function is restored after the obstruction is relieved.

This functional test is also applicable to other abdominal conditions which will be discussed in detail in a subsequent article.

SUMMARY

The extended application of intravenous urography has been employed for accurate determination and exact localization of ureteral obstruction.

The radiological signs. significant of ureteral obstruction have been described in detail and they consist of: (*a*) The early radiological evidence of ureteral block. (*b*) The impregnation of the renal parenchyma. (*c*) The stasis. (*d*) Reverse visualization of the collecting system.

The early localization of ureteral obstruction has been shown to be most important if the kidney function is to be saved.

To determine the residual renal function in cases of ureteral obstruction repeated intravenous urographies are strongly recommended. If the stasis is getting less, surgical intervention should be withheld. However, if the stasis is increasing the ureteral obstruction must be relieved as soon as possible if the kidney is to be saved.

CONCLUSION

A method of radiological localization of ureteral obstruction by means of the intravenous pyelogram has been described. The roentgenological signs whereby such obstruction, be it opaque or non-opaque, may be recognized and accurately localized have been discussed in detail. The localization and relief of this obstruction is most important and must not be neglected if the kidney function is to be saved. The intravenous pyelogram is the best and easiest method to ascertain *individual* kidney function.

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ALLOXAN DIABETES*

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THE intravenous injection of alloxan‡ induces a triphasic modification of the blood sugar level; (*a*) initial hyperglycæmia; (*b*) secondary hypoglycæmia; and (*c*) final hyperglycæmia.

The liver is essential for the initial hyperglycæmia since this does not appear in hepatectomized dogs[11, 12] or toads[9] or in eviscerated dogs.[11, 12] The initial hyperglycæmia was observed in dogs after splanchnicectomy[11, 12] in adrenalectomized dogs[11, 12] or toads[9] but not in adrenalectomized rats.[12] In the dog the injection of alloxan produces a rise in blood pressure which is not due to the liberation of adrenaline as shown by suprareno-jugular anastomosis (Houssay and Rapela, unpublished data).

The secondary hypoglycæmia is not due to the liberation of insulin, but to an extrapancreatic effect; probably lack of glucose production by the liver. It is observed in dogs which have been pancreatectomized 30 minutes before the injection of alloxan, but not, or seldom, in those pancreatectomized 24 hours or more previously[11, 12] (Table I). Alloxan produces the secondary hypoglycæmia also in pancreatectomized toads and lessens the diabetogenic action of the hypophysis in hypophysectomized-pancreatectomized toads.[9] In hypophysectomized or adrenalectomized rats the secondary hypoglycæmia is very pronounced and may be counteracted by the administration of adrenocortical extract (Martinez, unpublished data).

The final hyperglycæmia is mainly due to the selective destruction of the beta cells of the islets of Langerhans. The pancreas thus damaged secretes very little or no insulin, as may be shown by grafting it into the neck of diabetic dogs.

In the rat and the rabbit a coagulation necrosis of the beta cells may be observed. In the dog there is degranulation, nuclear alterations and gradual destruction. The beta cells diminish in number from the 4th day; only 50% are to be found at about the 8th day and later on they are still more scarce. At the end

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‡ The ureide of mesoxalic acid.

TABLE I.

BLOOD SUGAR CHANGES (MGM./100 C.C.) PRODUCED BY INTRAVENOUS INJECTION OF ALLOXAN INTO PANCREATECTOMIZED CHLORALOSED DOGS

Weight (kg.)	Time (hours) 0	½	1	2	3	4	5	6	Survival-time (hours)
Pancreatectomized ½ hour before—Alloxan injected									
10.0	95	86	72	63	50	50	..	..	4½
7.5	96	78	69	51	53	28	..	..	5
10.0	94	128	119	100	87	..	87	85	..
7.0	106	102	115	115	84	79	79	81	..
4.5	83	72	50	40	..	43	58	52	..
5.2	82	110	93	52	48	32	24	..	6
7.9	126	154	159	150	97	57	34	48	..
6.8	62	64	81	56	52	52	44	34	..
6.9	72	82	163	164	115	83	65	..	..
Pancreatectomized ½ hour before—No Alloxan									
13.0	78	69	100	114	158	180	185	180	..
13.0	87	78	78	103	103	140	131	149	..
..	82	70	72	108	126	148	158	166	..
..	91	76	78	116	132	156	168	176	..
Pancreatectomized 24 hours before—Alloxan injected									
9.2	260	313	345	369	..	419	..	471	..
9.0	222	228	260	266	260	280	284	294	..
9.0	241	219	294	367	370	373	382	382	..
..	240	..	236	284	320	340	362	378	..
5.8	217	199	189	182	182	168	134	136	..
5.6	245	232	241	296	304	321	376	439	..

of 1 to 6 months only 1 to 4 beta cells are found in each islet, while the alpha-cells persist and even increase in number. In the rat there is an early regeneration of insular cells due to mitosis of centroacinous cells or of those of the wall of the small ducts.

The exocrine tissue of the pancreas is not always undamaged. In 22% of the diabetic dogs which die, fatty necrosis is found (25 out of 111 cases;[1, 7] Figs. 1 and 2). In the lungs congestive or ecchymotic patches are frequently observed; with high doses (100 to 200 mgm./kg.) acute pulmonary œdema is sometimes produced. In the liver there is fatty infiltration and some cellular lesions (Fig. 3). If the dose is a high one (100 to 200 mgm./kg.) centro-lobular or massive necrosis and hepatosis with icterus and diminution of plasma prothrombin may be produced. In dogs which have been diabetic for more than 40 days there is always a marked fatty degeneration of the centrolobular cells.

In the kidney there is glomerular congestion and lesions of the cells of the convoluted tubules and Henle's loop (albuminous degeneration, fatty infiltration and glycogen deposits). If the dose is a high one (75 to 100 mgm./kg.) coagulation necrosis is produced, similar to that due to mercurial salts, in which case the dogs die with uræmic diabetes. With smaller doses (50 mgm./kg.) there is an increase in the blood non-protein nitrogen, which is transitory if the

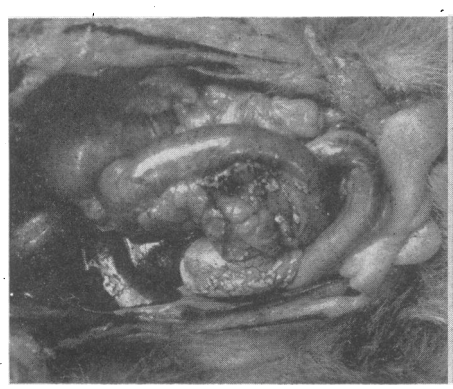

Fig. 1

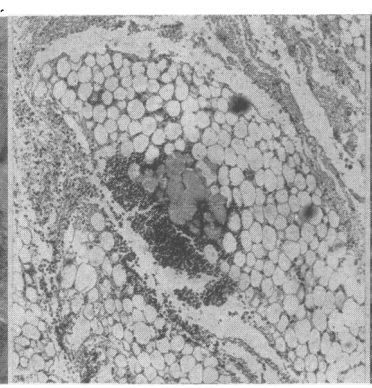

Fig. 2a

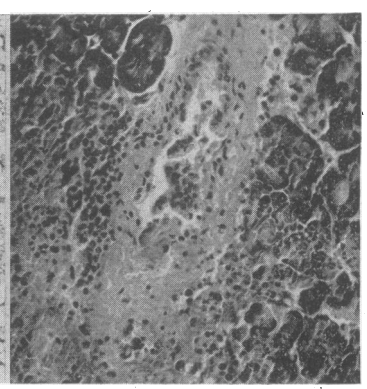

Fig. 2b

Fig. 1.—Fatty necrosis on pancreas, mesentery and kidney perirenal fat, after injection of alloxan in the dog. **Fig. 2a.**—Interlobular fatty necrosis of dog pancreas after alloxan; infiltration of small cells. **Fig. 2b.**—Necrosis of the wall of a pancreatic duct after alloxan, dog.

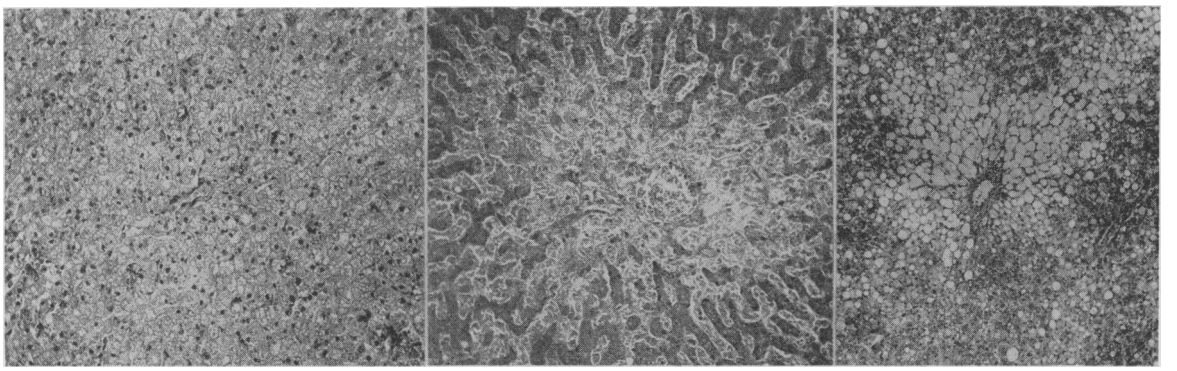

Fig. 3 Fig. 3a Fig. 3b

Hepatic lesions after alloxan in dog. **Fig. 3.**—After 48 hours: acute lesions, fatty infiltration, pyknosis, and some centrolobular necrosis. **Fig. 3a.**—After 8 days: congestion centrolobular necrosis. **Fig. 3b.**—After 248 days: centrolobular and mediozonal fatty degeneration.

dogs survive, but which may increase until the dogs die in uræmia in about 5 to 8 days.

The initial lesions of the lung, liver and kidney may be transitory and reversible. The diabetes is transitory or permanent; the transitory form is more frequent when small doses are given (Table IIa).

TABLE IIa
TRANSIENT DIABETES WITH DIFFERENT DOSES OF ALLOXAN IN THE DOG

	Transient diabetes in relation to permanent		*Permanent diabetes in relation to total number of dogs injected*	
Dose mgm./kg.	*No. of animals*	*% diabetic*	*No. of animals*	*%*
40	5/16	31	16/35	45
50	3/70	4	70/89	78
75	0/28	0	28/30	93

TABLE IIb
INCREASED RESISTANCE AFTER INCREASING WEEKLY DOSES OF ALLOXAN IN THE DOG

		Permanent diabetes in relation to total number of dogs injected	
Week No.	*Dose (mgm./kg.)*	*No. of animals*	*% diabetic*
1	30	0/12	0
2	40	0/12	0
3	50	0/12	0
4	75	3/12	25
5	100	2/8	25

The action of alloxan is rapid and depends on its reaching a sufficient concentration in the blood. As it disappears rapidly the rate of injection is very important. It is better to inject into the saphenous vein rather than into the jugular vein as acute pulmonary œdema is thus frequently avoided. In the dog a dose of 100 to 200 mgm./kg. produces death by acute pulmonary œdema, acute hepatosis with jaundice or uræmic diabetes. With 75 mgm./kg. the majority of the animals die with uræmic diabetes. The most favourable dose is 50 mgm./kg. (0.2 c.c. of a 1% solution per kg. per second; Table IIa). A partial resection of the pancreas (6/7 of its mass) does not increase the sensitivity of dogs to the diabetogenic action of alloxan, while making them very sensitive to the diabetogenic action of anterohypophysis or thyroid, which produce diabetes by a different mechanism (Table III).

The diabetogenic action of alloxan is not modified in dogs deprived of adrenal medulla, thyroids or parathyroids; or in dogs in hypoglycæmia caused by insulin or phloridzin; or in hyperglycæmia caused by the administration of glucose. Many animals die in the first week following the injection of alloxan; with 50 mgm./kg. a greater number survive than with higher doses. Among 170 dogs 35 survived from 8 to 240 days.

Accumulation of effects may be observed in various species. In the dog a single dose of 40 mgm./kg. provokes diabetes in 35 to 45% of cases; but if this dose is repeated during 3 to 10 consecutive days most of the dogs will become diabetic;[7] on the other hand resistance to the drug is produced if increasing doses (30, 40, 50, 75, 100 mgm./kg.) are injected once a week[7] (Table IIb).

Diabetes appears very soon; with a single injection it appears in the dog after one day (60%) or two days (24%). Its onset is later when caused by reinjection of smaller doses. A transitory diabetes is observed with small doses and rarely with higher doses. Diabetes is,

TABLE III.

DIABETOGENIC DOSE OF ALLOXAN IN DOGS: CONTROLS (INTACT PANCREAS) OR PARTIALLY PANCREATECTOMIZED (PANCREAS REDUCED TO 1/7)

Alloxan mgm./kg.	*Dogs*	*Permanent diabetes*	*Transient diabetes*	*No diabetes*	*% of diabetes*
75	Controls	13	0	1	93
75	Pancreatectomized	11	0	0	100
50	Controls	19	3	7	65
50	Pancreatectomized	7	1	3	64
40	Controls	3	0	8	28
40	Pancreatectomized	4	2	9	27

at the beginning, of moderate intensity (Table IV), but becomes gradually more severe, being at the end of severity comparable to the diabetes due to pancreatectomy.[7]

TABLE IV.

AVERAGE VALUES IN META-ALLOXANIC DIABETES

Blood sugar mgm./100 c.c	180-450
Glycosuria gm./kg./day	0.9-2.8
Urinary N gm./kg./day	0.4-1.3
G/N quotient	2-2.7
Ketone bodies mgm./kg./day	10-50 to 210

Intravenous glucose tolerance curves are of the diabetic type in the dog.[7] In the rat with alloxan diabetes glucose given by stomach tube produces a higher hyperglycæmia and less glycogen deposit in the liver and muscles than in the controls[10] (Fig. 4). The rate of intestinal absorption of glucose is increased during diabetes and becomes normal when the blood sugar returns to normal (Penhos, unpublished experiments in rats).

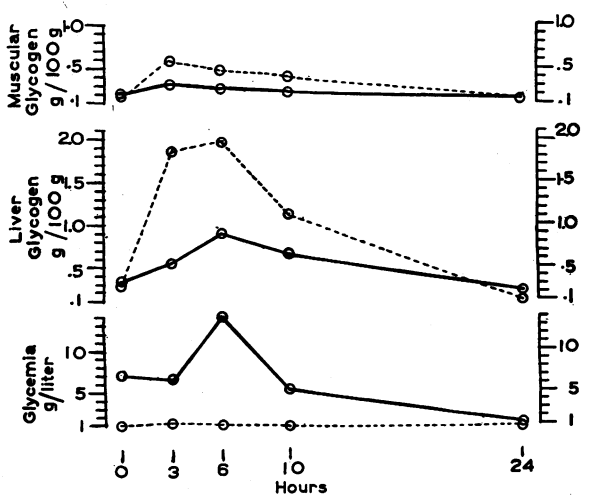

Fig. 4.—Modifications of blood sugar, liver glycogen and muscle glycogen of normal rats (o- - -o) and rats after 48 hours injection of alloxan (o——o) 160 mgm./kg. —— Ingestion of glucose (6 gm./kg.) at 0 hour after 15 hours of fasting. —— Each number is the average of 5 rats. (Houssay, B. A. and Mazzocco, P.)

Alloxan produces a transitory increase in metabolism whether it produces diabetes or not. If the animal remains in hyperglycæmia an increase in metabolism is observed when the diabetes is severe.[7] Coincident with the hyperglycæmia an increase of inorganic phosphorus in plasma occurs. Hepatectomy produces, as in any other type of diabetes, a rapid fall of blood sugar. In only two cases the fall was slow.[7] As the lesions of the beta cells are rapidly produced, only in a few dogs was it possible to cure the diabetes by daily injections of insulin or phloridzin during some weeks (Table V), and this only if treatment was begun promptly. When treatment was delayed for a few weeks, insulin controlled the hyperglycæmia but did not cure the diabetes.

TABLE V.

THE AMELIORATION OF ALLOXAN-DIABETES BY PRECOCIOUS TREATMENT

No. of dogs	18	23
Precocious treatment with	Phloridzin	Insulin
Dead	12	14
Cured	4	3
Not cured	2	4

As originally found by Carrasco-Formiguera we have confirmed that thyroid administration causes diabetes in dogs with islet lesions produced by recent injections of alloxan and transitory hyperglycæmia;[7] but it does not cause diabetes in those in which alloxan has not produced hyperglycæmia nor islet lesions (Table VI).

TABLE VI.

DIABETES BY THYROID TREATMENT AFTER THE ACTION OF ALLOXAN IN THE DOG

	No diabetes	*Diabetes*
Without previous transient alloxen diabetes	5	0
With transient alloxan diabetes... (With 1, 1, 1, 2, 4 treatments with thyroid)	0	5

The effect of previous diet has been studied in the rat by Martinez.[15] A diet rich in lard diminishes greatly the resistance to alloxan, a defect which can be corrected by the addition of methionine or thiouracil but not by choline. Some fats (olive oil, butter) have little effect, while others increase the resistance (oleomargarine, corn and especially cocoanut oil).

The endocrine system is important. In the rat thyroidectomy increases definitely the resistance to alloxan,[13, 14] and thiouracil has an even greater effect than thyroidectomy.[17] In thyroid feeding experiments the resistance is diminished at the 20th day and increased at the 60th day. In the dog thyroidectomy did not modify meta-alloxanic diabetes.[7] Adrenalectomy diminishes the resistance to alloxan in the rat (Martinez, De Majo) and the dog; in the former it causes a marked secondary hypoglycæmia. In the dog with meta-alloxanic diabetes adrenalectomy is followed by a rapid decrease of the blood sugar to normal or subnormal levels. After alloxan injections there is a decrease of adrenalin, ascorbic acid and cholesterol of the adrenals (De Majo).

Alloxan produces a more marked secondary hypoglycæmia in female than in male rats (Martinez). Subtotal pancreatectomy does not modify the resistance of the dog to alloxan[7] but increases it in the rat.[19] This effect is possibly due to modification of the beta cells of the pancreatic remnant or to an increased resistance of the newly formed beta cells.

Alloxan injection in high doses diminishes the diabetogenic action of the hypophysis in the toad[9] but not in the rat.[8] In the latter only the gonadotrophic action is diminished while the other actions are not modified (growth, thyrotrophic, adrenotrophic). Alloxan is a toxic substance with multiple initial actions (liver, kidney, pancreas and sometimes lungs). These lesions may be transitory and reversible if the animal survives, except in the pancreatic islets where they are irreversible. The selective destruction of the beta cells which accompanies diabetes is a proof that these cells secrete insulin. A very interesting type of experimental diabetes is produced, characterized by its evolution and by the conservation of the alpha cells and of the exocrine pancreatic tissue.

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NOTES ON CHOLECYSTECTOMY

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THE item of cholecystetomy seems to merit more than average consideration both from the standpoint of decision for or against operation, and of technique. The latter problem is discussed very briefly in this paper.

THE INCISION

A transverse incision, in our experience, gives the best exposure unless the patient has a very acute costal angle. Such an abdomen should be entered through a vertical incision. This is best placed at least 3 cm. from the midline so that a large piece of fascia is available for closure. After the anterior rectus sheath has been separated from the muscle at the transverse attachments and the corresponding vessels ligated, the muscle is displaced laterally. The skin towels are sutured to the fascia (anterior rectus sheath) before the peritoneum and transversus structures are incised. The length of the skin incision is longer than that in the rectus sheath, which in turn is longer than the opening in the transversalis and peritoneum. The fascia and peritoneal incision should never be longer than the skin. This predisposes to inadequate and unsatisfactory suturing. Neither should the muscles be separated by pulling and tearing the fibres apart. Good healing and painless wounds are dependent upon minimum trauma and sharp knife dissection.

The transverse incision starts approximately half way between the umbilicus and the