Section VIII.

Further Observations on the Effect of Anterior Pituitary Extract in Alloxan Diabetes.

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Ogilvie (1949) concluded that crude ox anterior pituitary extract through its regenerative effect on the pancreatic islets brought about a marked temporary improvement of the persistent alloxan - diabetes in four of five rabbits. The preliminary production of such a permanent diabetes for subsequent treatment with anterior pituitary extract entailed the administration of alloxan to three pairs of littermates in a larger series of rabbits. Of the littermates, the first pair were both made persistently diabetic ; the second pair showed persistent and transitory diabetes respectively ; and the third pair both responded with transitory diabetes. The permanently diabetic members of the first and second pairs were described in the above publication (Section VII) as rabbits 42, 43 and 45, while the animals in the third pair, having recovered from their diabetes, were used in one case for injection with anterior pituitary extract and in the other as a control. The present work deals with the third pair of rabbits.

Material and Methods

The material and methods were the same as in Section VII except that (1) the animals were a pair of young, adult, male, English rabbits from the same/

same litter and (2) the size of the pancreatic islets was based on the examination of 300 unselected samples from the head, body and tail of each organ.

Results

Clinical data. Rabbit 38 had a normal blood sugar of 136 mg. per cent and received 100 mg. alloxan per kg. body weight on the 16th and 25th days (Fig. 1). It responded to the first injection of alloxan with a blood sugar of 238 mg. per cent. The hyperglycaemia lasted until the 33rd day and was accompanied by glycosuria and polyuria, but no ketonuria. The glycosuria was interrupted by a sugar-free period of 2 days following the second dose of alloxan and before and after this interval rose respectively to 8 per cent and 5 per cent.* The polyuria, although only moderate in amount, was followed after the disappearance of the glycosuria by a less markedly increased urinary excretion. The body weight fell slightly during the first period of glycosuria, but ended above the control figure. The daily food consumption was on the average very constant throughout the experiment. The second injection of alloxan had a doubtful effect in accentuating and prolonging the diabetic condition.

Rabbit 39 with a normal blood sugar of 138 mg. per cent was given 100 mg. alloxan per kg. body weight/

* These figures refer to the percentage of dietary polysaccharides excreted in the urine over a 24 hour period.

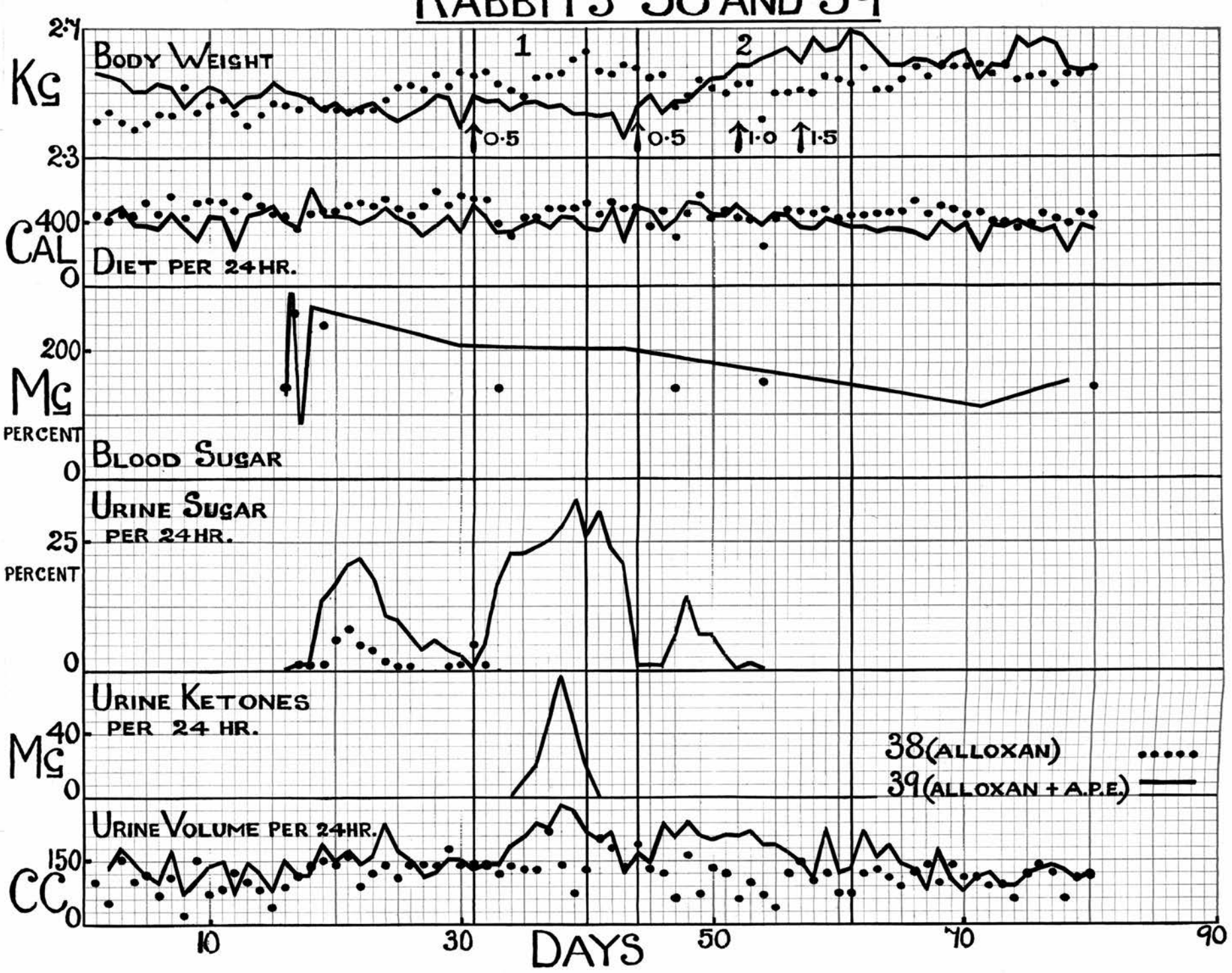
RABBITS 38 AND 39
BODY WEIGHT
1
2
0·5
0·5
1·0
1·5
Kg
2·7
2·3
CAL
400
0
DIET PER 24HR.
200
Mg
PERCENT
0
BLOOD SUGAR
URINE SUGAR
PER 24HR.
25
PERCENT
0
URINE KETONES
PER 24 HR.
Mg
40
0
38(ALLOXAN)
39(ALLOXAN + A.P.E.)
URINE VOLUME PER 24HR.
CC
150
0
10
30
DAYS
50
70
90

Figure 1.

weight on the 16th and 26th days (Fig. 1). It reacted to the first dose of alloxan with a blood sugar of 268 mg. per cent and then entered a phase of glycosuria and polyuria without ketonuria. Having risen to 22 per cent the glycosuria subsided to almost zero on the 31st day, while the polyuria at its height was moderately marked. The body weight during the earlier and later phases of the glycosuria respectively fell and then returned to normal. The diet was normal throughout the glycosuria. The second injection of alloxan had no obvious influence on the severity and duration of the diabetic state.

The animal thereupon received two courses of anterior pituitary extract. These lasted from the 31st day to the 40th day and from the 44th day to the 61st day and consisted in the daily administration during the first course of 0.5 g. anterior lobe per kg. body weight and during the second course of 0.5 g., 1.0 g. and 1.5 g. per kg. body weight for respectively 8 days, 5 days and 5 days. The first course resulted in glycosuria, ketonuria, polyuria and loss of weight. The glycosuria reached 33 per cent, but on withdrawal of the extract fell rapidly to a low level. The second course was characterised by glycosuria, polyuria and increase in weight, but no ketonuria. The glycosuria after touching 14 per cent fell to zero on the 54th day, while the increase in weight amounted to 10 per cent. The animal with the cessation of treatment returned to a normal urinary excretion and was finally still heavier than the/

the normal. The caloric value of the food consumed during the first and second courses was on the average respectively reduced by 2 per cent and increased by 5 per cent.

Histological data. These data refer to the pancreatic islets and ducts as follows :-

(1) Number and size of islets. Rabbits 38 and 39 were characterised by a marked diminution in the number and size of their islets. The exact amount of reduction numerically was indeterminable without actual islet counts, but a measure of the diminution dimensionally is given below on the section on regeneration.

(2) Atrophy of islets to groups of A-cells. This condition entailed the same stages in the reduction of the B-cells and the same arrangements of the remaining A-cells as described in Section VII. It involved many of the islets in both rabbits and in each of them had reduced about 5 per cent of the islets to small masses of purely A-cells (Fig. 2).

(3) Regeneration of islets was evident in enlargement, budding and a suggestive growth of new islets from the ducts.

(1) Enlargement. The average area of the islets in rabbit 38, rabbit 39 and the mean of 10 normal rabbits, estimated at a magnification of 145, amounted respectively to 0.59 sq. cm., 0.72 sq. cm. and 1.07 sq. cm., or 55 per cent, 67 per cent and 100 per cent. In other words, the islets of the rabbit injected with anterior pituitary extract, although/

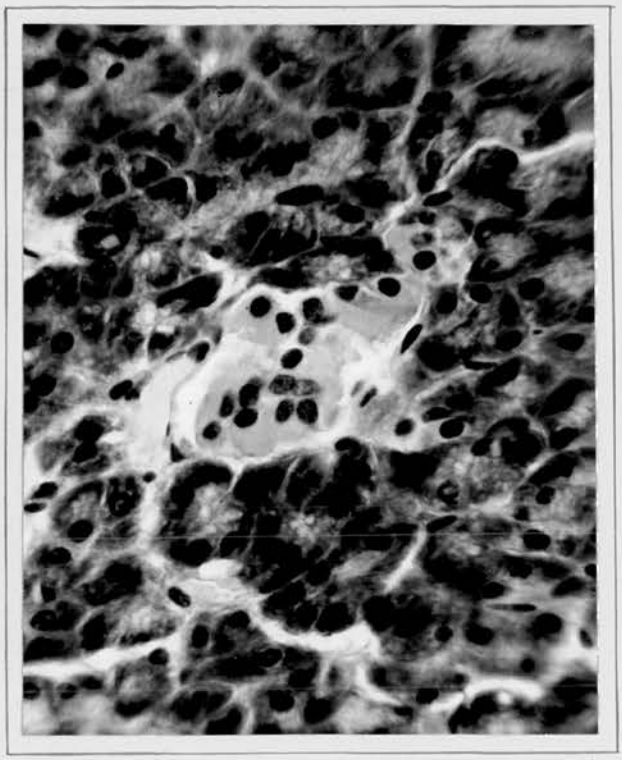

Fig. 2. Pancreas. Rabbit 38. The islet consists wholly of red-staining A-cells. Haematoxylin and Eosin. x 575.

although still abnormally small, averaged 22 per cent larger than those of the control (Figs. 3 and 4).

(ii) Budding. This phenomenon was described in Section VII. Budding islets always consisted of B-cells only or of mixed A- and B-cells, whereas purely A-cell islets were never so distorted as to suggest regeneration. As in the previous section, a feature of the budding islets made up of mixed A- and B-cells was again the frequent arrangement of the A-cells in one or two main foci indicating previous atrophy of the islets. Budding islets were observed in rabbits 38 and 39 to the extent respectively of 14 per cent and 26 per cent of the general islet population (Figs. 5-8).

(iii) Islets from ducts. The extent to which the islets and ducts remain attached to and become separated from each other has never been defined for the rabbit pancreas. At the same time, the fact that islets and ducts are not usually seen apposed to each other normally suggests that the islets frequently become detached from the ducts. Now, rabbit 38 showed only rare apposition of islets and ducts whereas a relatively large number of associated islets and ducts was observed in rabbit 39 (Figs. 9 and 10). The inference accordingly was that a normal relation of islets and ducts obtained in rabbit 38, while rabbit 39 suggested a growth of new islets from the ducts. Such islets in rabbit 39 were placed in relation to the/

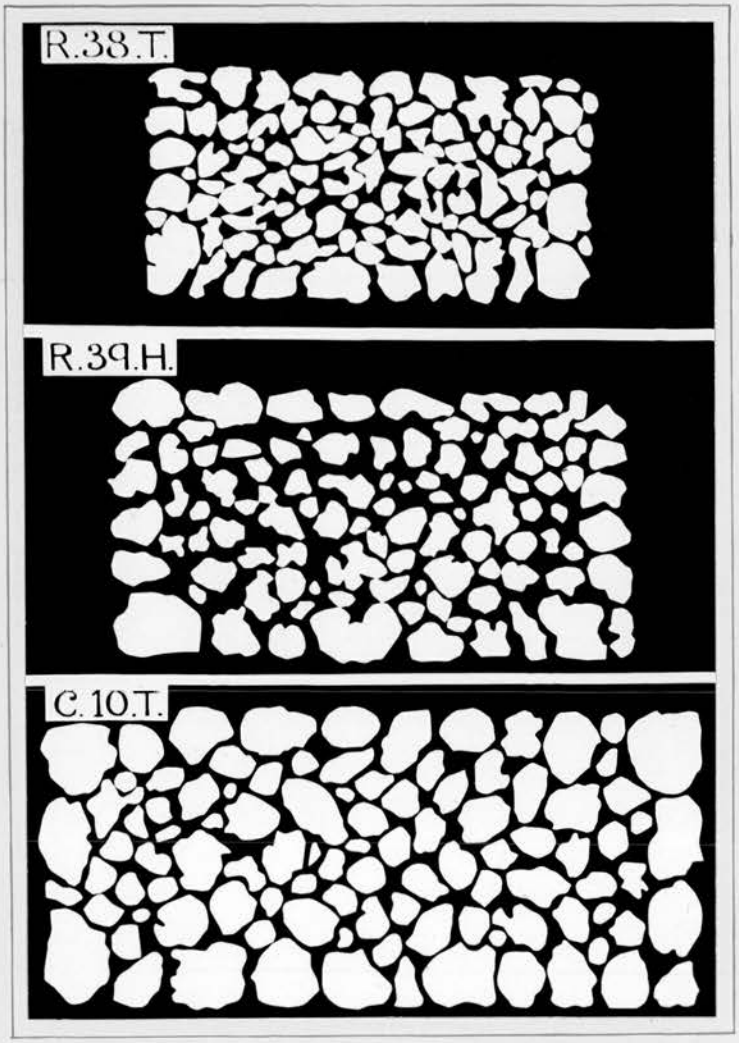

Fig. 3. The upper, middle and lower groups each consist of 100 unselected islets taken from the pancreas of respectively rabbit 38, rabbit 39 and a normal rabbit. The islets of rabbit 39, although abnormally small, are on the average larger than those of rabbit 38. x 35.

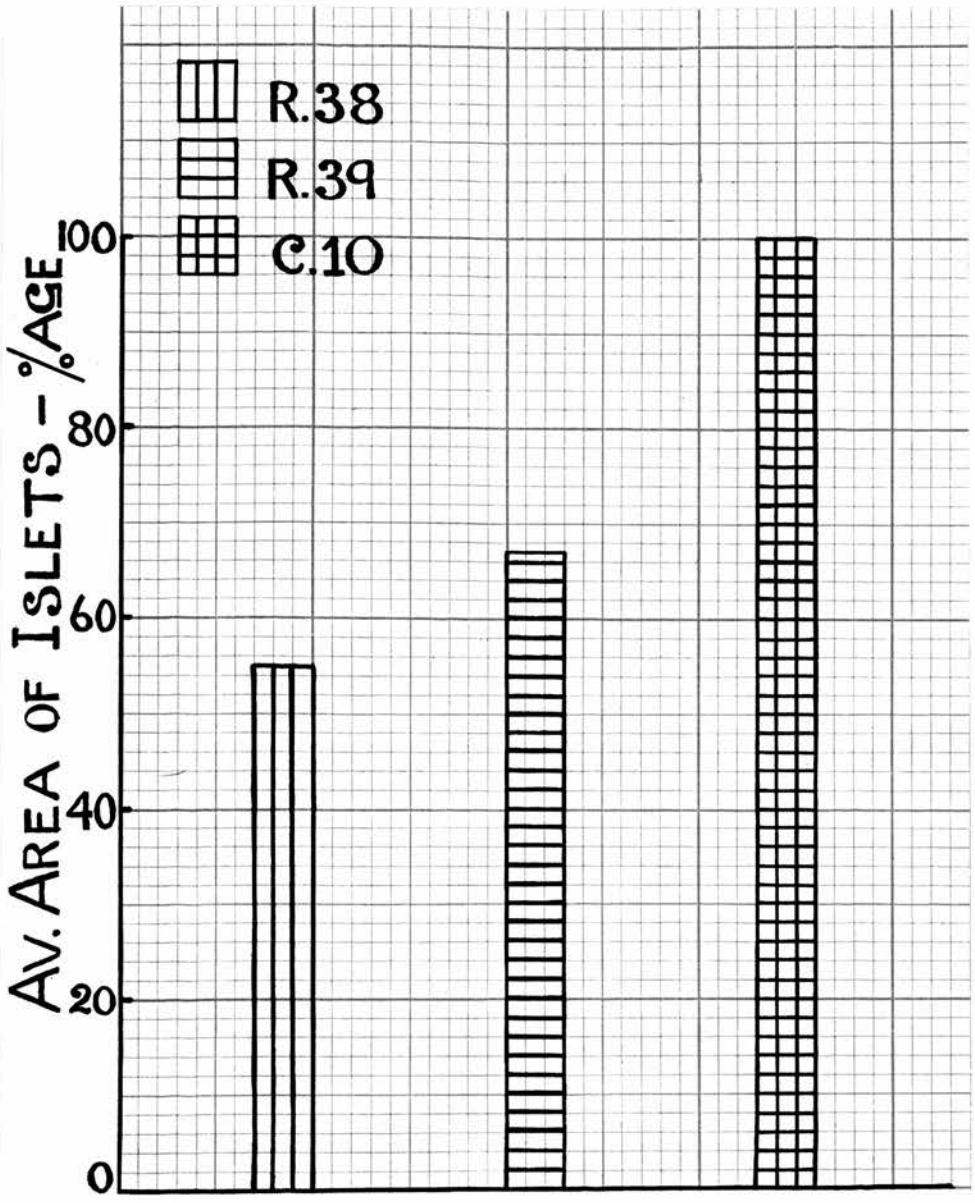

Fig.4. The columns represent the average square area (calculated as a percentage of the normal) of 300 unselected islets from rabbit 38, rabbit 39 and a normal rabbit.

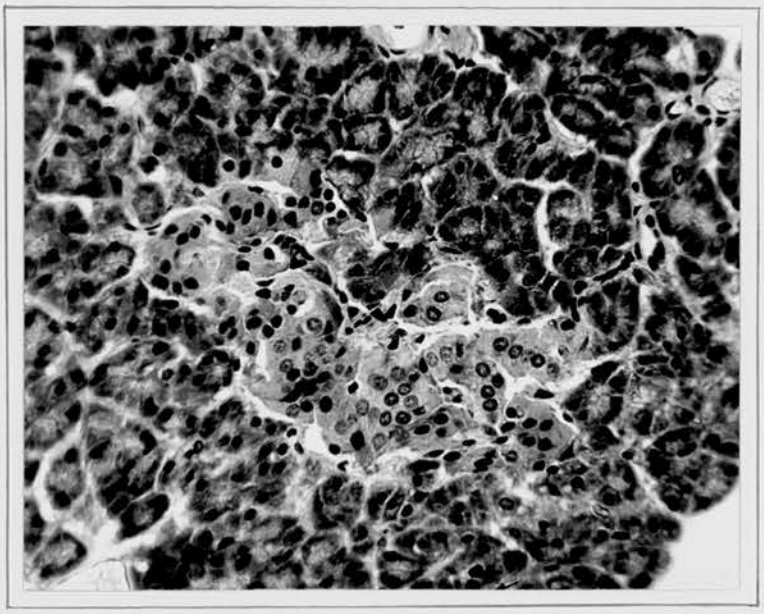

Fig. 5. Pancreas. Rabbit 38. The islet has thrown out short processes, especially along the upper margin. Haematoxylin and Eosin. x 300.

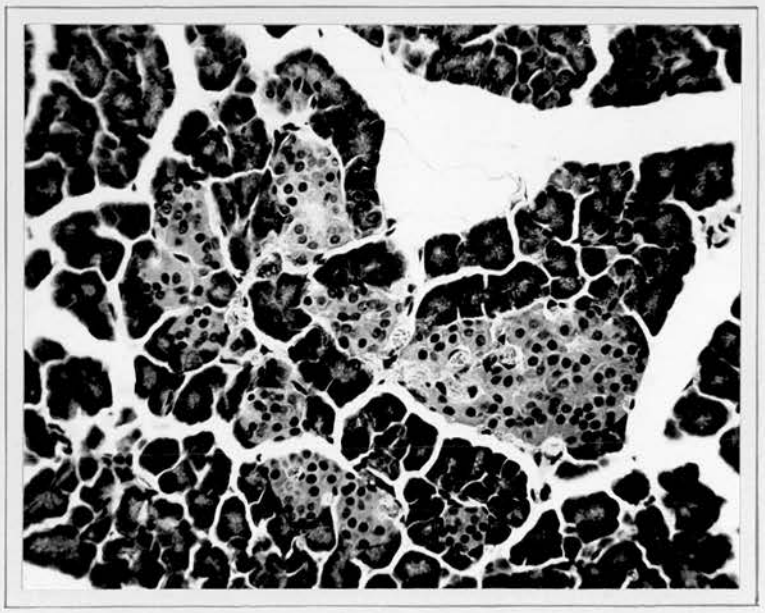

Fig. 6. Pancreas. Rabbit 38. The islets have budded at various points. Haematoxylin and Eosin. x 250.

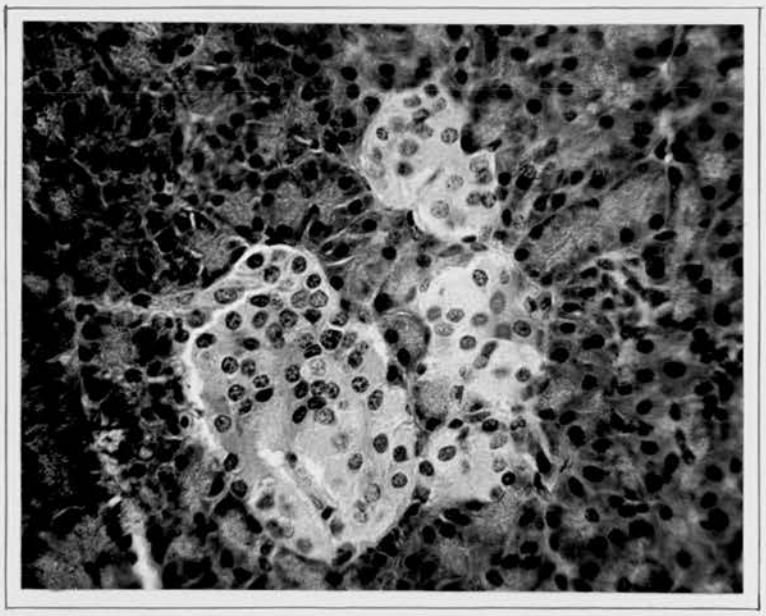

Fig. 7. Pancreas. Rabbit 39. The islet has given off a nodular process at its right lower margin. Haematoxylin and Eosin. x 375.

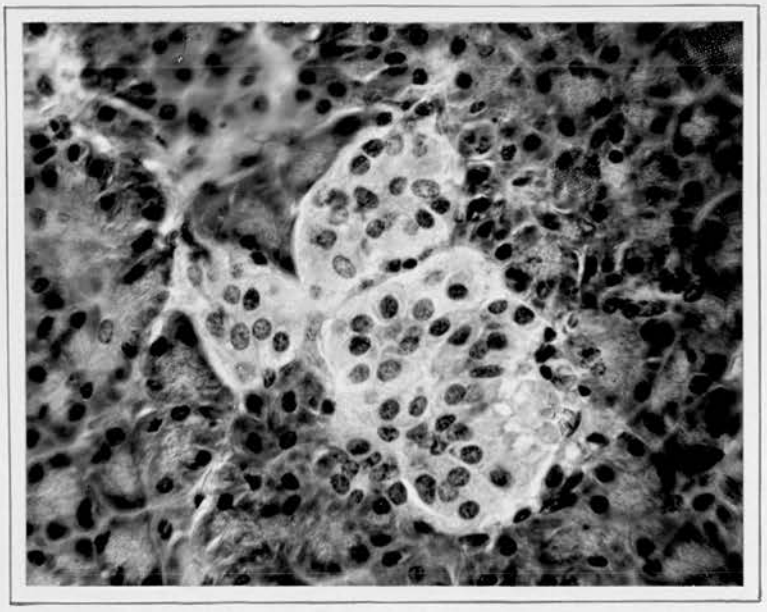

Fig. 8. Pancreas. Rabbit 39. The islet has budded on its left margin. Haematoxylin and Eosin. x 450.

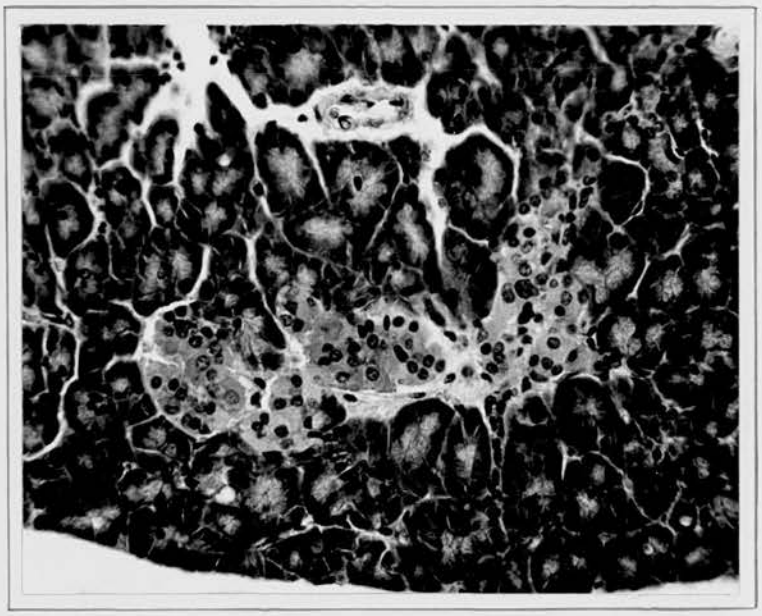

Fig. 9. Pancreas. Rabbit 39. The islet has arisen from the penicillar duct (bottom right) and has given off marginal buds. Haematoxylin and Eosin. x 300.

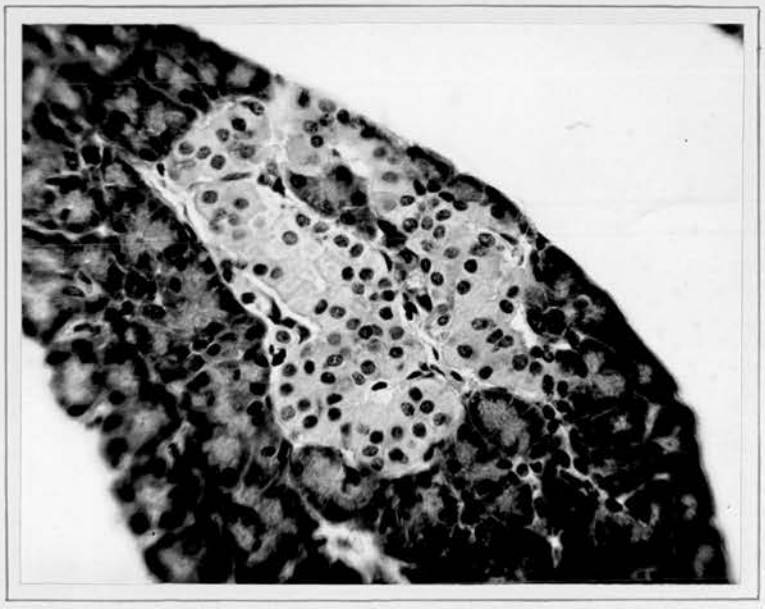

Fig. 10. Pancreas. Rabbit 39. An islet is seen in apposition with a penicillar duct (bottom right). Haematoxylin and Eosin. x 325.

the penicillar ducts, made up of B-cells only or of mixed A- and B-cells, and sometimes characterised by marginal budding. Neither of the animals showed any mitotic acitivity in either enlarged pre-existing islets or islets apposed to ducts.

(iv) A-cells and B-cells. Both of these cell types were histiologically normal with no evidence particularly of degranulation, hydrops or hyalinisation in the B-cells.

(v) Ducts. The interlobular and intralobular ducts of both rabbits 38 and 39 showed no degenerative or regenerative condition such as hydrops or local proliferation.

Discussion

Littermate rabbits 38 and 39 reacted to similar amounts of alloxan with a transitory diabetes of rather more severe grade in rabbit 39 than in rabbit 38. Now, according to personal observations, the same dose of alloxan (100 mg. per kg.) given to twelve English rabbits produced persistent and transitory diabetes in respectively seven and four animals, whereas one rabbit proved refractory. Rabbits 38 and 39 thus belonged to the lesser group of partly or completely resistant animals with rabbit 38 more refractory than rabbit 39. The reaction of littermates 38 and 39 may further be considered along with that of the other two pairs mentioned in the preamble inasmuch as

all/

all the rabbits received the same initial dose of alloxan (100 mg. per kg.). The animals of one of these pairs were both made persistently diabetic, while the members of the other pair showed persistent and transitory diabetes respectively. Assessed on the response of the three pairs, littermate animals accordingly may, like unrelated individuals of the same species, be similar or in varying degrees dissimilar as regards their sensitivity to the diabetogenic action of alloxan. Again, the way in which more alloxan had little or no effect on the waning diabetic condition of rabbits 38 and 39 is in keeping with the fact, as noted by Kennedy and Lukens (1944), that alloxan given to a rabbit with established alloxan diabetes produces no change in the blood sugar. Rabbits which have been made diabetic with alloxan may thus subsequently show an increased resistance to the compound. Similar refractoriness to alloxan was also observed by Goldner and Gomori (1943) in dogs treated with an ineffective first dose. Such variable sensitivity to the diabetogenic action of alloxan on the part of different animals of the same species and litter and of the same animal at different times is largely obscure as regards cause, but Kass and Waisbren (1945) have appositely observed that rats which had previously proved refractory to alloxan could be made susceptible to the same dose of alloxan by withholding food for a time. The possibility of this dietetic reduction operating through/

through a fall in the blood glutathione level is further suggested by the recent investigation of Griffiths (1948).

Rabbit 39, as already noted, was made more diabetic by alloxan than rabbit 38 and thus presumably suffered more damage to its islet tissue. In other words, the islets of rabbit 39 were probably reduced more dimensionally and numerically than those of rabbit 38. Yet rabbit 39 after injection with anterior pituitary extract showed on the average larger islets than rabbit 38 and incidentally more budding and a suggestive growth of new islets from the ducts. Enlargement of the islets after injection with anterior pituitary extract has been noted in rats by Richardson and Young (1937 - 38) and, along with a differentiation of new islets from the small pancreatic ducts, in both intact and alloxan-diabetic rabbits by Ogilvie (1944, 1945, 1949). Further, Marks and Young (1939, 1940) have shown that the new tissue has a normal capacity to secrete insulin. Anterior pituitary extract has thus been reaffirmed by the present investigation in respect of its potentiality to increase the islet tissue and both this effect and the functional ability of the new tissue have, as already mentioned in Section VII, been attributed by Ogilvie (1944) to a direct pancreotropic influence of the extract. Finally, the absence of any hydropic affection of the B- cells in rabbits 38 and 39 contrasts with the striking occurrence/

occurrence of this condition in persistent alloxan-diabetic animals. Now, hydrops of the B- cells according to Kennedy and Lukens (1944) is an exhaustive effect of the hyperglycaemic state whereas the blood sugar in the present rabbits was ultimately within normal range. The contrasting absence and presence of hydrops of the B- cells in the present and persistent alloxan-diabetic animals respectively is thus probably explained by the differing glycaemias in the two groups of subjects.

The response of the intact English rabbit to a constant daily amount of anterior pituitary extract is regarded by Ogilvie (1944) as consisting essentially of a diabetic phase preceded and followed by latent and refractory periods respectively. The diabetic condition may show itself in glycosuria or ketonuria or both and the glycosuria usually begins on the sixth day, rises to 10.4 g. per 24 hr., and disappears after 10 days. The reaction of rabbit 39 to anterior pituitary extract was thus average as regards the occurrence of transitory glycosuria and ketonuria and the maximum amount of sugar in the urine, but differed therefrom inasmuch as the glycosuria was immediate and more lasting. These departures from the usual were probably due to the depletion of the islet tissue and available insulin produced by the alloxan. The prepared diabetogenic influence of the treatment, having little opposition, was thus evident immediately, while the pancreotropic action, with a reduced quota of/

of material on which to work, was naturally longer in effecting a sufficient increase of islet tissue and insulin to neutralise the diabetogenic tendency of a constant daily amount of the extract. In the end, the islets averaged more than one fifth larger than before treatment and no glycosuria was induced by three times the amount of extract as was originally enough to cause an immediate increase of sugar in the urine. The reaction of rabbit 39 to anterior pituitary extract, in other words, further resembled that of the intact animal inasmuch as its resistant phase was of an ultimately permanent nature probably by reason of the production, as also in the normal rabbit, of a sufficiency of protective islet tissue through the pancreotropic influence of the treatment.

Rabbit 39 during its first and second treatments with anterior pituitary extract respectively lost and gained weight on nearly the same diet as was normally just sufficient to maintain a more or less constant body weight. The initial loss of weight was slight, but the secondary increase resulted in the animal being substantially heavier than at the beginning of the experiment. The explanation of this apparent paradox is to be found in the relation of anterior pituitary extract to growth. Thus, an increase in weight during treatment with the extract on a diet previously just sufficient to maintain a steady body weight has been observed in the rabbit (Ogilvie, 1945/

1945), dog, cat and rat (Young, 1945) and evidence has been adduced by Young (1945) to show that the extract achieves this result by effecting the partial replacement of carbohydrate and protein combustion by that of fat or, in other words, by invoking in the non-fasting animal the basic metabolic pattern characteristic of the fasting state. The observations of Mirsky (1939) and others, moreover, indicate that the influence of anterior pituitary extract in enhancing protein storage is mediated, at least in part, through the secretion of insulin. Now, the islets of rabbit 39, having been enlarged through the pancreatropic influence of the first treatment with the extract, would during the second course be a source of increasingly more abundant insulin. Further, the difference quantitatively in the glycosuria incidental to the two courses of the extract infers a less marked loss of energy during the second than the first treatment. In other words, the forces induced by the first and second courses of anterior pituitary extract were such as to result respectively in negative and positive growth effects, that is, in a loss and gain in weight.

Summary

(1) Two littermate English rabbits each received two injections of 100 mg. alloxan per kg. body weight and responded thereto with a transitory diabetes.

(2)/

(2) The second injection of alloxan had no evident influence on the existing diabetes.

(3) The animal which had exhibited the severer diabetes was subsequently given two courses of anterior pituitary extract, while the other animal was used as a control.

(4) The treated rabbit showed exacerbations of the diabetes during its courses of anterior pituitary extract, but from about the middle of the second treatment onwards proved resistant to the diabetogenic action of increasing amounts of the extract.

(5) Both rabbits as regards their pancreatic islets were characterised by (i) reduction in number and size and (ii) regeneration. The growth of new islet tissue, however, was more marked in the treated than the control animal as evident in (i) the larger size of the islets ; (ii) a greater proportion of budding islets ; and (iii) a suggestive formation of new islets from the small pancreatic ducts.

(6) The treated rabbit during its two courses of anterior pituitary extract respectively lost and gained weight on nearly the same diet as was normally just sufficient to maintain a steady body weight.

(7) The phenomena observed in the treated rabbit are interpreted in terms of the diabetogenic and pancreatropic actions of anterior pituitary extract.

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PROTOCOLS.

Rabbit 38. (Male)

Date	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
0.12.45	2405	98	85 g.bran 175 g.cab. 14 g.hay 22 cc.water	427	-	136(f)	-
1.12.45	2435	54	70 g.bran 210 g.cab. 13 g.hay 19 cc.water	397	-	-	-
2.12.45	2405	145	75 g.bran 275 g.cab. 14 g.hay 16 cc.water	459	-	-	-
3.12.45	2385	104	70 g.bran 215 g.cab. 14 g.hay 17 cc.water	405	78	-	-
4.12.45	2405	123	95 g.bran 280 g.cab. 14 g.hay 22 cc.water	526	100	-	-
5.12.45	2425	74	80 g.bran 230 g.cab. 14 g.hay 20 cc.water	446	85	-	-
6.12.45	2430	105	105 g.bran 280 g.cab. 14 g.hay 16 cc.water	557	106	-	-
7.12.45	2515	20	75 g.bran 210 g.cab. 14 g.hay 19 cc.water	417	80	-	-
8.12.45	2400	147	90 g.bran 300 g.cab. 12 g.hay 35 cc.water	515	97	-	-
9.12.45	2455	71	95 g.bran 280 g.cab. 14 g.hay 19 cc.water	526	100	-	-
0.12.45	2475	78	90 g.bran 295 g.cab. 14 g.hay 23 cc.water	519	99	-	-

Rabbit 38.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
10.12.45	-	-	-	Blank = 29*	-	-
11.12.45	-	-	-	-	-	-
12.12.45	-	-	-	-	-	-
13.12.45	-	-	-	-	-	-
14.12.45	-	-	-	-	-	-
15.12.45	-	-	-	-	-	-
16.12.45	-	-	-	-	-	-
17.12.45	-	-	-	-	-	-
18.12.45	-	-	-	-	-	-
19.12.45	-	-	-	-	-	-
20.12.45	-	-	-	-	-	-

* Blank has been deducted from total, but not percentage ketones.

Rabbit 38.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
21.12.45	2435	124	85 g.bran 240 g.cab. 13 g.hay 20 cc.water	465	88	-	-
22.12.45	2400	95	110 g.bran 265 g.cab. 14 g.hay 19 cc.water	564	108	-	-
23.12.45	2430	83	95 g.bran 220 g.cab. 14 g.hay 20 cc.water	488	94	-	-
24.12.45	2465	40	85 g.bran 210 g.cab. 14 g.hay 18 cc.water	449	86	-	-
25.12.45	2455	86	85 g.bran 190 g.cab. 14 g.hay 21 cc.water	437	84	-	-
26.12.45	2450	105	50 g.bran 210 g.cab. 14 g.hay 45 cc.water	338	64	M.183 E.152	0.7
27.12.45	2480	131	75 g.bran 255 g.cab. 15 g.hay 30 cc.water	449	85	231	0.2
28.12.45	2450	148	80 g.bran 250 g.cab. 14 g.hay 33 cc.water	459	87	238	0.7
29.12.45	2450	142	75 g.bran 280 g.cab. 15 g.hay 25 cc.water	465	87	-	3.7
30.12.45	2435	164	74 g.bran 320 g.cab. 15 g.hay 27 cc.water	491	91	-	4.6
31.12.45	2450	90	100 g.bran 235 g.cab. 15 g.hay 29 cc.water	515	99	-	6.7

Rabbit 38.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
21.12.45	-	-	-	-	-	-
22.12.45	-	-	-	-	-	-
23.12.45	-	-	-	-	-	-
24.12.45	-	-	-	-	-	-
25.12.45	-	-	-	-	-	Alloxan 100 mg.per kg = 5.0 cc.(5% soln)
26.12.45	0.8	0.7	1	-	-	-
27.12.45	0.3	0.2	0.2	-	-	-
28.12.45	1	1	0.7	-	-	-
29.12.45	5	5	6	-	-	-
30.12.45	7	7	8	-	-	-
31.12.45	6	5	5	-	-	-

Rabbit 38.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
1.1.46	2450	119	88 g.bran 245 g.cab. 14 g.hay 22 cc.water	487	94	-	3.6
1.46	2475	141	94 g.bran 295 g.cab. 15 g.hay 24 cc.water	539	102	-	1.2
3.1.46	2515	109	90 g.bran 240 g.cab. 13 g.hay 13 cc.water	480	92	-	0.3
4.1.46	2530	138	65 g.bran 270 g.cab. 15 g.hay 32 cc.water	427	80	-	0.2
5.1.46	2510	136	90 g.bran 270 g.cab. 14 g.hay 22 cc.water	503	96	-	-
6.1.46	2560	139	105 g.bran 330 g.cab. 15 g.hay 22 cc.water	592	111	-	-
7.1.46	2520	175	90 g.bran 265 g.cab. 14 g.hay 18 cc.water	500	96	-	0.2
8.1.46	2565	141	100 g.bran 315 g.cab. 14 g.hay 35 cc.water	564	107	-	0.5
9.1.46	2560	139	95 g.bran 310 g.cab. 14 g.hay 21 cc.water	545	103	-	4.1
0.1.46	2570	144	90 g.bran 345 g.cab. 14 g.hay 18 cc.water	551	104	-	0.1
1.1.46	2525	121	65 g.bran 215 g.cab. 13 g.hay 68 cc.water	385	74	-	-

Rabbit 38.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
1.1.46	4	4	4	-	-	-
2.1.46	2	2	2	-	-	-
3.1.46	0.3	0.3	0.3	-	-	Alloxan 100 mg.per kg. = 5.0 cc. (5% soln.)
4.1.46	0.3	0.3	0.4	-	-	-
5.1.46	-	-	-	-	-	-
6.1.46	-	-	-	-	-	-
7.1.46	0.4	0.3	0.3	-	-	-
. 1.46	0.7	0.6	0.6	-	-	-
9.1.46	6	5	5	-	-	-
10.1.46	0.1	0.1	0.1	-	-	-
11.1.46	-	-	-	-	-	-

Rabbit 38.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
12.1.46	2510	139	30 g.bran 275 g.cab. 13 g.hay 33 cc.water	313	57	-	-
13.1.46	2485	134	60 g.bran 275 g.cab. 15 g.hay 40 cc.water	415	77	-	-
14.1.46	2550	129	60 g.bran 280 g.cab. 14 g.hay 35 cc.water	415	77	-	-
15.1.46	2545	220	65 g.bran 370 g.cab. 13 g.hay 23 cc.water	484	89	-	-
16.1.46	2570	141	75 g.bran 320 g.cab. 13 g.hay 23 cc.water	484	90	-	-
17.1.46	2610	70	80 g.bran 285 g.cab. 14 g.hay 23 cc.water	481	91	-	-
18.1.46	2630	129	85 g.bran 305 g.cab. 14 g.hay 21 cc.water	510	96	-	-
19.1.46	2570	196	75 g.bran 285 g.cab. 9 g.hay 22 cc.water	448	96	-	-
20.1.46	2560	175	80 g.bran 340 g.cab. 14 g.hay 18 cc.water	517	96	-	-
21.1.46	2585	126	75 g.bran 300 g.cab. 14 g.hay 16 cc.water	475	89	-	-
22.1.46	2580	185	70 g.bran 330 g.cab. 14 g.hay 20 cc.water	478	89	-	-

Rabbit 38.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
12.1.46	-	-	-	-	-	-
13.1.46	-	-	-	-	-	-
14.1.46	-	-	-	-	-	-
15.1.46	-	-	-	-	-	-
16.1.46	-	-	-	-	-	-
17.1.46	-	-	-	-	-	-
18.1.46	-	-	-	-	-	-
19.1.46	-	-	-	-	-	-
20.1.46	-	-	-	-	-	-
21.1.46	-	-	-	-	-	-
22.1.46	-	-	-	-	-	-

Rabbit 38.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
23.1.46	2550	129	50 g.bran 265 g.cab. 13 g.hay 24 cc.water	370	69	-	-
24.1.46	2555	118	75 g.bran 285 g.cab. 13 g.hay 28 cc.water	461	87	-	-
25.1.46	2455(f)	55	35 g.bran 250 g.cab. 11 g.hay 35 cc.water	307	55	140(f)	-
26.1.46	2485	155	60 g.bran 330 g.cab. 14 g.hay 24 cc.water	447	82	-	-
27.1.46	2540	70	105 g.bran 280 g.cab. 14 g.hay 34 cc.water	557	106	-	-
28.1.46	2510	133	70 g.bran 245 g.cab. 14 g.hay 15 cc.water	424	81	-	-
29.1.46	2500	116	80 g.bran 245 g.cab. 14 g.hay 20 cc.water	456	87	-	-
30.1.46	2530	62	75 g.bran 220 g.cab. 14 g.hay 19 cc.water	424	81	-	-
31.1.46	2525	97	75 g.bran 230 g.cab. 13 g.hay 33 cc.water	426	81	-	-
1.2.46	2420(f)	74	40 g.bran 130 g.cab. 10 g.hay 46 cc.water	242	47	147(f)	-
2.2.46	2500	43	70 g.bran 250 g.cab. 14 g.hay 31 cc.water	427	81	-	-

Rabbit 38.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
23.1.46	-	-	-	-	-	-
24.1.46	-	-	-	-	-	-
25.1.46	-	-	-	-	-	-
26.1.46	-	-	-	-	-	-
27.1.46	-	-	-	-	-	-
28.1.46	-	-	-	-	-	-
29.1.46	-	-	-	-	-	-
30.1.46	-	-	-	-	-	-
31.1.46	-	-	-	-	-	-
1.2.46	-	-	-	-	-	-
2.2.46	-	-	-	-	-	-

Rabbit 38.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g. %
3.2.46	2495	122	75 g.bran 295 g.cab. 14 g.hay 23 cc.water	472	89	-	-
4.2.46	2510	146	70 g.bran 305 g.cab. 13 g.hay 26 cc.water	458	86	-	-
5.2.46	2500	103	80 g.bran 240 g.cab. 12 g.hay 30 cc.water	446	84	-	-
6.2.46	2545	117	75 g.bran 300 g.cab. 12 g.hay 20 cc.water	468	87	-	-
7.2.46	2540	73	75 g.bran 225 g.cab. 12 g.hay 24 cc.water	420	80	-	-
8.2.46	2525	65	80 g.brsn 205 g.cab. 13 g.hay 30 cc.water	426	82	-	-
9.2.46	2575	124	55 g.bran 330 g.cab. 13 g.hay 24 cc.water	427	78	-	-
10.2.46	2505	126	85 g.bran 215 g.cab. 13 g.hay 21 cc.water	449	86	-	-
11.2.46	2510	108	80 g.bran 250 g.cab. 13 g.hay 13 cc.water	455	86	-	-
12.2.46	2535	93	75 g.bran 300 g.cab. 11 g.hay 17 cc.water	465	86	-	-
13.2.46	2575	121	105 g.bran 260 g.cab. 10 g.hay 27 cc.water	531	101	-	-

Rabbit 38.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
3.2.46	-	-	-	-	-	-
4.2.46	-	-	-	-	-	-
5.2.46	-	-	-	-	-	-
6.2.46	-	-	-	-	-	-
7.2.46	-	-	-	-	-	-
8.2.46	-	-	-	-	-	-
9.2.46	-	-	-	-	-	-
10.2.46	-	-	-	-	-	-
11.2.46	-	-	-	-	-	-
12.2.46	-	-	-	-	-	-
13.2.46	-	-	-	-	-	-

Rabbit 38.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
14.2.46	2545	142	75 g.bran 270 g.cab. 11 g.hay 20 cc.water	446	83	-	-
15.2.46	2575	99	85 g.bran 290 g.cab. 10 g.hay 24 cc.water	488	91	-	-
16.2.46	2575	138	95 g.bran 225 g.cab. 9 g.hay 18 cc.water	474	91	-	-
17.2.46	2575	105	70 g.bran 290 g.cab. 10 g.hay 24 cc.water	440	82	-	-
18.2.46	2585	108	80 g.bran 285 g.cab. 9 g.hay 20 cc.water	464	87	-	-
19.2.46	2560	92	65 g.bran 225 g.cab. 11 g.hay 24 cc.water	385	73	-	-
20.2.46	2575	94	75 g.bran 185 g.cab. 12 g.hay 17 cc.water	394	76	-	-
21.2.46	2540	58	65 g.bran 170 g.cab. 13 g.hay 23 cc.water	356	69	-	-
22.2.46	2545	120	45 g.bran 295 g.cab. 14 g.hay 17 cc.water	377	70	-	-
23.2.46	2555	135	65 g.bran 300 g.cab. 14 g.hay 21 cc.water	445	83	-	-
24.2.46	2525	120	60 g.bran 270 g.cab. 13 g.hay 19 cc.water	405	75	-	-

Rabbit 38.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E
14.2.46	-	-	-	-	-	-
15.2.46	-	-	-	-	-	-
16.2.46	-	-	-	-	-	-
17.2.46	-	-	-	-	-	-
18.2.46	-	-	-	-	-	-
19.2.46	-	-	-	-	-	-
20.2.46	-	-	-	-	-	-
21.2.46	-	-	-	-	-	-
22.2.46	-	-	-	-	-	-
23.2.46	-	-	-	-	-	-
24.2.46	-	-	-	-	-	-

Rabbit 38.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
25.2.46	2555	61	70 g.bran 195 g.cab. 14 g.hay 35 cc.water	392	76	-	-
26.2.46	2565	107	80 g.bran 240 g.cab. 12 g.hay 16 cc.water	446	84	-	-
27.2.46	2580	115	70 g.bran 280 g.cab. 13 g.hay 22 cc.water	442	83	137(f)	-

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Rabbit 38.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
25.2.46	-	-	-	-	-	-
26.2.46	-	-	-	-	-	-
27.2.46	-	-	-	-	-	-

31.

Rabbit 38.

Blood Sugar Series.

	Time.	Blood Sugar in mg.%
25.12.45	10 a.m.	187 (not fasting)
	Alloxan 100 mg. per kg. = 5.0 cc. (5 % soln.)	
	11.30 a.m.	258
	12.30 p.m.	205
	2.45	136
	4.45	113
	6.45	96
26.12.45	10 a.m.	183
	7 a.m.	152
27.12.45	10 a.m.	231
28.12.45	10 a.m.	238

Rabbit 39. (Male).

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
19.11.45	2560	-	-	-	-	-	-
20.11.45	2550	130	75 g.bran 230 g.cab. 13 g.hay 25 cc.water	426	81	-	-
21.11.45	2535	176	80 g.bran 310 g.cab. 10 g.hay 17 cc.water	484	90	-	-
22.11.45	2500	146	60 g.bran 240 g.cab. 10 g.hay 22 cc.water	377	70	-	-
23.11.45	2500	124	60 g.bran 240 g.cab. 11 g.hay 44 cc.water	380	70	-	-
24.11.45	2520	102	50 g.bran 250 g.cab. 10 g.hay 41 cc.water	351	65	-	-
25.11.45	2510	169	70 g.bran 285 g.cab. 13 g.hay 30 cc.water	445	84	-	-
26.11.45	2455	65	70 g.bran 130 g.cab. 14 g.hay 30 cc.water	350	69	-	-
27.11.45	2495	111	45 g.bran 140 g.cab. 13 g.hay 23 cc.water	274	53	-	-
28.11.45	2515	137	55 g.bran 310 g.cab. 14 g.hay 17 cc.water	418	77	-	-
29.11.45	2505	153	60 g.bran 280 g.cab. 14 g.hay 20 cc.water	415	77	-	-
30.11.45	2460(f)	68	35 g.bran 135 g.cab. 10 g.hay 29 cc.water	230	44	138(f)	-

Rabbit 39.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
19.11.45	-	-	-	-	-	-
20.11.45	-	-	-	-	-	-
21.11.45	-	-	-	-	-	-
22.11.45	-	-	-	-	-	-
23.11.45	-	-	-	-	-	-
24.11.45	-	-	-	-	-	-
25.11.45	-	-	-	-	-	-
26.11.45	-	-	-	-	-	-
27.11.45	-	-	-	-	-	-
28.11.45	-	-	-	Blank = 21 *	-	-
29.11.45	-	-	-	-	-	-
30.11.45	-	-	-	-	-	-

* Blank has been deducted from total, but not percentage ketones.

Rabbit 39.

Date	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
1.12.45	2490	136	65 g.bran 315 g.cab. 10 g.hay 13 cc.water	440	82	-	-
2.12.45	2495	116	75 g.bran 275 g.cab. 14 g.hay 23 cc.water	459	87	-	-
3.12.45	2530	83	95 g.bran 220 g.cab. 14 g.hay 30 cc.water	488	94	-	-
4.12.45	2505	152	60 g.bran 270 g.cab. 12 g.hay 18 cc.water	402	74	-	-
5.12.45	2495	120	60 g.bran 215 g.cab. 14 g.hay 24 cc.water	374	71	M. 85 E.177	0.7
6.12.45	2480	119	110 g.bran 340 g.cab. 13 g.hay 19 cc.water	608	114	268	1.3
7.12.45	2450	188	60 g.bran 335 g.cab. 14 g.hay 30 cc.water	450	83	-	6.7
8.12.45	2465	145	70 g.bran 280 g.cab. 14 g.hay 68 cc.water	446	84	-	10.7
9.12.45	2445	171	65 g.bran 275 g.cab. 14 g.hay 42 cc.water	427	81	-	10.9
10.12.45	2460	135	65 g.bran 230 g.cab. 14 g.hay 46 cc.water	398	76	-	13.3
11.12.45	2470	161	55 g.bran 325 g.cab. 14 g.hay 28 cc.water	428	79	-	9.5

Rabbit 39.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
1.12.45	-	-	-	-	-	-
2.12.45	-	-	-	-	-	-
3.12.45	-	-	-	-	-	-
4.12.45	-	-	-	-	-	Alloxan 100 mg. per kg. = 5.0 cc (5 % soln.)
5.12.45	0.8	0.8	1	-	-	-
6.12.45	2	1	0.9	-	-	-
7.12.45	13	12	14	-	-	-
8.12.45	16	14	17	-	-	-
9.12.45	19	17	21	-	-	-
10.12.45	19	17	22	-	-	-
11.12.45	15	14	18	-	-	-

Rabbit 39.

Date	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
12.12.45	2440	227	65 g.bran 370 g.cab. 14 g.hay 19 cc.water	488	90	-	4.7
13.12.45	2420	167	65 g.bran 275 g.cab. 14 g.hay 43 cc.water	427	81	-	5.4
14.12.45	2440	150	50 g.bran 300 g.cab. 14 g.hay 36 cc,water	396	73	-	3.9
15.12.45	2460	106	25 g.bran 300 g.cab. 14 g.hay 32 cc.water	317	57	-	1.7
16.12.45	2495	125	50 g.bran 280 g.cab. 13 g.hay 12 cc.water	379	70	-	1.3
17.12.45	2490	150	65 g.bran 275 g.cab. 14 g.hay 16 cc.water	427	81	-	2.4
18.12.45	2395(f)	150	40 g.bran 265 g.cab. 11 g.hay	332	61	209(f)	1.6
19.12.45	2495	126	70 g.bran 370 g.cab. 15 g.hay 15 cc.water	507	93	-	0.2
20.12.45	2480	140	70 g.bran 290 g.cab. 14 g.hay 24 cc.water	453	85	-	3.3
21.12.45	2485	137	30 g.bran 300 g.cab. 14 g.hay 27 cc.water	333	60	-	7.9
22.12.45	2455	191	40 g.bran 240 g.cab. 14 g.hay 89 cc.water	326	61	-	8.4

Rabbit 39.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
12.12.45	11	10	11	-	-	-
13.12.45	9	8	10	-	-	-
14.12.45	6	5	7	-	-	Alloxan 100 mg.per kg. = 5.0 cc.(5% soln).
15.12.45	2	2	4	-	-	-
16.12.45	4	4	6	-	-	-
17.12.45	4	3	4	-	-	-
18.12.45	2	2	3	-	-	-
19.12.45	0.3	0.2	0.2	-	-	0.5 g.per kg.(5.0cc.)
20.12.45	5	4	5	-	-	0.5 g.per kg.(5.0cc.)
21.12.45	11	10	17	-	-	0.5 g.per kg.(5.0cc.)
22.12.45	16	14	23	-	-	0.5 g.per kg.(5.0cc.)

Rabbit 39.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
23.12.45	2470	205	40 g.bran 315 g.cab. 15 g.hay 74 cc.water	377	69	-	8.3
24.12.45	2475	236	55 g.bran 275 g.cab. 15 g.hay 17 cc.water	399	74	-	8.5
25.12.45	2460	233	50 g.bran 255 g.cab. 13 g.hay 132 cc.water	363	68	-	8.3
26.12.45	2465	278	50 g.bran 370 g.cab. 14 g.hay 20 cc.water	441	80	-	8.7
27.12.45	2445	271	55 g.bran 330 g.cab. 14 g.hay 81 cc.water	431	79	-	10.7
28.12.45	2445	219	25 g.bran 380 g.cab. 14 g.hay 65 cc.water	368	65	-	8.8
29.12.45	2435	201	35 g.bran 315 g.cab. 15 g.hay 64 cc.water	362	65	-	10.9
30.12.45	2445	222	60 g.bran 390 g.cab. 14 g.hay 26 cc.water	486	88	-	10.7
31.12.45	2365(f)	115	40 g.bran 150 g.cab. 14 g.hay 42 cc.water	268	52	201(f)	10.1
1.1.46	2455	166	55 g.bran 400 g.cab. 15 g.hay 40 cc.water	479	86	-	0.2
2.1.46	2490	145	65 g.bran 315 g.cab. 15 g.hay 15 cc.water	456	85	-	0.2

Rabbit 39.

Date.	Total Urinary Glucose per 24 hr.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
23.12.45	17	16	23	+	+	0.5 g.per kg.(5.0 cc)
24.12.45	20	18	24	29	19	0.5 g.per kg.(5.0 cc)
25.12.45	19	17	25	+	+	0.5 g.per kg.(5.0 cc)
26.12.45	24	22	28	48	76	0.5 g.per kg.(5.0 cc)
27.12.45	29	26	33	+	+	0.5 g. per kg.(4.8 cc)
28.12.45	19	17	26	30	20	0.5 g.per kg.(4.8cc)
29.12.45	22	20	31	-	-	-
30.12.45	24	21	24	-	-	-
31.12.45	12	11	21	-	-	-
1.1.46	0.3	0.3	0.3	-	-	0.5 g.per kg.(5.0 cc)
2.1.46	0.3	0.3	0.4	-	-	0.5 g.per kg.(5.0 cc)

Rabbit 39.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
.1.46	2435	236	30 g.bran 310 g.cab. 14 g.hay 17 cc.water	339	61	-	0.1
.1.46	2470	205	40 g.bran 350 g.cab. 15 g.hay 17 cc.water	399	72	-	2.3
.1.46	2475	240	70 g.bran 375 g.cab. 14 g.hay 51 cc.water	507	94	-	5.9
.1.46	2510	210	65 g.bran 390 g.cab. 14 g.hay 23 cc.water	501	92	-	3.2
.1.46	2545	198	80 g.bran 215 g.cab. 15 g.hay 21 cc.water	440	84	-	3.5
.1.46	2550	205	50 g.bran 345 g.cab. 14 g.hay 33 cc.water	425	78	-	1.1
.1.46	2585	206	70 g.bran 365 g.cab. 14 g.hay 18 cc.water	501	93	-	-
0.1.46	2585	220	50 g.bran 365 g.cab. 14 g.hay 18 cc.water	438	80	-	0.1
1.1.46	2610	188	55 g.bran 270 g.cab. 14 g.hay 30 cc.water	393	73	-	-
2.1.46	2620	185	60 g.bran 330 g.cab. 14 g.hay 18 cc.water	447	82	-	-
3.1.46	2635	166	70 g.bran 275 g.cab. 15 g.hay 19 cc.water	446	84	-	-

Rabbit 39.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
3.1.46	0.2	0.2	0.3	-	-	0.5 g.per kg.(4.8 cc)
4.1.46	5	4	6	-	-	0.5 g.per kg.(5.0 cc)
5.1.46	14	13	14	-	-	0.5 g.per kg.(5.0cc)
6.1.46	7	6	7	-	-	0.5 g.per kg.(5.0 cc)
7.1.46	7	6	7	-	-	0.5 g.per kg.(5.0 cc)
8.1.46	2	2	3	-	-	0.5 g.per kg.(5.0 cc)
9.1.46	-	-	-	-	-	1.0 g.per kg.(10.4cc)
10.1.46	0.2	0.2	0.3	-	-	1.0 g.per kg.(10.4cc)
11.1.46	-	-	-	-	-	1.0 g.per kg.(10.4cc)
12.1.46	-	-	-	-	-	1.0 g.per kg.(10.4cc)
13.1.46	-	-	-	-	-	1.0 g.per kg.(10.4cc)

Rabbit 39.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
14.1.46	2605	154	65 g.bran 205 g.cab. 14 g.hay 16 cc.water	382	74	-	-
15.1.46	2675	107	45 g.bran 290 g.cab. 14 g.hay 19 cc.water	374	69	-	-
16.1.46	2630	223	50 g.bran 330 g.cab. 14 g.hay 22 cc.water	415	76	-	-
17.1.46	2640	115	60g.bran 260 g.cab. 13 g.hay 26 cc.water	398	74	-	-
18.1.46	2695	132	40 g.bran 325 g.cab. 14 g.hay 26 cc.water	380	70	-	-
19.1.46	2680	215	50 g.bran 280 g.cab. 12 g.hay 22 cc.water	376	69	-	-
20.1.46	2630	160	40 g.bran 260 g.cab. 15 g.hay 16 cc.water	341	63	-	-
21.1.46	2585	185	50 g.bran 245 g.cab. 14 g.hay 25 cc.water	361	68	-	-
22.1.46	2580	135	45 g.bran 260 g.cab. 14 g.hay 28 cc.water	354	66	-	-
23.1.46	2605	133	40 g.bran 250 g.cab. 14 g.hay 35 cc.water	332	62	-	-
24.1.46	2600	82	35 g.bran 215 g.cab. 14 g.hay 25 cc.water	295	55	-	-

Rabbit 39.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
24.1.46	-	-	-	-	-	1.5 g.per kg.(15.6cc)
25.1.46	-	-	-	-	-	1.5 g.per kg.(16.2cc)
26.1.46	-	-	-	-	-	1.5 g.per kg.(15.6cc)
27.1.46	-	-	-	-	-	1.5 g.per kg.(15.6cc)
28.1.46	-	-	-	-	-	1.5 g.per kg.(16.2cc)
29.1.46	-	-	-	-	-	-
30.1.46	-	-	-	-	-	-
31.1.46	-	-	-	-	-	-
1.2.46	-	-	-	-	-	-
2.2.46	-	-	-	-	-	-
3.2.46	-	-	-	-	-	-
4.2.46	-	-	-	-	-	-

Rabbit 39.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
25.1.46	2580	177	50 g.bran 300 g.cab. 14 g.hay	396	73	-	-
26.1.46	2615	113	30 g.bran 285 g.cab. 15 g.hay 17 cc.water	326	59	-	-
27.1.46	2630	78	65 g.bran 205 g.cab. 15 g.hay 25 cc.water	385	74	-	-
28.1.46	2540(f)	107	30 g.bran 120 g.cab. 14 g.hay 15 cc.water	218	42	110(f)	-
29.1.46	2585	122	50 g.bran 265 g.cab. 15 g.hay 33 cc.water	377	70	-	-
30.1.46	2580	85	60 g.bran 200 g.cab. 15 g.hay 17 cc.water	367	69	-	-
31.1.46	2680	94	50 g.bran 295 g.cab. 15 g.hay 23 cc.water	396	73	-	-
1.2.46	2650	122	50 g.bran 235 g.cab. 15 g.hay 20 cc.water	357	67	-	-
2.2.46	2670	128	35 g.bran 270 g.cab. 14 g.hay 25 cc.water	330	60	-	-
3.2.46	2655	139	45 g.bran 270 g.cab. 15 g.hay 21 cc.water	364	67	-	-
4.2.46	2580(f)	134	25 g.bran 160 g.cab. 13 g.hay 25 cc.water	223	42	151(f)	-

Rabbit 39.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
25.1.46	-	-	-	-	-	-
26.1.46	-	-	-	-	-	-
27.1.46	-	-	-	-	-	-
28.1.46	-	-	-	-	-	-
29.1.46	-	-	-	-	-	-
30.1.46	-	-	-	-	-	-
31.1.46	-	-	-	-	-	-
1.2.46	-	-	-	-	-	-
2.2.46	-	-	-	-	-	-
3.2.46	-	-	-	-	-	-
4.2.46	-	-	-	-	-	-

46.

Rabbit 39.

Date.	Body Weight in g.	Urine Volume per 24 hr. in cc.	Diet per 24 hr.	Total Calories per 24 hr.	Total Dietary PolyCHO per 24 hr. in g.	Blood Sugar in mg.%	Urine Sugar in g.%
5.2.46	2575	107	60 g.bran 225 g.cab. 13 g.hay 26 cc.water	376	71	-	-
6.2.46	2580	115	50 g.bran 240 g.cab. 13 g.hay 29 cc.water	354	66	- KILLED.	-

47.

Rabbit 39.

Date.	Total Urinary Glucose per 24 hr. in g.	Total Urinary PolyCHO per 24 hr. in g.	%age Dietary PolyCHO excreted in urine per 24 hr.	Urine Ketones in mg.%	Total Urine Ketones per 24 hr. in mg.	A.P.E.
5.2.46	-	-	-	-	-	-
6.2.46	-	-	-	-	-	-

Rabbit 39.

Blood Sugar Series.

	Time.	Blood Sugar in mg.%
4.12.45	10 a.m.	133 (not fasting)
	Alloxan 100 mg. per kg. = 5.0 cc. (5% soln.)	
	11 a.m.	286
	12 noon	216
	2.15 p.m.	133
	4.15	90
	6.15	98
5.12.45	10 a.m.	85 (not fasting)
	6 p.m.	177
6.12.45	10 a.m.	268

SECTION IX

Duodenal Diverticula and Their Complications with Particular Reference to Acute Pancreatic Necrosis.

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SECTION IX.

Duodenal Diverticula and Their Complications with Particular Reference to Acute Pancreatic Necrosis.

Edwards (1939) in his book on Diverticula and Diverticulitis of the Intestine states that " the association of pancreatitis with diverticula of the second part of the duodenum has received considerable attention in the literature ..... The association is a vague one .... It may be - and indeed is usually likely to be - accidental ... A further possibility is the causation of pancreatic disorder by the pressure of a 'perivaterien' diverticulum upon the pancreatic duct at the ampulla of Vater. There has, however, been no authentic description from postmortem findings of such an occurrence." In view of these comments the four cases reported below are noteworthy inasmuch as they show that, first, a perivaterine diverticulum may produce undoubted obstruction of the pancreatic duct and, secondly, the association of acute pancreatic necrosis with a perivaterine diverticulum may be neither vague nor accidental, but reasonably explained on the basis of this very factor of duct obstruction. Finally, the opportunity is taken in the discussion of this series of cases to review the complications of duodenal diverticula as revealed by a study of the literature.

Case Reports.

Case 1.

Clinical History :

A miner, aged 69, had for nine weeks complained of a yellow face, dark yellowish brown urine, poor appetite, excessive thirst, loss of weight and clay-coloured stools. His previous history revealed nothing of importance.

The patient was poorly nourished and distinctly jaundiced. His abdomen was scantily covered, but moved freely with respiration. Palpation failed to reveal any abnormal muscular resistance, although slight discomfort was elicited deeply in the epigastrium to the right of the middle line. The liver, gall bladder and spleen were of normal size and no free fluid was present in the cavity. Digital examination of the rectum revealed nothing unusual, while no occult blood was present in the stool. A fractional test meal yielded average figures. The pulse was increased to 112 per minute and a cough produced some frothy, bile-stained sputum, but the cardiovascular and respiratory systems were otherwise normal. The urine contained much bile and the icteric index was 83, while the van den Bergh reaction was biphasic.

The patient after being admitted to hospital showed increasing jaundice, complete loss of appetite, and a temperature between 98°F and 102°F. He ultimately became comatose and died seventeen days after admission. The provisional diagnosis was carcinoma of the head of the pancreas.

Post Mortem Examination :

Macroscopical : The body was that of a well built, elderly, moderately jaundiced male. The duodenum showed two, round, shallow ulcers side by side in the posterior wall of its first and also a diverticulum medial to and above the ampulla of Vater, being separated therefrom by only a thin mucous fold (Fig. 1). The oval ostium measured 0.5 cm. in its greatest diameter and gave into a sac 2.6 cm. deep and 2 cm. in diameter at its maximum. The sac passed upwards and medially into the head of the pancreas and lay both posterior to and in close contact with the common bile and pancreatic ducts. It was very thin walled and expansile and incidentally lined by a folded mucous membrane showing a particularly marked, diaphragm-like flap near the ostium. The sac contained brownish fluid.

The pancreas was moderately atrophied and unusually tough and on section reduced to a relatively narrow layer with thickened interlobular septa. The pancreatic duct was grossly dilated along/

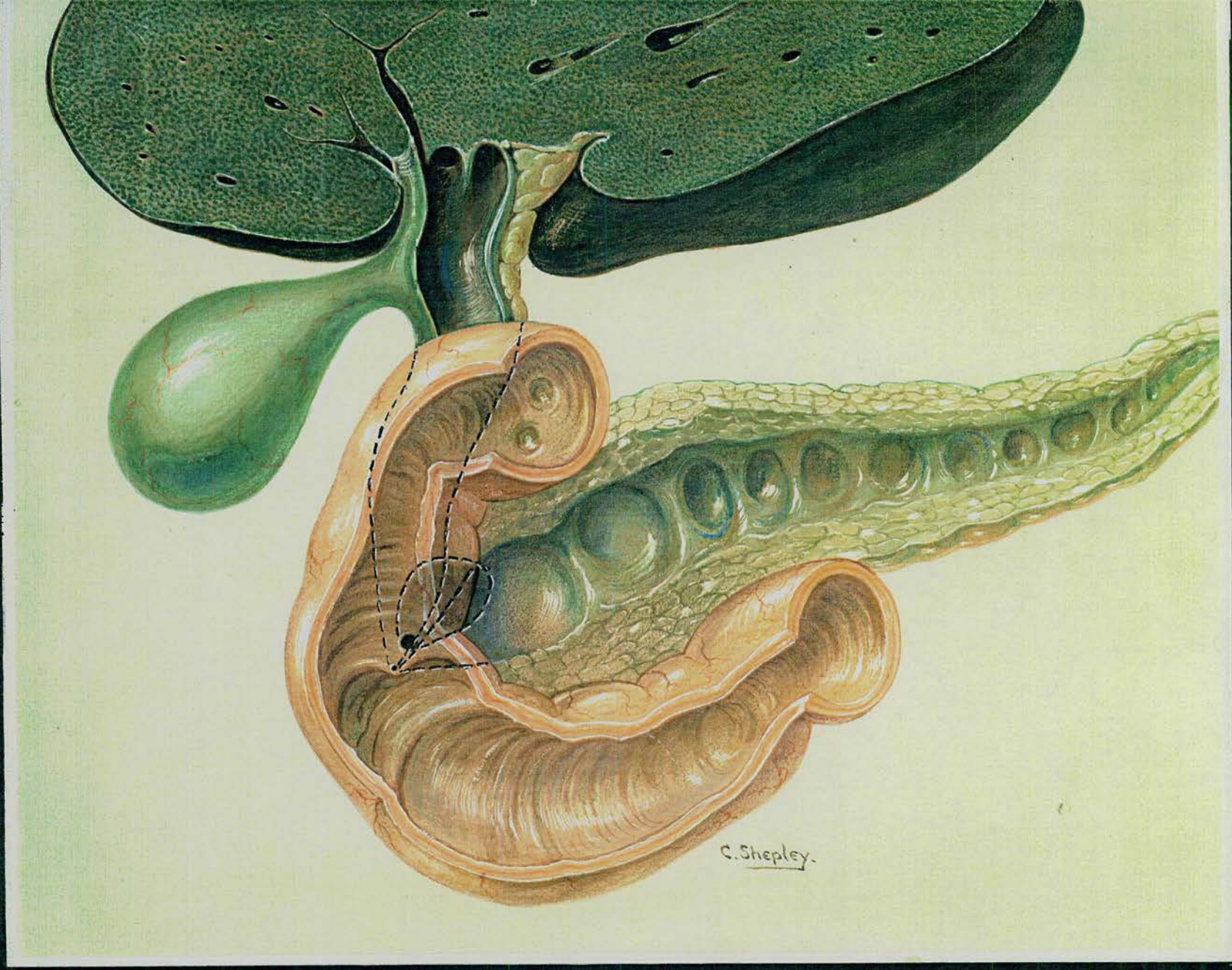

Fig. 1. Case 1. The second part of the duodenum shows a diverticulum, the ostium of which is situated immediately above and medial to the ampulla of Vater. The pancreatic duct is grossly dilated and marked distension also affects the common bile and cystic ducts and the gall bladder. The pancreas is atrophied and the liver is mottled from chronic venous congestion.

along its whole length and measured 4 cm. and 2 cm. in circumference in the head and tail respectively. It was distinctly sacculated, lined by a healthy-looking mucous membrane, and characterised by an exit with the common bile duct into a recess type of ampulla. The accessory pancreatic duct was not located.

The liver was average in size, shape and consistence and on section had a mottled, bile-stained surface showing an obviously distended condition of the small bile ducts. Dilatation also affected both hepatic ducts, the common bile duct and the cystic duct so that these were 1.5 cm., 5 cm., and 2 cm. in circumference respectively. The gall bladder was similarly very distended and unusually thin walled. It was lined by a healthy mucosa and filled with dark green bile, but contained no gall stones.

The other organs displayed no features requiring mention.

Microscopical : The pancreas showed similar changes in all regions. The interlobular and even more the intralobular ducts were dilated and lined by flattened epithelium (Fig. 2). Both types of channel sometimes contained inspissated secretion in the form of either small homogeneous masses or concentrically laminated bodies like corpora amylacea. No ducts, however, were affected by the transitional epithelial hyperplasia of Rich and Duff (1936). The acini were shrunken, average in size or enlarged. They were mostly of average dimensions, but even so were usually lined by flattened epithelium and a similar state of the epithelium was apparent also in the shrunken and enlarged acini. The abnormal acini, moreover, were more or less devoid of zymogen granules and excessively separated, especially in relation to the shrunken glands, by fibrous tissue. The interlobular septa incidentally were thickened, congested, oedematous and characterised by many narrow fibrous offshoots into the lobules. The pancreatic islets were normal. The essential findings in the pancreas were thus (1) obstructive dilatation of the ducts and (2) fibrotic atrophy of the acinar tissue.

The liver showed chronic venous congestion. The liver cells and bile canaliculi, chiefly in the inner half of the lobules, sometimes contained granules or small masses of inspissated bile pigment, while deposits of such material had also caused swelling of many of the Kupffer cells. The small bile ducts were almost always dilated, lined by flattened epithelium and filled with inspissated bile and scanty polymorphs (Fig. 3). An excessive infiltration with polymorphs and round cells, mainly the latter, was also present throughout the portal connective tissue. The principal features in the liver were thus (1) chronic venous congestion ; (2) obstructive dilatation of the biliary system ; and (3) chronic cholangitis.

The/

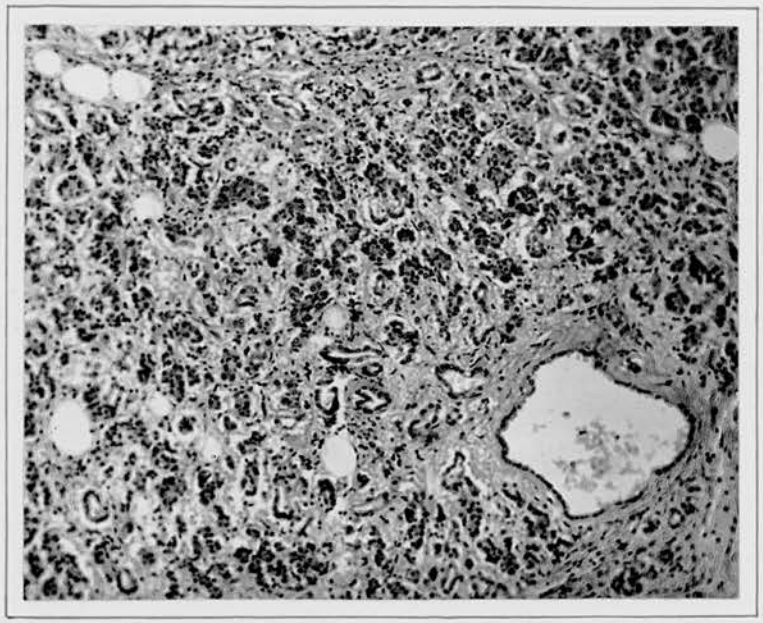

Fig. 2. Case 1. Pancreas. The interlobular duct at bottom right is dilated and lined by flattened epithelium. Several small intralobular ducts also show distension and flattening of their epithelium. The acinar tissue is atrophied and partly replaced by fibrous tissue. Haematoxylin & Eosin. x 75.

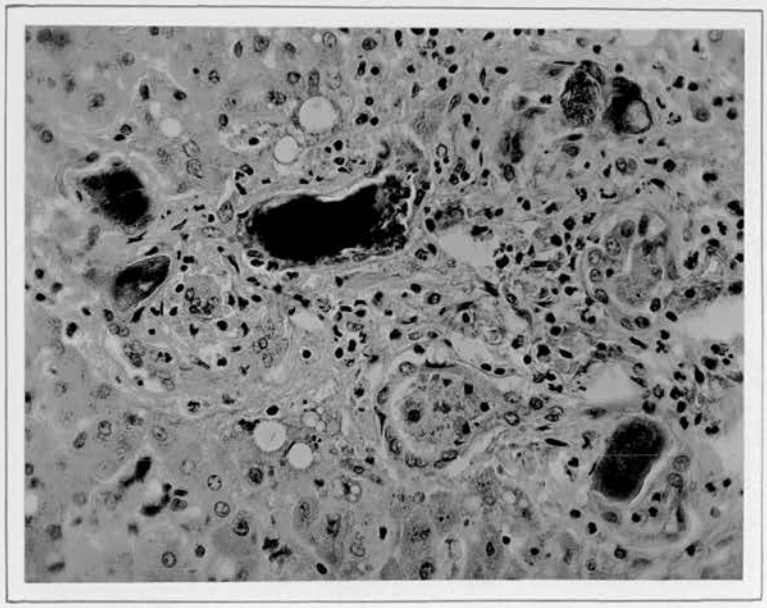

Fig. 3. Case 1. Liver. The bile ducts in the portal tract illustrated are dilated, lined by flattened epithelium, and filled with inspissated bile. Some fatty infiltration is present in the neighbouring liver cells. Haematoxylin & Eosin. x 240.

The other organs were devoid of interest.

Case 2.

Clinical History :

A married woman, aged 73, had for two years experienced attacks of abdominal discomfort. The attacks were unrelated to meals and never severe, but nevertheless accompanied by jaundice. The patient was seized about five hours before admission to hospital with sudden, severe, upper abdominal pain and vomiting. She was found on admission to be collapsed and pale, but not emaciated or jaundiced. The pulse, respirations and temperature were 76 per minute and of poor volume, 36 per minute and 97°F respectively. The abdomen was boarded and acutely tender in its upper half, but only slightly so affected below the umbilicus. Operation revealed some brownish fluid in the upper abdomen and small necrotic areas in the fat of the gastrohepatic omentum and hepatorenal recess. The pancreas was palpated through an opening in the gastrocolic omentum, but found to be of average consistence. Stomach, duodenum and gall bladder appeared normal. The damaged areas in the fat pointed to a diagnosis of acute pancreatic necrosis and the abdomen was accordingly closed in layers without drainage. The patient died fourteen hours later.

Post Mortem Examination :

Macroscopical : The body was that of a well nourished, elderly female. The abdomen showed patches of fat necrosis around the head of the pancreas, in the lesser omentum, and also low down in the right flank.

A diverticulum was found in the duodenum with its circular ostium, 2.5 cm. in diameter, placed 0.5 cm. above and medial to the ampulla of Vater (Fig. 4). It was flask-shaped being 5 cm. deep and 4.5 cm. broad and passed upwards, medially and slightly dorsally so as to be inferior, lateral and posterior to the head of the pancreas and antero-medial to the common bile duct. The diverticulum was thin walled and distensible, lined by a folded mucous membrane, and filled with liquid, brown, faecal material.

Pancreas was of average size, shape and consistence. It showed some fat necrosis on its anterior surface and associated oedema and focal haemorrhage in its head. The main pancreatic duct and common bile duct opened into a common ampulla unguarded by any definable sphincter of Oddi. The pancreatic duct was traced horizontally through the head and found to end blindly about 0.5 cm. from the lumen of the duodenum at a level 3 cm. proximal to the opening of the diverticulum.

The other organs exhibited no features worthy of mention.

Microscopical /

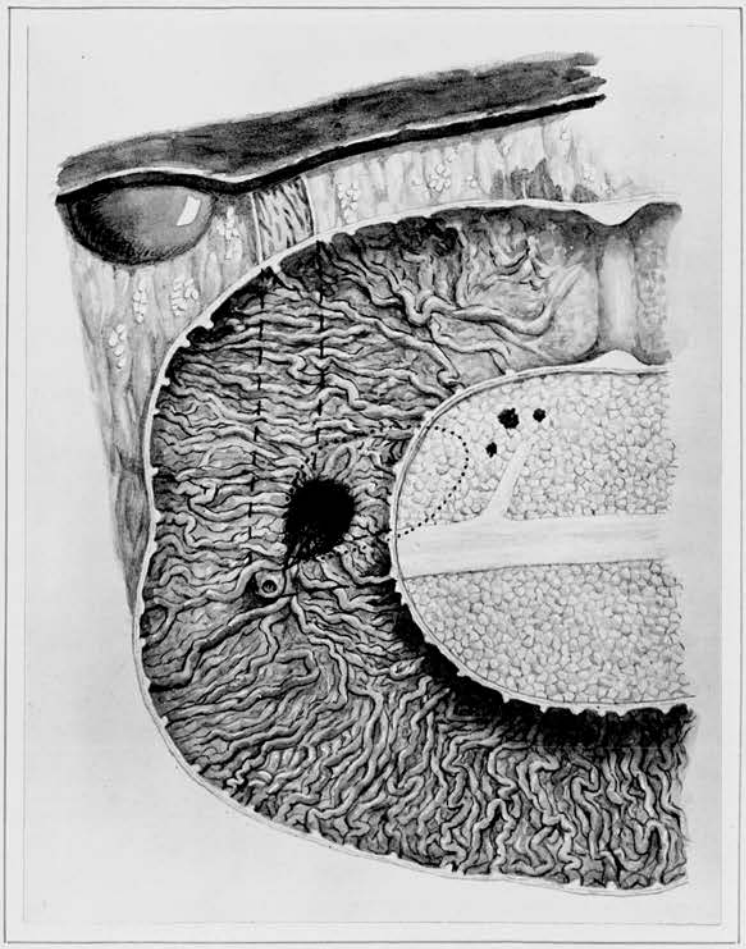

Fig. 4. Case 2. The second part of the duodenum shows a diveticulum, the ostium of which is placed immediately above and medial to the ampulla of Vater. The pancreatic duct is dilated, but the common bile duct and gall bladder are normal. The upper part of the head of the pancreas is marked by three small areas of haemorrhage and in the lesser omentum there are numerous foci of fat necrosis.

Microscopical : The pancreas showed associated chronic and acute changes in all regions, principally the head. Many of the interlobular and some of the intralobular ducts were dilated and lined by flattened epithelium (Figs. 5 & 6). The distended interlobular channels were sometimes characterised by a content of inspissated secretion, desquamated epithelium and polymorphs, and by a slight infiltration of their supporting stroma with round cells, while the dilated intralobular passages occasionally included a few polymorphs. No interlobular ducts, however, were affected by the hyperplastic epithelial metaplasia of Rich and Duff (1936). At the same time, the interlobular arteries and veins were sometimes necrotic, occluded by fibrin, and infiltrated with blood (Figs. 7 & 8). The blood usually extended into the neighbouring tissues and was accompanied by a variable admixture of serous fluid, blood and fibrin. Both the acinar and adipose tissues surrounding the necrotic vessels were also extensively degenerated. The acini had lost their zymogen granules and nuclei and been in places completely replaced by acidophile debris, blood and polymorphs, while the adipose tissue showed the features of fat necrosis. The acinar tissue apart from such necrotic foci was healthy and the pancreatic islets were likewise devoid of change. Briefly, the findings in the pancreas were thus (1) obstructive dilatation of the ducts and (2) acute pancreatic necrosis.

The other organs displayed no features of note.

Case 3.

Clinical History :

The patient was a sparely nourished man, aged 34. He had suffered from diabetes mellitus for eighteen years and had lately been very haphazard about his diet and insulin. One forenoon he experienced an upper abdominal pain which became rapidly worse after lunch and caused him to vomit in the evening. Next day, examination in hospital revealed the presence of acetone +++ in his breath and sugar++, acetone++, albumin++, and granular casts+++ in his urine. The abdomen did not move with respiration and was rigid and tender generally, particularly in the epigastrium. The pulse and temperature were 125 per minute and 99°F respectively. The patient was considered unfit for operation, was treated palliatively, and died four days later.

Post Mortem Examination :

Macroscopical : The body was that of a sparely nourished, young adult male. The duodenum included a diverticulum with its stoma situated 0.5 cm. above/

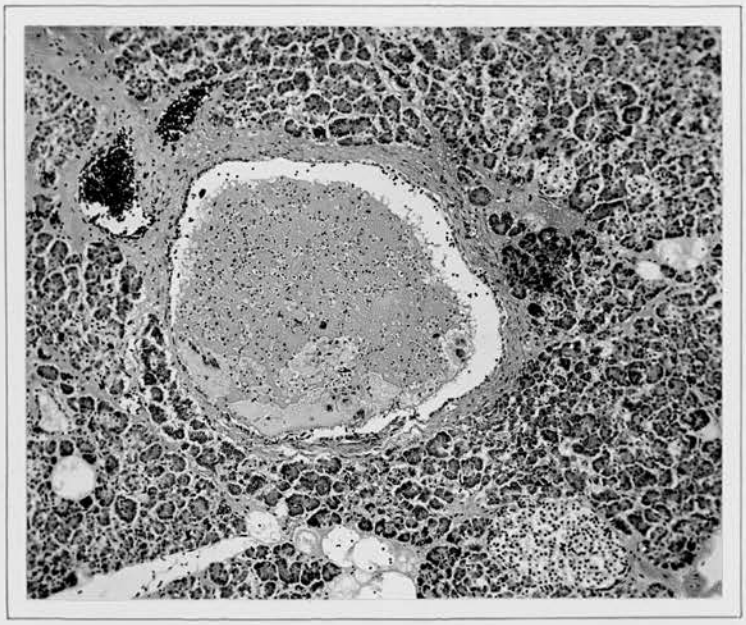

Fig. 5. Case 2. Pancreas. The interlobular duct at centre is distended, lined by flattened epithelium and filled with retained secretion in which are some desquamated cells and many polymorphs. Haematoxylin & Eosin. x 60.

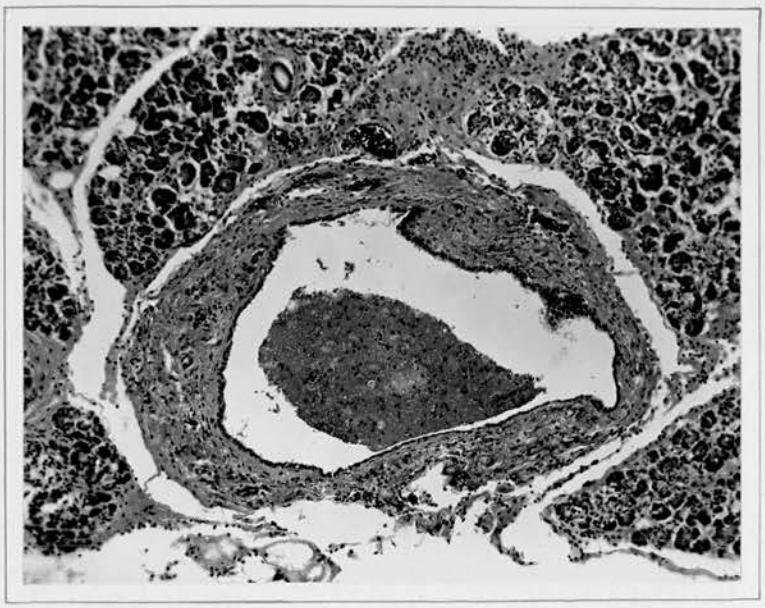

Fig. 6. Case 2. Pancreas. The interlobular duct is distended, lined by flattened epithelium and partly filled with inspissated secretion, polymorphs, round cells, and desquamated epithelium, while the peri-ductal fibrous tissue is slightly infiltrated with inflammatory cells similar to those in the lumen. Haematoxylin & Eosin. x 80.

Fig. 7. Case 2. Pancreas. The interlobular vessel at centre is in great part swollen, hyaline, and necrotic, while the surrounding fibrous and glandular tissues are oedematous and infiltrated with leucocytes and blood. Haematoxylin & Eosin. x 110.

Fig. 8. Case 2. Pancreas. Several interlobular vessels have hyaline, necrotic walls and the septal connective tissues are copiously infiltrated with serous fluid, fresh blood and inflammatory cells. Haematoxylin & Eosin. x 110.

above and medial to the ampulla of Vater (Fig. 9). The ostium was circular being about 0.5 cm. in diameter and gave into a sac 1.75 cm. in depth. The sac was thin walled, expansile, and lined by a healthy mucous membrane. It consisted of a large lateral recess and smaller medial one so that the diverticulum as a whole had a bicornuate appearance. The larger horn was placed medial and posterior to the common bile duct, while the smaller horn was related inferiorly to the pancreatic duct. The horns were separated from the ducts by slips of tissue rather thicker relative to the larger than the smaller horn. The sac contained a little brownish fluid.

The pancreas was of normal size and shape, but unusually firm. The interlobular septa in all regions between the head and the tail showed congestion, localised haemorrhages, and streaks of fat necrosis. The pancreatic duct was normal in size and lined by a healthy mucosa. No accessory duct could be located. The peripancreatic fat was stippled with small patches of fat necrosis, but no evidence of peritonitis was found in the abdominal cavity.

The other organs were devoid of any noteworthy feature.

Microscopical : The pancreas showed a mixture of chronic and acute changes in all parts of its extent. The interlobular and intralobular ducts were often dilated, lined by flattened epithelium and partly occluded by inspissated secretion and desquamated cells (Figs. 10 - 13). No interlobular ducts, however, were affected by the transitional hyperplasia of Rich and Duff (1936). The acinar tissue even apart from the undermentioned necrotic areas was everywhere abnormal, although more so in some parts than others. Thus, the acini were reduced, average or increased as regards size and lined, even in many of average dimensions, by flattened epithelium. Local atrophy and disappearance of the acini had been followed by a certain amount of fibrous overgrowth both within and around the lobules, while the new fibrous material was slightly infiltrated with polymorphs, round cells and foamy histiocytes. These chronic, diffuse changes, however, were overshadowed by the much more acute, focal phenomena ranging from congestion to necrosis. The necrosis affected the arteries and veins, fat and acinar tissue, but involved the fat more extensively than either the vessels or acinar tissue (Fig. 14). The congested and necrotic areas were infiltrated with polymorphs, round cells and foamy histiocytes, while variable amounts of fibrin and blood were also sometimes present in the necrotic parts. About half of the pancreatic islets were hyaline. The main findings in the pancreas were thus (1) obstructive dilatation of the ducts ; (2) early fibrotic atrophy of the acinar tissue ; (3) acute pancreatic necrosis/

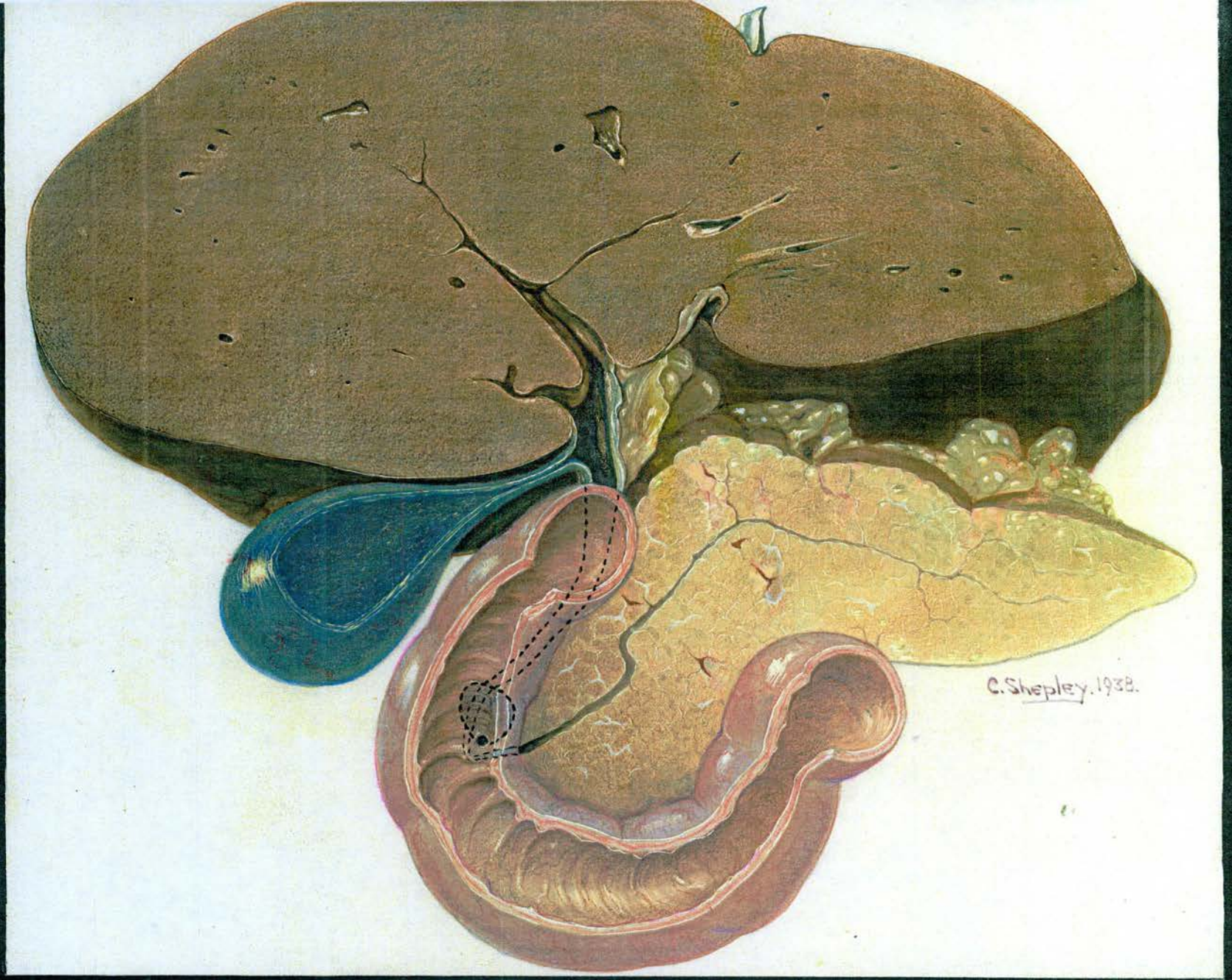

Fig. 9. Case 3. The second part of the duodenum shows a diverticulum, the ostium of which is situated immediately above and medial to the ampulla of Vater. The pancreatic and common bile ducts and the gall bladder are of normal dimensions. Pale streaks of fat necrosis are present throughout the pancreas and in the fat along its upper border, while the body of the pancreas is also characterised by several dark lines of haemorrhage.

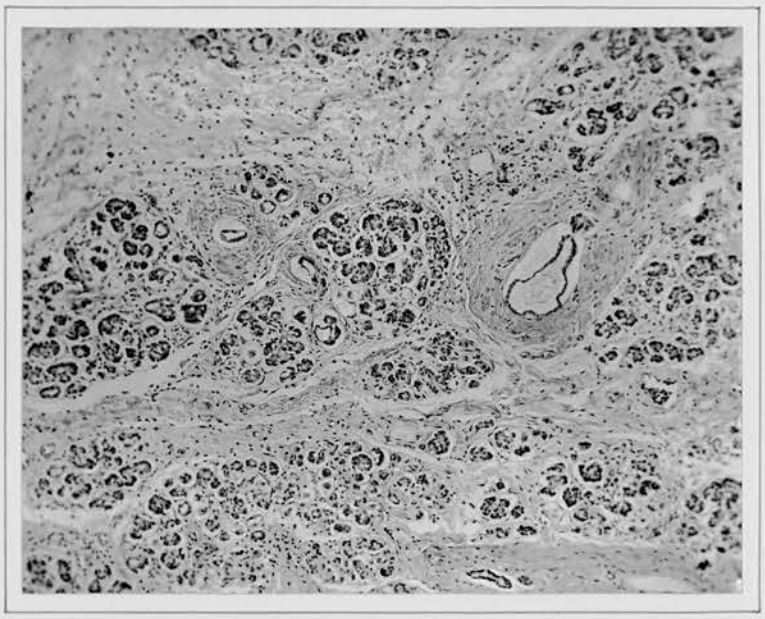

Fig. 10. Case 3. Pancreas. The interlobular duct to right of centre is distended and lined by distinctly flattened epithelium. The acinar tissue shows atrophy and has to a considerable extent been replaced by intersecting bands of fibrous tissue. Haematoxylin & Eosin. x 55.

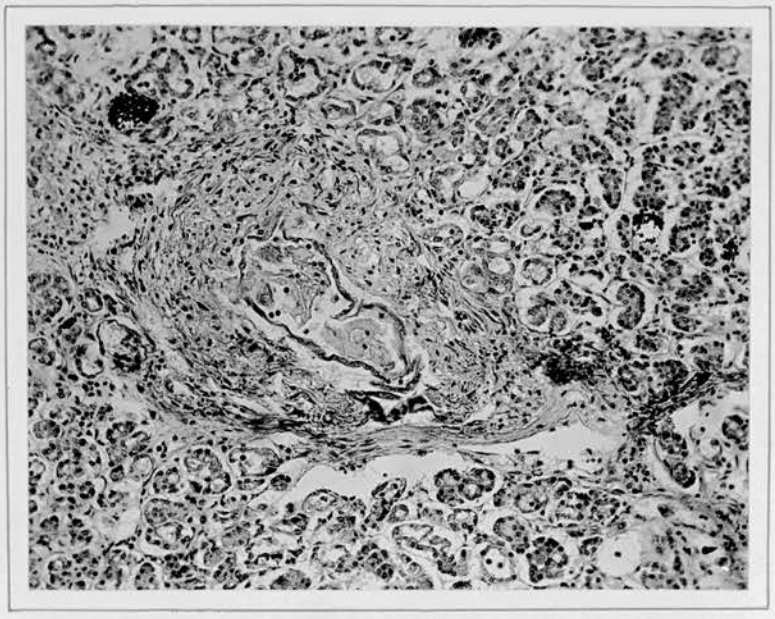

Fig. 11. Case 3. Pancreas. The interlobular duct to left of centre is dilated and lined by flattened epithelium. Both in the secretion within the duct and in the oedematous periductal stroma there are a few inflammatory cells. In the neighbourhood many of the acini show flattening of their epithelium and are incidentally shrunken or distended. Haematoxylin & Eosin. 90.

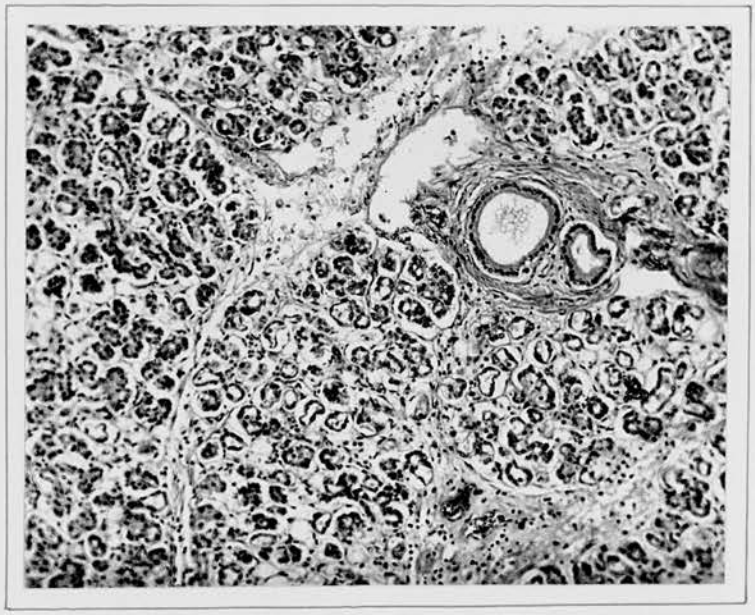

Fig. 12. Case 3. Pancreas. The larger of the two interlobular ducts to right of centre is slightly dilated, while many of the acini are distended or shrunken and lined by flattened epithelium. The periductal, interlobular and interacinar fibrous tissue is slightly increased and scantily infiltrated with chronic inflammatory cells. Haematoxylin & Eosin. x 90.

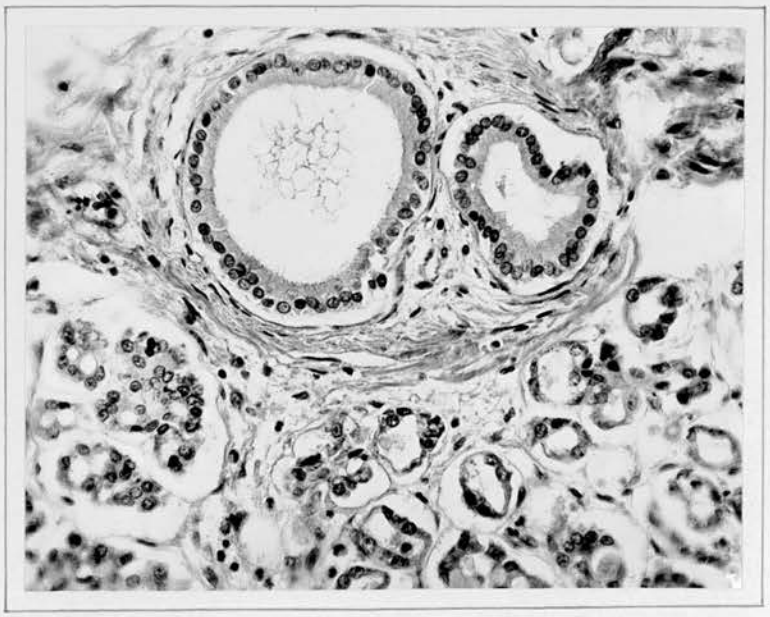

Fig. 13. Case 3. Pancreas. Part of same field as in Fig. 13. The larger of the two interlobular ducts is slightly dilated, while the acini are mostly distended or shrunken and lined by flattened epithelium. Haematoxylin & Eosin. x 270.

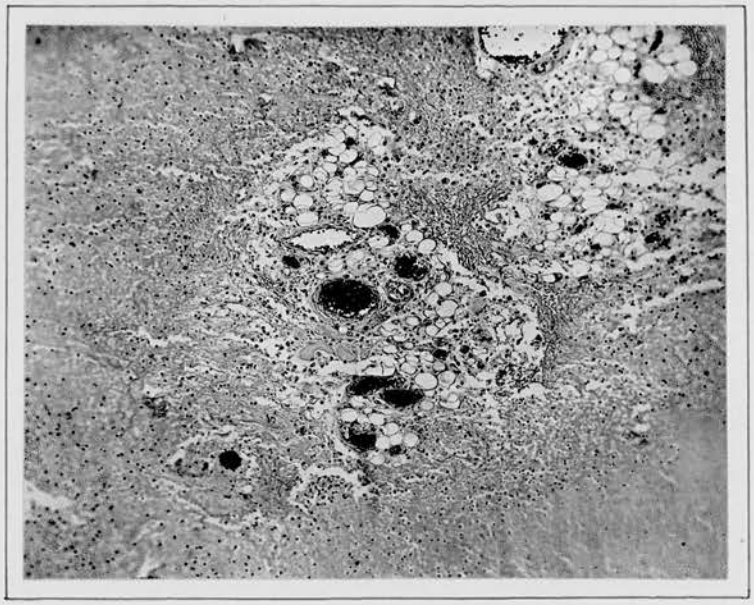

Fig. 14. Case 3. Pancreas. Small areas of congested adipose tissue are present in the centre & at top right. Elsewhere the fat has undergone necrosis and has been replaced by granular debris. Haematoxylin & Eosin x 50.

necrosis; and (4) hyalinisation of the islets.
The other organs were without important features.

Case 4.

Clinical History :

A married woman, aged 46, had for some years been subject after meals to bouts of abdominal discomfort, flatulence and occasionally vomiting. About 7 a.m. one day, she experienced a particularly severe attack of such discomfort and flatulence and at 1 p.m. was struck down by a sudden, agonizing abdominal pain. This symptom was first felt only in the epigastrium, but later over the entire abdomen and subsequently led to repeated vomiting. Examination in hospital at 7 p.m. revealed widespread rigidity and tenderness, most marked in the epigastrium. The breathing was purely thoracic and the liver dulness was diminished. The face was grey and the extremities were cold, while the pulse was impalpable and the temperature was 100.8°F. Treatment consisted in the administration of morphia and digitalin. The patient, however, continued to deteriorate and died nine hours after admission.

Post Mortem Examination :

Macroscopical : The body was that of a well nourished, middle aged female. The abdominal cavity contained about 200 cc. of clear, brownish fluid. The second part of the duodenum included a very thin walled diverticulum. This structure had a circular ostium, 0.5 cm. in diameter, placed immediately medial to the ampulla of Vater and a spherical cavity with a diameter of 3 cm. Its lateral half was situated posterior to the lower end of the common bile duct, while its medial half lay posterior to and above the termination of the pancreatic duct. The sac was completely filled by a firmly impacted calculus. The said stone was relatively soft, made of alternating yellow and brown layers with a slightly fibrous structure, and built up from cholesterol and faecal matter. The duodenal mucosa was normal in appearance.

The pancreas was swollen and soft and marked in its head, body and tail by patchy haemorrhage. This phenomenon was more or less restricted to the interlobular septa and so emphasised the lobular pattern of the tissue. All regions of the organ, particularly the head, showed areas of fat necrosis and further foci of the same condition were found in the fat of the lesser peritoneal sac. The main pancreatic duct was dissected out along its whole length and proved to be normal in both calibre and appearance.

The liver was average in size and shape, but unusually soft and pale. The gall bladder was of normal/

normal dimensions, lined by a healthy mucosa and devoid of stones. The cystic duct was average in calibre, but the common bile duct was dilated to measure 2 cm. in circumference along its whole length. Both ducts were lined by a normal mucous membrane.

The other organs exhibited no features of relevant interest.

Microscopical : All the blocks of tissue taken for examination were so autolysed as to be useless for descriptive purposes.

Discussion.

Duodenal diverticula have, since the publications of Odgers (1929) and Edwards (1935), generally been classified as primary, secondary and vaterine. The diverticulum in each of the above reports exhibited the characteristics of the primary type. Such primary diverticula of the duodenum, as a result of both post mortem [Baldwin (1911), Linsmayer (1914), Nagel (1925), Horton and Mueller (1932), Grant (1935)] and radiological [Case (1920), Cole and Roberts (1920), Andrews (1921), Spriggs and Marxer (1925), Cryderman (1927), Larimore and Graham (1927), Lemmel (1934), Wheeler (1938), Edwards (1939)] investigations, are now recognised as being of relatively common occurrence. Experience has shown that despite this frequency duodenal diverticula are, nevertheless, seldom associated with pathological affections, either of their own structure or of neighbouring organs. Indeed, the earliest authors [see Baldwin (1911)] regarded them as anatomical curiosities with no clinical significance. This view, however, was questioned and rendered untenable/

untenable by Bassett (1907) and Rosenthal (1908) who drew attention to duodenal diverticula as a possible cause of dangerous and even fatal complications. Case (1916) by radiological methods in 1913 demonstrated the existence of a duodenal diverticulum during life and so paved the way to excision of the abnormality as first reported by Forssell and Key (1915), Stewart (1916), Basch (1917), and Ritchie and McWhorter (1917). Since then, the combined observations of post mortem, radiological and operative experience have led to a much increased understanding of duodenal diverticula, particularly regarding the complications to which they are subject or to which they may give rise.

These complications may be detailed as follows :-

1. Obstruction.

(i) Obstruction of duodenum. The following examples of this sequel have been recovered from the literature. Bauer (1912) records the case of a male, aged 52, who suffered from projectile vomiting two or three hours after meals. Post mortem examination revealed a very dilated stomach and two perivaterine diverticula, of which the larger had compressed the more proximal duodenum. According to Basch (1917), a female, aged 36, complained of heartburn, flatulence, and an aching pain in the right upper abdomen. These symptoms were found by Xrays and at operation to be due to a large diverticulum originating from the duodenum at/

at the angle between its second and third parts. The second portion of the duodenum was markedly hypertrophied and dilated, while the third portion was normal in size. Jacquelin and Quénu (1927) report the case of a female, aged 54, who experienced attacks of abdominal pain, vomiting and diarrhoea. A diverticulum 8 cm. long was noted radiologically and at operation with its ostium situated just proximal to the duodenojejunal junction and its fundus presenting between the gall bladder and the duodenal bulb. Resection of the diverticulum effected a complete disappearance of symptoms and a return of the duodenum to its normal shape and position. Cromie (1933) relates how a female, aged 38, experienced a stabbing epigastric pain which came on immediately after food and was relieved by vomiting. Radiological examination disclosed a diverticulum of the fourth part of the duodenum and such a pouch was actually found and excised at the subsequent operation. Cromie suggests that the vomiting which ceased with the operation was caused mechanically by pressure of the pouch on the duodenum.

(ii) Obstruction of common bile duct. Marie (1899) in an autopsy on a male, aged 45, describes the larger of two duodenal diverticula as perivaterine and placed immediately behind the second part of the duodenum. The common bile duct was incidentally dilated. The distension of the duct was regarded by Marie as congenital, but may

more/

more reasonably be interpreted as having been a pressure effect of the perivaterine diverticulum. Rosenthal (1908) records the case of a female, aged 70, who developed increasing jaundice and died. Autopsy revealed an inflamed diverticulum of the perivaterine type, a dilated common bile duct, and areas of fat necrosis on and in the pancreas. According to Bauer (1912), a female of 80 became jaundiced before death. Post mortem examination showed a dilated condition of the bile ducts and gall bladder in association with a diverticulum which arose some centimetres distal to the ampulla of Vater. Wilkie (1913) details two similar cases. A male, aged 58, was seized with abdominal pain, rapidly became collapsed, and died sixteen hours after the onset of his illness. Autopsy disclosed a large diverticulum about 2.5 cm. above the ampulla of Vater, dilatation of both common bile and pancreatic ducts, and evidence of acute pancreatic necrosis. Post mortem a female, aged 47, had a perivaterine diverticulum in immediate lateral relationship to a distended common bile duct. Bell (1921) describes two cases with no symptoms referable to the diverticulum. A male aged 42, showed a perivaterine diverticulum in association with a slightly dilated common bile duct, and another male, aged 61, had two duodenal diverticula, of which the more proximal amounted to a dilatation of the ampulla and lay in front of a moderately distended common bile duct. Bengolea (1928)

reports/

reports the case of a female, aged 46, with a history of two attacks of painless, afebrile jaundice. Radiological investigation revealed a calculus in the gall bladder and a perivaterine diverticulum. At operation, a distended gall bladder was removed and the common bile duct was proved to be free of gall stones, yet jaundice reappeared two months later and was attributed to obstruction of the bile duct by the diverticulum. Odgers (1929) draws attention to the presence in the Royal College of Surgeon's Museum (London) of a pouch 2 cm. above the biliary papilla with some associated dilatation of both common and cystic ducts. Nicholson (1935) records the case of a male, aged 66, who complained of epigastric discomfort and severe jaundice. Post mortem, a duodenal diverticulum was found firmly attached by fibrous adhesions to the common duct and duodenum. The common and cystic ducts were dilated, but the condition of these channels was overshadowed by an enormous enlargement of the gall bladder which actually held 300 cc. of dark green bile.

Evidence of interference with the bile passages occurred in cases 1, 2 and 4 of the above reported series. In case 1, a male aged 69 was admitted to hospital with the symptoms and signs of obstructive jaundice. The post mortem findings were a typical perivaterine diverticulum and a markedly dilated condition of all the biliary passages. Indeed, the degree of dilatation of the common/

common bile duct in this case appears to be the greatest ever recorded as having been produced by a diverticulum of the duodenum. In case 2, a woman of 73 had for two years experienced attacks of abdominal discomfort and jaundice. She died from acute pancreatic necrosis. Post mortem examination revealed a perivaterine diverticulum, but no abnormality of the biliary passages. The dilated condition of the pancreatic duct was nevertheless suggestive of the jaundice having been due to temporary obstruction of the common bile duct by the diverticulum. In case 4, a woman aged 46 was subject after meals to attacks of abdominal discomfort and vomiting. She died from acute pancreatic necrosis and at autopsy showed a perivaterine diverticulum and dilatation of the common bile duct.

(iii) Obstruction of pancreatic duct. Case 1 was remarkable not only for a grossly dilated biliary system, but also for the markedly distended state of the main pancreatic duct and its tributaries. The amount of dilatation of the duct of Wirsung in this subject is unique in my experience and would also appear to surpass that of all other examples of the condition noted in the literature.

Cases 2, 3 and 4 were similar inasmuch as each was characterised by a perivaterine diverticulum and acute pancreatic necrosis. Cases 2 and 3 showed additional resemblance in that the ducts of the pancreas/

pancreas were in each instance dilated and lined by flattened epithelium. In case 2, this dilatation affected principally the main duct and its interlobular tributaries, while the intralobular twigs were affected in less measure. Case 3 had a main duct of normal calibre, but both interlobular and intralobular ducts were considerably dilated. Indicative of obstruction, such distension of the pancreatic ducts is explicable as a pressure effect of the diverticulum which was present in each instance at the exit of the main pancreatic duct. The occurrence of acute pancreatic necrosis in both cases 2 and 3 was thus obviously preceded by obstructive dilatation of the ducts of the pancreas and accordingly by a definite increase in the pancreatic intraductal pressure. The main duct of case 4 was average in calibre. This finding, as proved by microscopical examination of case 3, by no means excludes possible dilatation of the lesser ducts, but the condition of these channels could not unfortunately be assessed owing to the autolysed state of the tissues. The observed dilatation of the common bile duct is, nevertheless, suggestive of some coincidental obstruction of the pancreatic duct having operated in this case also.

The literature includes several records of associated perivaterine diverticulum and acute pancreatic necrosis. According to Bassett (1907), a male, aged 78, was admitted to hospital with a sacral abscess and died from exhaustion. Post mortem/

mortem, haemorrhage in the head of the pancreas was accompanied by necrosis of the fat both within and around the organ. The main pancreatic duct and its branches were dilated, while the glandular tissue was atrophied and fibrous. The duodenum was characterised a short distance proximal and medial to the ampulla of Vater by a diverticulum with inflamed and haemorrhagic wall. The gall bladder and bile ducts were normal in size and free of stones. Rosenthal (1908), as mentioned, records the case of an elderly female who developed jaundice and died. Autopsy revealed an inflamed diverticulum of the perivaterine type and areas of fat necrosis both on and in the pancreas. The pancreatic duct, however, was of normal calibre. The first of the series of duodenal diverticula reported by Wilkie (1913) is also an example of the association. A male, aged 58, was seized with abdominal pain and died sixteen hours later. Autopsy showed a large diverticulum with its ostium situated on the inner aspect of the duodenum about 2.5 cm. above the ampulla of Vater. The main pancreatic duct was dilated and haemorrhage and necrosis in the pancreas were accompanied by fat necrosis both around the pancreas and in the omenta. Molesworth (1929) describes how a male, aged 45, had three attacks of severe abdominal pain. Post mortem, the terminal 4 cm. of the pancreas were necrotic and haemorrhagic, while some focal necrosis was present in the neighbouring fat. A duodenal diverticulum/

diverticulum burrowed into the head of the pancreas about 2 cm. distal to the ampulla. The gall bladder contained three small calculi, but the common bile duct which opened with the duct of Wirsung was free of stones. Rich and Duff (1936) record another relevant case. Autopsy on a male aged 64 showed a duodenal diverticulum in the head of the pancreas, obstruction of the main pancreatic duct, dilatation of the ductules and acini in the pancreas, and the features of acute pancreatic necrosis.

A review of the literature thus discloses five examples of associated perivaterine diverticulum and pancreatic necrosis. Furthermore, the pancreatic duct in the four of these cases in which its condition is mentioned is described as normal in one and dilated in three. These three cases may thus reasonably be accredited with a raised pressure throughout the duct system of the pancreas prior to the acute haemorrhagic incident. The same conclusion regarding intraductal pressure was justifiable in two of the three cases of pancreatic necrosis reported above. Five of the combined group of seven cases in which the condition of the ducts was investigated thus exhibited the common factor of a raised intraductal pressure, while a similar state cannot be denied as possibly having obtained also in the remaining subjects.

Rich and Duff (1936) basing their observations on both post mortem and experimental material regard all/

all the phenomena of acute pancreatic necrosis as explicable on the grounds of an escape of pancreatic juice from the ducts into the surrounding tissues. The tryptic ferment in the form of either already active trypsin or activated trypsinogen then produces hyaline necrosis of the arteries and veins with resultant haemorrhage, while the lipase splits the neutral fat of the adipose tissue with consequent fat necrosis. An escape of pancreatic juice into the organ infers destruction or rupture of the ducts or acini and such damage may in the opinion of the above authors be brought about by a variety of mechanisms including (a) external trauma; (b) infarction ; (c) infection ; (d) retrojection of bile into the pancreatic duct ; and (e) obstruction of the ducts either from outside the pancreas or within its substance.

Trauma must, despite the reported association of pancreatic necrosis with violence by Drennen (1922), Armstrong (1939) and Adams (1939), be regarded as on the whole of minor etiological significance. Rich and Duff (1936) describe how in one case the occurrence of pancreatic necrosis was preceded by focal infarction of the organ, but such a phenomenon, like trauma, can again only be classed as a rare cause of the condition.

Infection as an exciting factor in the disease still remains unproven. No doubt, bacteria may spread to the pancreas from various sources and in several ways, e.g., from an infected biliary system via lymphatics/

lymphatics or pancreatic duct, from the intestine by the retrojection of infected juice along the duct of Wirsung, or from a distant focus of inflammation by the blood stream, but spread of infection to the pancreas has been assumed to have occurred much more often than it has ever been demonstrated. Moreover, the mere entry of infection into the pancreatic duct will not of itself provoke pancreatic necrosis unless it leads, as an intermediate effect, to disruption of the ducts or acini with liberation of potent tryptic ferment. The retrojection of bile into the pancreatic duct has been cited as a cause of the disease ever since Opie (1901) and Bunting (1906) published cases of pancreatic necrosis entailing obstruction of the ampulla of Vater by a gall stone. Such an occurrence, however, is uncommon and acts, according to Rich and Duff, not by reason of the fact that bile is an irritant or activator, but simply because it raises the intraductal pressure to such an extent as to rupture the duct-acinar system, mechanically. This opinion is supported by the observation that several agents other than bile, e.g., gastric juice, acids, alkalis and formaldehyde, have been found by Dragstedt, Haymond and Ellis (1934) to be capable of producing pancreatic necrosis experimentally.

Obstruction of the duct system of the pancreas, however, is in the opinion of Rich and Duff (1936) by far the commonest cause of pancreatic necrosis./

necrosis. This obstruction sometimes occurs in relation to the main duct and is due to such factors as a duodenal diverticulum, pancreatic calculus [Rienhoff and and Lewis (1934)] , and gall stone in the lower end of the common bile duct, but is usually found in the tributaries of the main duct within the pancreas and takes the form of a proliferative and transitional metaplasia of the lining epithelium. Cole (1938) reviewing the pathogenesis of acute pancreatic necrosis also emphasises the importance of duct obstruction and this theory is further supported by the above eight examples of associated pancreatic necrosis and perivaterine diverticulum, and particularly by the five of those cases wherein obstruction was evident in the dilated pancreatic ducts and acini.

Duct obstruction, however, cannot be regarded, in view of the non-occurrence of pancreatic necrosis in case 1, in the not uncommon instances of carcinoma of head of pancreas with associated compression of the main duct and in many animals subjected to ligation of the pancreatic duct, as being always or necessarily provocative of pancreatic necrosis. Such exceptions may very reasonably be explained on the grounds of variation in the secretory activity of the pancreatic acini, as suggested by two observations : first, Eggers (1924) was able to produce pancreatic necrosis by duct ligation only when carried out during active digestion ; secondly, pancreatic necrosis/

necrosis often develops shortly after the patient has indulged in a large meal or a bout of alcoholism. The epigastric pain heralding the onset of the disease in case 2, it may be remembered, developed in the forenoon and became worse after lunch. The frequency of pancreatitis in obese persons is probably a related observation inasmuch as such individuals sometimes eat large meals. The absence of necrosis in case 1 may thus have been due to the fact that the glands were markedly atrophied and so capable of secreting only small amounts of juice.

2. Diverticulitis. The relative immunity of duodenal diverticula towards this complication is probably dependent on three factors : (i) the sterility of their content ; (ii) their retro-peritoneal situation permitting of ready distension ; and (iii) their inverted position and the usually wide mouthed character of their ostium, together tending to effect free drainage into the bowel. On the other hand, (iv) the ostium, as in the first three of the above cases, is often concealed among the plicae circulares of the duodenum and (v) little or no muscle is present in the wall of the sac. These facts taken together suggest that duodenal diverticula, once filled, may not readily empty themselves. Thus, Case (1920), while regarding the average emptying time of the sac as eleven hours, not uncommonly noted retention of barium beyond forty eight hours and in one subject for seven/

seven days. Stagnation of the content favours bacterial growth and consequently infection of the wall and diverticulitis.

The rarity of duodenal diverticulitis may be gauged from the small number of recorded cases and is emphasised by the frequency of diverticulitis of the ileum and especially colon. Bassett (1907), Rosenthal (1908), and Bauer (1912) were the first to record cases of inflamed duodenal diverticula and accounts of these have already been given. Downes (1922) describes how operation in a female, aged 39, who complained of upper abdominal pain and vomiting, disclosed two acutely inflamed diverticula springing from the third part of the duodenum. Huddy (1923) removed from a female, aged 27, with a history of epigastric pain and vomiting, a perivaterine diverticulum showing severe congestion, haemorrhage, acute inflammatory infiltration, and necrosis. Butler and Ritvo (1925) record the case of a male, aged 40, who suffered from attacks of epigastric pain, vomiting and diarrhoea. A diverticulum with marked inflammatory changes took origin from the junction between the first and second parts of the duodenum and inversion of the abnormality was followed by complete relief of symptoms. The cases mentioned later under peri-diverticulitis may naturally be included as examples of diverticulitis. Again, Downes (1922), Maclean (1923, 1927), Lund (1928), and others describe cases in which the symptomatology was suggestive of diverticulitis,/

diverticulitis, but wherein the diagnosis remained without either macroscopical or microscopical confirmation.

Diverticulitis may in turn lead to one or other of several sequelae, but all of these, according to a review of the literature, are like diverticulitis itself in being rare occurrences :-

(i) Perforation. Monsarrat (1926) records the case of a female, aged 58, who developed a severe pain below the ribs and at operation showed, springing by a stalk from the second part of the duodenum, a pouch which had perforated at its apex. According to Beaver (1938), a male aged 54 experienced severe abdominal pain and vomited several times. Post mortem a diverticulum was found on each side of the ampulla of Vater ; the pouch to the right was acutely inflamed and had ruptured at its apex. Boland (1939) describes the case of a 59 years' old male who was seized with intense upper abdominal pain and died after a laparotomy. Autopsy revealed a perivaterine diverticulum which had perforated at its apex.

(ii) Peridiverticulitis. Case (1916) records the case of a female, aged 45, who had gastric symptoms for six years and proved radiologically to have a diverticulum of the third part of the duodenum. The pouch was so intimately adherent to the surrounding pancreatic tissues a to be impossible of excision. Maclean (1927) details two relevant cases. A male, aged 37, complained of epigastric/

epigastric pain and was found on radiological examination to have a diverticulum of the fourth part of the duodenum. Operation further revealed the presence of fibrous adhesions between the right half of the transverse colon and duodenum. Since no other abnormality was found in the neighbourhood, the adhesions were attributed to involvement of the peritoneum in an inflammatory process taking origin in the diverticulum. A female who complained of epigastric pain was proved by X-rays and operation to have a diverticulum of the third part of the duodenum. Simultaneously, the duodenum was obscured by an"inflammatory veil", the source of which was attributed to the pouch. According to Lucinian (1930), a female aged 36 complained of epigastric pain unrelated to food ; radiological investigation revealed a duodenal diverticulum and the pouch at operation was found to be perivaterine in position and walled off from the head of the pancreas by inflammatory tissue. Nicholson (1935) describes how a male of 66 complained of epigastric discomfort and severe jaundice and how autopsy disclosed a perivaterine diverticulum attached by dense fibrous adhesions to the common bile duct and duodenum.

(iii) Duodenitis. This is a rare sequel. Bauer (1912) as already mentioned, relates how a female, aged 80, developed jaundice and how post mortem a diverticulum some centimetres distal to the ampulla was associated with an inflamed duodenum covered/

covered with mucus. Wilkie (1913), as also quoted, describes two cases of considered duodenitis. As evidence of this condition, however, he only mentions a coating of tenacious mucus in the duodenum of the first of his cases.

(iv) Cholangitis. Bauer (1912) in the second of his two cases describes inflammation of the bile ducts as a sequel to diverticulosis and diverticulitis of the duodenum, but this is the only record of the association in the literature.

3. Content of calculi.

(i) Enteroliths. Case 4 of this series, despite the many published accounts of duodenal diverticula, is the first to describe a calculus in a duodenal pouch. The reasons for the rarity of lithiasis in such a diverticulum are probably similar to those preventing the occurrence of diverticulitis. The usual outcome of the factors concerned is to effect free drainage into the bowel, but this favourable result must obviously have been replaced in case 4 by an unusually sluggish ebb and flow of intestinal fluid out of and into the pouch.

(ii) Gall stones. Chomel (1710) in a female of 80 discovered a duodenal pouch containing 22 stones. Odgers (1929) reviewing this case, which is in effect the first record of duodenal diverticulosis, considers that the pouch was probably a dilated ampulla of Vater and that the stones in it were biliary calculi. Harley (1857) in a male, aged 87, describes at a point midway between the/

the pylorus and Vater's ampulla a diverticulum containing a large gall stone. The diverticulum here, in view of the gall bladder being thickened and buried in adhesions, was probably a traction pouch into which the gall stone had ulcerated. Harries (1932) operating on a female, aged 49, who experienced acute pain in the right hypochondrium discovered a perivaterine diverticulum with a large, annular, mainly cholesterol stone. He suggests that the component parts of the stone originated in the gall bladder and became fused in the diverticulum.

4. Carcinoma. Morrison and Feldman (1925, 1926) report the only case of malignancy in association with a duodenal diverticulum. A diverticulum in a man of 59 took origin from the duodenal cap and showed at its mouth a small, indurated carcinoma which had led to secondary invasion of the regional lymph glands and liver. The absence of a post mortem examination unfortunately leaves undecided the exact nature of this pouch and its relation to the growth at its entrance.

Summary.

(1) Four cases of perivaterine diverticulum are described.

(2) The diverticulum in case 1 produced gross obstruction and dilatation of both the pancreatic and common bile ducts, with resultant atrophy of the/

the pancreas and death from obstructive jaundice.

(3) The diverticulum in each of cases 2, 3 and 4 was associated with acute pancreatic necrosis.

(4) The aetiology of acute pancreatic necrosis is discussed and is shown, on the basis of cases 2, 3 and 4, to involve a considerable obstructive element, at least in some cases.

(5) The complications of duodenal diverticula are classed as :-

(i) obstruction of (a) duodenum ; (b) common bile duct ; and (c) pancreatic duct :

(ii) diverticulitis, of which the possible sequelae are (a) perforation ; (b) peridiverticulitis ; (c) duodenitis ; and (d) cholangitis :

(iii) content of calculi : (a) enteroliths ; and (b) gall stones.

(iv) carcinoma.

These complications, despite the known frequency of duodenal diverticula as revealed post mortem and radiologically, are rare, but examples of each are culled from the literature.

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