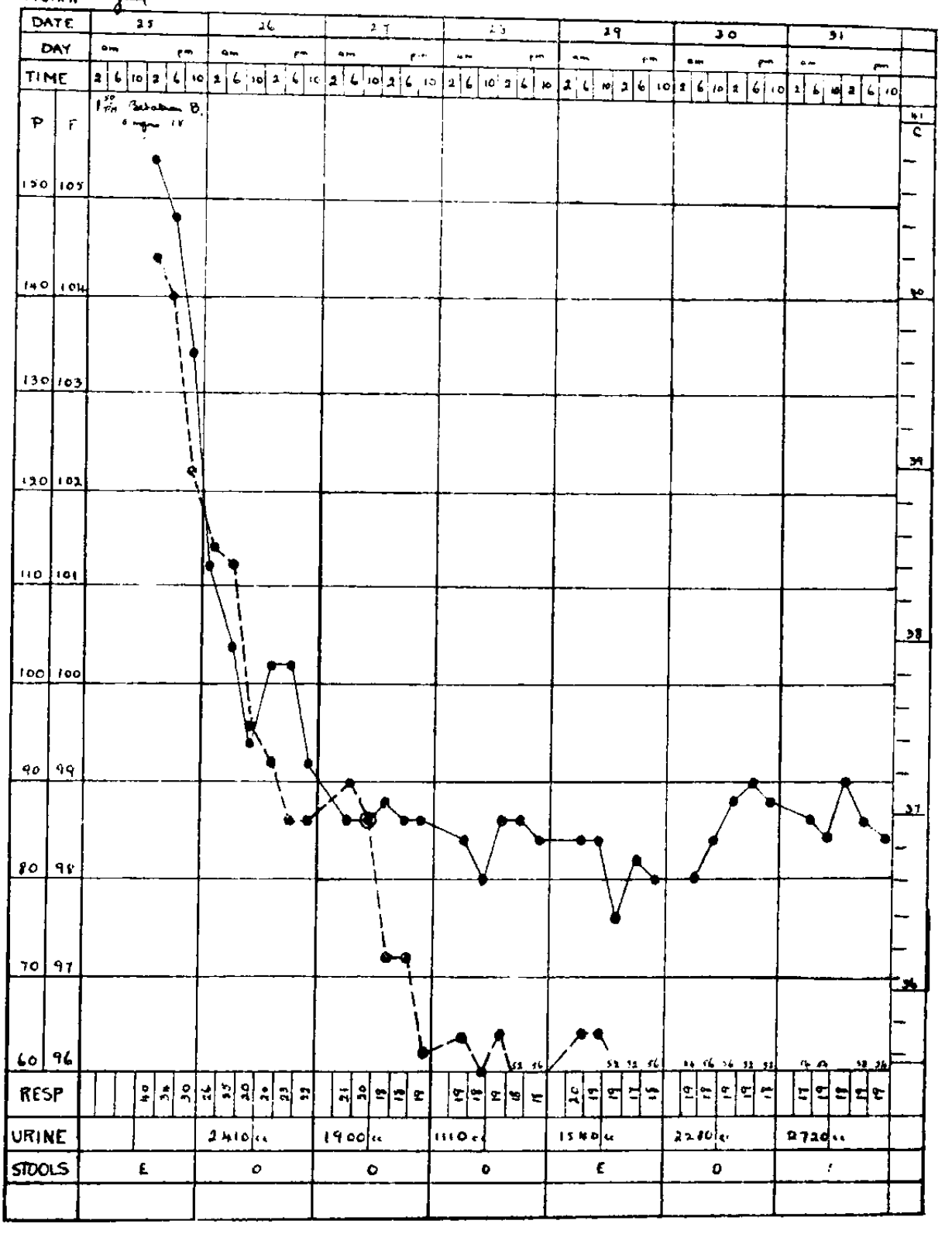
He was treated with I.V.I. of Betabion 5 mgs., 6 c.c. of 30% sucrose solution by mouth every 15 minutes, and boracic fomentations were applied every four hours to the septic legs. He consumed 868 gms. of sucrose in 12 hours. Within 36 hours of treatment, the patient's temperature and pulse came down to normal (see temperature chart). The fall of the temperature was too dramatic to be a coincidence. He made an uneventful recovery and was discharged 6 weeks later.

Following the unexpected recovery of this case, I made some observations on the effect of oral and parental administration of sugar on the non-fulminating beri-beri patients. During the period of

1939

Case 2602 Febrile Fulminating Beri-beri

Month July



(●—●—●) Temperature

(●·····●·····●·····●) Pulse rate

observation they were strictly kept on complete rest, and fed on the same diet. They were divided into three groups.

One group was used as control, and no sugar was given. The pyruvic acid value was estimated on the same day as the other two groups.

A second group was given 60 c.c. of 30% sucrose solution by mouth every 2 hours from 6 a.m. to 6 p.m. for a week. During this period, patients showed increased excretion of urine and the oedema to a certain extent subsided. The pyruvic acid level showed slight increase, but never reached the value of the fulminating type, i.e., 3 mgs. and above. This increase in pyruvic acid could not entirely be attributed to sucrose for some of the control cases also give similar increase; and the difference of increase in the two groups was not significant.

To the third group 100 c.c. of 50% glucose in normal saline was given intravenously. No ill-effect was observed. Five minutes after the injection, the pyruvic acid level dropped to half of the original value, but rose up again after 30 minutes.

This observation differs from that obtained in experimental dogs fed on vitamin B_1 free diet. Increased consumption of carbohydrate hastened the appearance of beri-beri symptoms in these animals in the form of anorexia. But it must be remembered that the diet of the patients under observation contained 150 to 200 I.U. of vitamin B_1 while the food of experimental dogs was completely free from B_1. This probably accounted for the different effect of increased carbohydrate consumption in clinical and experimental beri-beri.

The symptom complex of beri-beri has been variously explained by different investigators but not one explanation has been met with universal acceptance. Some consider that it is due to a toxaemia of intestinal or bacterial origin; and others to that of a metabolic derangement. As the febrile fulminating beri-beri cases have been in the past considered invariably fatal (Platt) it is interesting to note that Case 2602 has been treated with sugar therapy in conjunction with vitamin B_1 administration with a surprisingly successful result. In this connection it is instructive to point out that in the terminal stage of acute beri-beri there is, at times, a state of hypoglycaemia (Case 2236). It appears that there is a definite connection between the two types of cases; and in view of this I suggest that a more extensive trial of giving sugar should be carried out in those otherwise fatal cases, especially as there is definite proof to show that glucose is an undoubted hepatic protector and an excellent diuretic for the kidneys.

Evidence of Biochemical Disturbance of the Brain in B_1 Deficiency.

Lately biochemical disturbance of the central nervous system has been suggested for some of the symptoms of vitamin B_1 deficiency.

Church (1935) has shown that the appearance of altered vestibular function precedes other neurologic symptoms in B_1 deficient rats. The functional change is referable to a biochemical change in the vestibular nuclei.

Peters 1935 a, b) and his associates have also shown that in vitamin B_1 deficiency the oxygen utilisation of the brain is reduced, while the pyruvic acid and B.B.S. formed are considerably increased. The degree of biochemical change is not the same in all parts of the brain. These workers suggest that the polyneuritic symptoms of avitaminosis in the rats and pigeons are of central origin.

It will be remembered that persistent vomiting is one of the constant features of fulminating beri-beri; and it is one of the earliest symptoms to disappear after injection of vitamin B_1. The increase of pressure, the accumulation of metabolites in the cerebro-spinal fluid, and the absence of permanent change of the central nervous system following recovery seem to show that the biochemical disturbance, rather than the organic degenerative lesions, is responsible for some of the fulminating symptoms.

Water-balance Maintaining Action of Vitamin B_1.

The only B_1 vitaminous tissue, other than the brain, which shows defective oxygen utilisation, is the renal tissue. It may be that this renal defect and the accumulation of non-protein nitrogenous substances sometimes found in the blood of acute beri-beri (e.g. case 2236) may cause a derangement of the water-balance of the body tissue which leads to oedema. The associated cardiac deficiency is also a factor which hastens or aggravates the appearance of oedematous beri-beri. In support of the dysfunction of the kidney is the diminution of urinary excretion during the acute stage and the occasional trace of albumin and granular casts in the urine of beri-beri. The dramatic effect in the relief of oedema of beri-beri or of a case of generalised oedema due to unknown causation with I.V.I. of 5 mgs. of *Betabion* may explain the water-balance action of vitamin B_1.

The Significance of B.B.S. and Pyruvic Acid in B_1 Deficiency Blood.

Of the two methods of quantitative estimation of pyruvic acid, the hydrazone determination is the better, for the simple reason that the substances containing an aldehyde or ketone group will form part of B.B.S. Therefore, it is not surprising that an increase of B.B.S. has been found in other conditions than B_1 deficiency by Wilkins *et al* (1937), and Wilson (1937) in cases such as acidosis, ketosis, anoxaemia and toxaemia.

A normal resting blood pyruvic acid does not exclude beri-beri. To do so is to go against clinical manifestations of the case. It simply suggests that the body is at equilibrium during complete rest and becomes unbalanced on the slightest exertion.

In the present stage of pyruvic acid investigation in clinical beri-beri, it is not possible to classify the degree of B_1 deficiency from a single determination of blood pyruvic acid; and to do so at this stage is fraught with difficulty and danger of mis-interpretation.

The difficulty one finds in interpreting and in assessing the significance of an isolated estimation of blood pyruvic acid is much the same as one finds in giving any significance to a single determination of blood sugar in latent, mild and moderate diabetes. A normal value of resting blood sugar cannot exclude the possibility of diabetes, no more can similar value of blood pyruvic acid exclude beri-beri. It is only by estimating and comparing the blood sugar curves produced in gluco-tolerance tests of the normal and of the diabetic that one realises the value and information derived from blood sugar estimation. In like manner, until one produces blood pyruvic acid curves of similar value, an isolated estimation of blood pyruvic acid will lose much of its significance and it may be futile for one to attempt its application in clinical medicine.

CONCLUSION AND SUMMARY.

1. The upper limit of blood pyruvic acid in a normal individual at rest is 0.7 mg. per 100 g.

2. Increasing values of day to day estimation of blood pyruvic acid are shown in the rapidly developing forms of acute beri-beri.

3. The blood pyruvic acid of the non-febrile fulminating beri-beri is significantly higher than the normal value.

4. Fulminating beri-beri requires treatment of massive doses of crystaline B_1, preferably given into the vein. A single dose of 5 mgs. of vitamin B_1 is sufficient to bring down the blood pyruvic acid level to normal in 15 to 20 hours. The time also corresponds with the remission of acute symptoms. In cases that fail to respond to vitamin B_1, the normal level is not reached and intense dyspnoea is the terminal picture.

5. Considerable increase in B.B.S. and pyruvic acid to the amount of 13.2 and 5.77 mgs. per 100 g. blood respectively has been obtained from fulminating beri-beri. The increase of B.B.S. may not be entirely due to pyruvic acid. This is so in cases complicated by pyrexia of 103° F. or more; the B.B.S. are usually more than 10 mgs. with a pyruvic acid value of less than 2 mgs. per 100 g. of blood.

6. The blood pyruvic acid curve and the vascular syndromes obtained by the injection of adrenaline reveal two different informations. The former gives information of the vitamin B_1 reserve of the patient while the latter indicates the tone of blood vessel wall. Therefore to find the true state of vitamin B_1 deficiency in a patient it is

advisable to perform the blood pyruvic acid adrenaline test, just as one would do a glucose tolerance test in a patient who suffers from glycosuria.

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Review of Books

A Manual of Practical Anatomy by J. Ernest Frazer and R. H. Robbins. Bailliere Tindall & Cox. 10/6 per volume.

The authors seek to give the student in manageable compass a guide to all that he should acquire from his course of study in the dissecting room. Two volumes contain instructions for the study of respectively the limbs and the abdomen and of the thorax, head and neck and central nervous system. The first volume is of 535 pages and the second of 455.

A stimulating and novel presentation will be expected from the pens of Professor Frazer and his colleague at St. Mary's by those who are familiar with "The Anatomy of the Human Skeleton" and the "Manual of Embryology." Reminders of both occur frequently in this new Manual.

Descriptions of the surface anatomy precede the sections on the different regions; these descriptions are short but informative.

Another welcome feature to be found in many places in these two volumes is a general description of a region, preceding the instructions for dissection and detailed accounts of individual structures. The axilla furnishes an example, and the description of the axillary sheath is novel.

In the descriptions of certain joints the authors have excelled. The hip-joint is presented in a vigorous way, not as a separate entity but in its relation to surrounding structures and the result is informative to a degree. The presentation of the knee-joint with "primary" and "secondary" coverings of the joint cavity will do much to avoid confusion between the "synovial membrane" and the "capsule" of this joint.

The abdomen gives an opportunity for a fresh method of exposition. The description of the "stomach bed" follows a novel method of dissection and exposition of the complicated arrangement of the peritoneum in the stomach region. A short account of the development of the peritoneum should materially assist in the understanding of the greater and the lesser peritoneal cavities. Some delightful sketches accompany the descriptions of the liver, of the bile passages and of the peritoneal fossae. For the thorax a dissection is recommended which should be commended by the clinician. The sternum is removed entire and the structures which lie behind it are examined in situ. When one considers that the clinician is limited in his examination of the all-important mediastinum, save for X-rays, to the anterior approach this method seems that most likely to give the student a useful visual impression of the mediastinum. The details of the thoracic viscera follow in their place and are lucidly described with a wealth of diagram.

A feature to be regretted in this Manual is the very short description of the cerebral meninges and of the subarachnoid spaces. This treatment is the more remarkable because the membranes of the spinal cord are described perhaps with more than usual amplitude.

The description of the brain is shorter than is found in many dissecting room Manuals; but it seems to be adequate and there is little repetition. The brief account of the development of the brain should add to the interest as well as to the comprehension of many details. The anatomy of the sense organs follows the central nervous system.

Throughout, both volumes are most liberally illustrated not only with drawings of dissected regions, for which the term "conventional" will not be misunderstood, but with innumerable "thumb-nail" sketches. It is in these small sketches, sometimes very diagrammatic indeed, that the draftsmanship of Professor Frazer is to be recognised and they constitute a great deal of the merit in this Manual. To select a few examples: sketches of the atlas and its contiguous structures, of the cavernous sinus, of the pharynx and the larynx, of the arch of the aorta, are all excellent.

Each volume contains an adequate index and a glossary. This glossary is of somewhat unequal value: in some places it seems to serve the purpose of giving the new terminology to the student where the author has slipped into the use of terms more familiar (i.e. O.T.); in other places and indeed for the most part this glossary is intended to present the real meaning of words to the student. Whether the student has an educational background in the Classical languages or not, it can often help if he knows the true meaning of a word and the force of the simile that was in the mind of the fathers of Anatomy who first named and classified the structures that make up the body.

A Short Practice of Surgery. By Bailey and Love.—4th Edition 1938.

Publishers.—H. K. Lewis & Co., Ltd., London.

The limitations of this book are, to some extent, enunciated in the preface, from which one may conclude that the exposition of advanced surgery is not its object and that brevity in its compilation was always borne in mind. In order to condense its matter, illustrations and diagrams are more than plentiful, as the authors "feel confident of the value of illustrations to lighten and shorten the text." With this there can be little disagreement provided that the pictures are arresting and clear. There must be few people who, having read Bland Sutton's book on Tumours, do not carry permanent and vivid impressions of the exquisite drawings in that book. In the book under review one cannot avoid the conclusion that a number of the pictures are unnecessary and botchily inartistic. For one example

the representation of a gangrenous appendix might well do for a gherkin or a caterpillar. A short description would have served the purpose much better. This criticism applies in general to other coloured reproductions. The diagrams are on the whole more satisfactory, though several are very inadequate. For instance the one substituted for a description of Johnathan Hutchinson's method of dealing with an inguinal hernia is quite incomprehensible.

The written matter leaves one with the feeling that here is a synopsis which the authors have attempted to expand and have done so very unequally. Important aspects of surgery, especially those which would concern the student or practitioner not specially qualified in surgery, are very meagrely presented. The tonsils and their diseases are given one page. There is a well written section on hernia, but in discussing strangulation, with which condition any medical man might have unexpectedly to deal, there is nothing given about the all important points in the decision as to the viability of the gut, except an unimportant "tip." The chapter on appendicitis is good and there is a clear account of the Ochsner Sherren treatment of this condition, which is strongly advocated, but not dogmatically. Serious omissions are, however, in not stressing the necessity for subsequent removal of the appendix after draining an appendicular abscess, and all considerations as the optimum time for so doing. A similar type of omission is found in the section on treatment of head injuries. There is no mention of the important convalescent period after concussion of the brain; nor, indeed, any mention of treatment at all beyond that given in the first 24 hours.

Sixty-six pages are given to a moderately good account of the treatment of fractures. The main principles are well set out but the details are totally inadequate for practical purposes.

In summing up, one might well liken this work to the cheaper type of motoring map, on which most of the outstanding features of the country are depicted in very little detail. With its aid alone one may as a rule find the way, but from time to time there will be a very strong wish for the full information of the standard of an ordinance survey map, which standard should be the minimum for a text book.

Therapeutic Notes

TREATMENT OF ASTHMA BY ORAL INHALATION.

The symptomatic treatment of mild to moderate attacks of asthma by means of oral inhalation of adrenaline solution of a strength of 1 in 100 is described by Graeser and Rowe in their original article (*Journal of Allergy*, 1935, 6:415). These authors found that in many cases the physiological effect of adrenaline occurred with greater rapidity from oral inhalation of a 1 in 100 solution than when hypodermic injection of the 1 in 1,000 solution was used; side effects such as nervousness, and tachycardia, were rarely caused; and the discomfort and inconvenience of hypodermic injection could well be avoided. A preparation of the requisite strength for this treatment is now made available by Burroughs Wellcome & Co. as "Vaporole" Solution of Adrenaline, 1 in 100. The solution is sprayed into the mouth from an atomiser while the patient inhales deeply; dosage is adjusted to individual needs and is easily found by experience. Any atomiser delivering a fine, evenly-distributed spray may be used, but for effectiveness and durability, no better apparatus could be selected than the "Paroleine" Atomiser which has a stainless steel delivery tube and is of exceptionally robust construction throughout.

"Vaporoloe" Solution of Adrenaline, 1 in 100, is issued in amber glass stoppered bottles of 5 c.c.