8. Insulin convulsions in rabbits may be relieved, and the animals restored to normal, by injection of adrenaline.

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THE ADMINISTRATION OF INSULIN BY INUNCTION.

BY

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DURING the course of recent experimental work in conjunction with Professor D. Noël Paton on the isolation and subsequent testing of insulin the possible methods of administering this preparation formed one of the subjects of consideration. The method of subcutaneous injection of sterilized aqueous solutions of known strength was employed in the determinations of "potency" of the insulin which was isolated from time to time in the laboratory. Hypodermic medication has also been employed habitually in the clinical use of this material. It is obvious, however, that if the drug is to be employed for long periods this method of administration might, in many cases, prove to be a serious drawback.

In considering the possible methods of administration, it occurred to me that the skin surface might be utilized for the absorption of the drug by inunction. The following experiments on rabbits were accordingly carried out, to ascertain primarily if the inunction of a paste in which insulin was incorporated would produce the effects obtained by direct injection of an insulin solution.

Simple ointments of varying strength were made by mixing weighed quantities of crude insulin, isolated from ox pancreas in the laboratory (by the method communicated by Dr. Dale of the National Institute for Medical Research) with small quantities of lanoline and with lard. The abdomen of each rabbit, which had been starved for seventeen hours, was shaved, care being taken to avoid injury to the skin surface, and the insulin paste gently rubbed in over the bare area.

TABLE I.—Inunction of Insulin in Rabbits.

	Weight of Crude Insulin used.	Blood Sugar.		Remarks.
		Time Intervals.	Glucose per cent.	
Experiment 1. Mar. 30, 1923.	0.3 gm. in 1 gms. hydrous lanoline	10.50 p.m. 12 noon 2.30 p.m. 5.0 p.m. 10.0 p.m.	0.152 0.59 0.045 0.056 0.084	Slight twitching of head at 2 p.m., but no convulsive movements.
Experiment 2. Apr. 4, 1923.	0.07 gm. in 2 gms. hydrous lanoline	11.5 a.m. 12.5 p.m. 2.50 p.m. 8.10 p.m.	0.108 0.091 0.091 0.11	No signs evident.
Experiment 3. Apr. 10, 1923.	0.3 gm. in 3 gms. "adepts preparatus"	11.35 a.m. 12.35 p.m. 2.58 p.m. 4.30 p.m. 8.10 p.m.	0.108 0.035 0.052 0.075 0.098	No convulsions.
Experiment 4. Apr. 10, 1923.	1 gm. in 5 gms. "adepts preparatus"	11.45 a.m. 12.45 p.m. 3.8 p.m. 4.10 p.m.	0.112 0.034 0.034 0.02	Animal somewhat collapsed at 3.30 p.m. Convulsive seizures at 4.10 p.m. Recovery. 1 gm. glucose injected. Animal ate green food, but at 6.40 p.m. convulsions occurred again. Recovery after injection of 2 gms. glucose.

TABLE II.—Subcutaneous Injection of Insulin in Rabbits.

	Weight of Crude Insulin injected.	Blood Sugar.		Remarks.
		Time Intervals.	Glucose per cent.	
Experiment 5. Mar. 1, 1923.	0.16 gm. (at 11.15 a.m.)	11.11 a.m. 11.45 a.m. 12.16 p.m. 12.46 p.m. 1.17 p.m. 2.30 p.m. 11.10 a.m.	0.107 0.09 0.077 0.031 0.038 0.018 0.094	Convulsions at 2.30 p.m. 1 gm. glucose injected. Convulsions at 3.1 p.m. 2 gms. glucose injected; recovery.
Experiment 6. Mar. 6, 1923.	0.075 gm. (at 11.25 a.m.)	11.23 a.m. 12 noon 1.0 p.m. 2.30 p.m.	0.162 0.075 0.064 0.051	No convulsions.
Experiment 7. Mar. 12, 1923.	0.067 gm. (at 11.15 a.m.)	11.12 a.m. 11.56 a.m. 12.50 p.m. 1.15 p.m.	0.127 0.073 0.053 0.041	Convulsions at 1.10 p.m. 1 gm. glucose injected; recovery.
Experiment 8. Mar. 16, 1923.	0.027 gm. (at 3.15 p.m.)	3.10 p.m. 4.20 p.m. 5.10 p.m.	0.133 0.08 0.031	No convulsions.

This procedure generally lasted about five minutes. The treated area was then covered with a piece of jaconet, held in position by a bandage. Samples of blood from the marginal vein of the ear were taken for estimations of blood sugar, immediately before and at intervals after the inunction of the paste. The results obtained are collected in Table I. For purposes of comparison the effects produced on the blood sugar of rabbits by subcutaneous injection of various quantities of crude insulin are given in Table II.

In the first experiment (No. 1, Table I) a relatively large amount of insulin was employed, to ascertain if any effects could be produced by inunction. As noted, there was a reduction of blood sugar to 0.045 per cent., though no convulsions were induced during this period. The hypoglycaemia was still pronounced twelve hours after administration. A much smaller amount of material was employed in Experiment 2. The fall in blood sugar was just observable. The hypodermic injection of the same quantity of insulin (Experiment 7, Table II) induced convulsions in another animal within two hours. In Experiment 3 the crude insulin was incorporated in lard. The inunction of the paste induced a very considerable fall in blood sugar within an hour, the period of hypoglycaemia lasting about ten hours. A large excess of insulin was employed in Experiment 4. Soon after inunction the animal became very lethargic, and within an hour its appearance suggested collapse, though there were no convulsions till 4.10 p.m., when glucose was injected subcutaneously. The animal remained in a collapsed condition for some time, but later seemed to be normal, and ate some green food. At 6.40 p.m. it was again in a strongly convulsed state; 2 grams of glucose were injected subcutaneously. At 10 p.m. it appeared to be recovering, but refused green food. On the following morning it had completely recovered and was actively running about. The reduction in the blood sugar was very pronounced in this experiment, and a considerable amount of insulin must have been rapidly absorbed through the skin.

An examination of the results obtained on the subcutaneous injection of crude insulin (Table II) shows that by this method of administration the maximum effects could be produced with very much smaller doses. In Experiment 8 the reduction of the blood sugar to 0.038 per cent. resulted about one hour after the injection of 0.027 gram, while in Experiment 7 convulsions occurred with the fall in blood sugar to 0.041 per cent. two hours after the injection of 0.067 gram.

In reviewing these results the chief conclusion appears to be that insulin can be introduced into the blood stream by means of inunction. This method of administration necessitates the use of much larger quantities of the drug than those required to produce comparable effects by subcutaneous injection. It is worthy of note, however, that in estimating the effects produced account must be taken chiefly of the duration of the hypoglycaemia. A sudden reduction, followed by an abrupt rise in the blood sugar, such as is indicated in Experiment 8, Table II, where a relatively small amount of the drug was injected, indicates a transient effect. The ideal method of utilization would appear to be indicated by a

prolonged period of hypoglycaemia maintained by slow absorption.

The results also suggest that advantage might be taken of this method to utilize crude insulin extracts. At the present time the cost of isolating the drug in a pure and active state for the purposes of hypodermic medication is such as to restrict seriously its application on a large scale. It is possible that more liberal use of cruder materials might with advantage be made by means of injection.

I have to thank Mr. Orr for performing the analyses of the blood.

The work was done under the Medical Research Council.

A Clinical Lecture

ON

SUBCUTANEOUS RUPTURE OF THE INTESTINE.

GIVEN AT GUY'S HOSPITAL ON MARCH 7TH, 1923,

BY

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CONTUSIONS, unlike bullet and other penetrating wounds, do not often cause multiple injuries of the bowel, but the individual lacerations of the intestine and mesentery are generally more severe. For instance, the small intestine is sometimes completely divided. Therefore it is clear that the hope of recovery without operation is more remote, but the operation itself is likely to be less tedious and troublesome.

CAUSE.

The bowel is most frequently ruptured by a wheel passing over the abdomen, by a squeeze or a crush, a blow or a kick. It may be crushed against the spine or torn from its mesenteric attachments, especially at the junction of movable and fixed parts, such as the duodeno-jejunal junction. Sometimes the reduction of a strangulated hernia has led to rupture of the bowel; a man was admitted to Guy's Hospital recently who had ruptured his own intestine in this way. In the large majority of cases, as pointed out by Massie, the contusion is below the umbilicus; there may be, however, no sign of injury on the surface of the abdomen at first, but a bruise may appear some days later.

SITE OF RUPTURE.

In an examination of 381 cases, published and unpublished, the site of rupture was as follows:

Duodenum	...	...	...	23 cases.
Jejunum	...	...	...	157 "
Ileum	...	...	...	158 "
Colon	...	...	...	43 "

In one-tenth of the cases there was more than one rupture; sometimes the large as well as the small intestine was torn.

NATURE OF DAMAGE.

As a rule the laceration runs for less than an inch across the axis of the bowel, but occasionally the latter is completely divided or severely bruised. The mucous membrane always pouts; the bowel dilates above and below the rupture, and rapidly becomes inflamed and oedematous. In nearly one-tenth of the cases there are complications, such as rupture of the mesentery or of one or more of the other abdominal viscera. In one-quarter of the cases there is fracture of the spine or pelvis, and sometimes severe injuries to other parts, such as the chest and head. The frequency and severity of these complications contribute very largely to the mortality.

SYMPTOMS AND SIGNS.

1. *Pain* is the most striking symptom. As a rule it comes on early and is very severe, being described by patients as "agonizing."

2. *Tenderness*.—This is at first local, near the site of the injury, but later it becomes general, as a result of peritonitis.

3. *Shock*.—This is nearly always severe. It occurs, and may even be fatal, very soon after the accident. In some cases it passes comparatively quickly.

4. *Vomiting* is almost always present, often constant and most persistent.

5. *Pulse and Temperature*.—The former is at first slow and weak from shock, then normal and deceptive; later increasingly rapid and weak as a result of peritonitis. Similarly the temperature is at first subnormal, then normal, and later raised.

6. *Rigidity*.—At first this may be local, but it soon becomes general. The abdomen may be flat at first, or even retracted, but later it becomes distended as a result of peritonitis, with effusion and tympanites.

7. *Dullness*.—There is usually shifting dullness in the flanks as a result of effusion. The liver dullness is often greatly diminished from free gas in the peritoneum.

8. *Transmission of Heart and Breath Sounds*.—The heart and breath sounds may be transmitted, through the gas and fluid, over the abdomen, far beyond the natural limits.

9. *Signs of Internal Haemorrhage*.—In many cases the patient is pale and restless as the result of haemorrhage, and examination of the blood confirms the evidence of this grave complication. The face is usually anxious, pale, cold and sweating, and is, in fact, a typical "abdominal facies."

Emphysema of the abdominal wall or of the loin generally implies rupture of the bowel in its extraperitoneal part. When it affects the right loin the ascending colon or duodenum is ruptured; on the left side, the descending colon. Later on, in such cases, a faecal abscess may form in the loin.

As a rule the minds of these patients are unusually active, and they often have a premonition of impending death.

DIAGNOSIS.

The diagnosis depends a great deal upon an accurate history of a severe abdominal injury. Anyone who has sustained such an injury should be kept under direct observation for a few days, for although there may be no bad signs at first these may rapidly develop. It is of the gravest importance to admit such a case into hospital at once.

Severe pain, tenderness, rigidity, and persistent vomiting following an abdominal injury should make us open the abdomen without delay, although the pulse and temperature and general condition of the patient may be good. It is by operating in the early stages that the appalling mortality of these catastrophes can be reduced.

It is often difficult to distinguish this condition from rupture of the spleen, liver, or mesentery, in which signs of internal haemorrhage and shock are the most prominent. Presence of free gas in the peritoneum, as shown by a tympanitic note, diminution of the liver dullness, and rapid onset of peritonitis, are strong indications in favour of rupture of the bowel; but accurate diagnosis is not so important as a realization of the presence of grave intra-abdominal injury and the urgent need of an operation to set it right.

TREATMENT.

Death is almost inevitable without early operation, therefore it should be carried out at the earliest possible moment, for mortality increases with delay. The following figures, taken from 376 operation cases collected by Siegel, illustrate this point:

Operation	Mortality.
within 4 hours	15.2 per cent.
" from 5 to 8 hours	44.4 "
" from 9 to 12 hours	63.6 "
" later	70.0 "

The mortality of this series was 51.6 per cent., and is very misleading, because fatalities are so often forgotten and not published.

Operation.

While preparing for the operation every endeavour must be made to combat shock by warmth, saline or subcutaneous infusions, or, in some cases, by transfusion of blood. Whenever possible spinal anaesthesia or gas and oxygen is chosen.

The abdomen is opened in the middle line, preferably by displacement of the right rectus outwards. The jejunum, being the most likely part to be affected, is at once examined and the small intestine traced downwards to the caecum. In many cases, however, the injured coil comes forwards into the wound directly the abdomen is opened, and gas and liquid escape. If no perforation is found in the jejunum or ileum the duodenum is most carefully examined; in many cases lacerations of the duodenum have been overlooked at the time of operation and have only been found *post mortem*. Lastly, the caecum and colon are examined.