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Enhancement of Intestinal Motility and Transit Time in Streptozotozin-Induced Diabetic Rats Treated with *Ocimum gratissimum*

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Authors' contributions

This work was carried out in collaboration between all authors. Author OUA designed the study, coordinated the research, and wrote the first draft of the manuscript. Author OAO managed the analysis and interpretation of data. Author ISO wrote the protocol and managed the literature searches. Author OEE supervised and guided the entire experimental procedure. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Acute changes in the blood glucose concentration have a substantial effect on intestinal motility in both diabetic and healthy subjects. This research work was therefore designed to assess the effect of DM on GIT motor activity and the impact of treatment with OG on same.
Methodology: The phytoconstituents and median lethal dose of the plant extract was determined before administration. Eighteen rats were used; the animals were divided into three groups of six rats each. Group 1 served as the control which was fed with normal feed. Group 2 was diabetic untreated rats (DM) while group 3 was OG treated diabetic rats (DMT). At the end of 28 days, the intestinal transit and motility were determined using graded doses of acetylcholine, adrenaline and atropine.
Results: The DMT intestine showed greater increase in contraction with increase in concentration of acetylcholine, application of adrenaline showed that the ileum of the DMT had a significantly lower (P=.001) percentage change in relaxation when compared

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to control or DM groups but there was no significant difference between DM and control group. While atropine caused a significant increase (P=.001) in percentage change in relaxation in the DMT group when compared to control and DM groups. There was no significant difference between the DM and control group. DM and the DMT groups had significantly higher (P=.05) percentage transit than the control group. There were no significant differences between DM and DMT groups.
Conclusion: These results demonstrate that impaired intestinal motor activity in type I STZ-induced diabetic rats is enhanced by treatment with OG, this may be possibly due to its hypoglycemic effect and its concomitant impact on related biochemical and neuroendocrine interplay that affect GI motor function.

Keywords: Ocimum gratissimum; diabetes mellitus; intestinal motility; intestinal transit; motor activity.

1. INTRODUCTION

The pathogenesis of disordered GIT motor activity in Diabetes Mellitus (DM) is without doubt, now considered to be multifactorial; those factors which appear to be dominant autonomic neuropathy and glycolic control are closely linked and may influence each other and are, therefore, dynamic rather than static entities. For example both acute [1] and chronic [2] changes in the blood glucose concentration may affect autonomic function.It is now recognized that acute changes in the blood glucose concentration have a substantial, and reversible, effect on gastric (as well as oesophageal, intestinal, gallbladder and anorectal) motility, in both healthy subjects and patients with diabetes [3,4].

Some studies have established that changes in the blood glucose concentration within the normal postprandial range also influence gastric emptying and motility [5], emptying of solids and nutrient-containing liquids is slower at blood glucose of 8mmol/l than at 4mmol/l in both healthy subjects and patients with Type1 diabetes. Studies using experimental animal models of diabetes have shown altered activity of many neurotransmitters known to be of important in preserving the integrity of intestinal motility, such as serotonin, calcitonin-related peptide, substance P, peptide Y and NO [6,7]. The profound effect of acute hyperglycemia on intestinal motor and sensory function has been confirmed in several studies [8,9]. These studies showed that blood glucose levels in the range 12-15 mmol reduced the number and propagation of pressure waves in the proximal small intestine [10], resulting in slower; small intestinal transit [11].

Researches that have investigated small intestinal motility in diabetes mellitus have revealed a wide spectrum of motor patterns, ranging from normal to grossly abnormal motility, as observed in patients with chronic intestinal pseudo-obstruction syndrome secondary to DM. Camilleri and Malagelada [12] reported that small intestinal motility was abnormal in 80 per cent of patients with long-standing DM who had delayed gastric emptying. While these observations suggest that small intestinal dysmotility is also evident in some patients who have normal gastric emptying [13], indicating that delayed gastric emptying is not a reliable predictor of small intestinal dysmotility.

In a study using radio-labeled isotopes, small intestinal transit was accelerated in diabetic patients with autonomic neuropathy, while those without neuropathy showed normal transit times [14]. Colonic transit has been assessed in several studies using radio-opaque markers. In studies by Kawagishi et al. [15] and Werth et al. [16], transit was markedly

delayed in patients with evidence of cardiovascular autonomic neuropathy, while normal transit was observed in those without. The increase in colonic transit time was attributable primarily to a delay in transit in the distal colon. Iber et al. [17] also used a radiographic technique to study colonic transit in asymptomatic male T2DM and those with upper and lower GI symptoms. Delayed colonic transit was observed in both groups, particularly in the symptomatic diabetics.

Ocimum gratissimum (OG) – Lamiaceas commonly known as 'scent' leave, has been used naturally in the treatment of different diseases [18,19]. The volatile aromatic oil from the leaves of this plant consists mainly of thymol (32-65 per cent) and eugenol: it also contains xanthones, terpenes, and lactones [21]. Also citral, ethyl cinnamate, geraniol and linalool have also been extracted from this oil [22]. The antispasmodic action of thymol contained in the aromatic volatile oil obtained from the leaves of *Ocimum gratissimum* could be associated with reduced intestinal motility. This action in conjunction with antibacterial property of the plant may be responsible for its observed action in diarrhea. In 2004, researchers carried out an in vitro study on the ileum of guinea pig. The effect of *Ocimum gratissimum* extract on intestinal motility was determined by the magnitude of contraction of isolated guinea pig ileum. Results showed that *Ocimum gratissimum* extract mimicked the action of Adrenaline on the isolated guinea pig ileum by abolishing the Acetylcholine – induced contraction of the smooth muscle of the ileum [21].

This research work was therefore designed to assess the effect of DM on GIT motor activity and the impact of treatment with OG on same.

2. MATERIALS AND METHODS

2.1 Plant Materials and Preparation of Aqueous Extract

The leaves of Ocimum gratissimum were obtained from the University of Calabar Botanical Garden and identified by the Chief Herbarium Officer of Botany Department of University of Calabar. The fresh leaves were rinsed with water to remove sand and debris and then allowed to drip off water. The leaves were then dried under shade for two days and then transferred into Astell Hearson Oven and dried at a temperature range of 40 – 45ºC.

The dried leaves were then ground in an electric blender into fine powder to give a gram weight of 527grams. This 527g weight was soaked in 2.65 liters of water (distilled water) and allowed over night for about 15 hours and stirred at interval. The mixture was filtered using a satin mesh material and the final filtrate was gotten by using Whatman's filter paper size 1. The final filtrate was dried in the Astell Hearson Oven at 45ºC to obtain a brown gummy paste. A mettler P163 electronic weighing balance was used to weigh the gummy paste before stock solution was prepared. The stock solution of the extract was prepared by dissolving 15gm of extract in 10ml of water to give a concentration of 1500mg/ml. The stock solution was labeled appropriately and refrigerated at 4ºC until required for use. The median lethal dose (LD_{50}) of the plant extract was determined by method of Lorke [23].

2.1.1 Determination of phytoconstituents

The phytoconstituents of the extracts was determined and were screened for the presence of carbohydrates, tannins, alkaloids, saponins, phenolics, anthraquinones and cardiac glycosides as described by Trease and Evans [24] and Sofowora [25].

2.2 Animals Preparation, Experimental Groupings and Treatment

Eighteen rats were used for the study, the animals were divided into three groups and were assigned randomly into each group which was made up of Six (6) rats each and housed in cages assigned to them.

The first group was made up of the control animals which were fed with normal rat chow (feed). The second group contained streptozotocin induced diabetic rat which were left untreated. The third group of animals contained the test group which were streptozotocin induced diabetic rats treated with aqueous leaf extract of Ocimum gratissimum. The experimental procedures involving the animals and their care were in line with the approved guidelines by the local research and ethical committee.

2.2.1 Induction of diabetes mellitus

Diabetes mellitus was induced by a single injection of 65mg/kg streptozotocin. The injection was given intraperitoneally. The state of diabetes was observed after 48 hours by the symptoms of polyuria and glucosuria and this state was confirmed using uristic test strip (Bayer Health Care LLC, USA). Also, the blood glucose level was tested 1 week after induction using a Glucometer (ACCU-CHECK Advantage II, Roche Diagnostics (GmbH, Germany) and ACCU-CHECK Advantage II test strips.

2.2.2 Extract administration and observation

One week after induction of diabetes, the extract was administered per oral to the DMT group at a dose of 1500 mg/kg body weight daily for 28 days. Administration was facilitated by the use of a syringe and Orogastic tube.

2.3 Intestinal Motility

Rats were starved 24 hours prior to experiment. The animals were sacrificed by stunning and incision quickly made through the linea Alba to expose the intestine. The proximal ileum was located and isolated, then placed in a container of tyrode solution and aerated. The ileum was then cut into segments of about 3cm long, and mounted at one end to a fixed support in an organ bath.

The other end of the ileum was fixed to a horizontal balance writing lever tangential to the kymograph drum. The tissue was allowed to equilibrate for 60 minutes during this period the bathing solution was replaced with tyrode solution at 15 minutes interval to avoid accumulation of metabolites. The tissue was later challenged with graded doses of acetylcholine (10^{-1} to 10^{-6}mg) and later on atropine (0.1mg), phentolamine (0.1mg) and adrenaline (10^{-1} to 10^{-6}mg) at an interval of 1 minute per administration.

2.4 Intestinal Transit

Experiment on intestinal transit was carried out following the method described by Uwagboe and Orimilikwe [26]. The rats in the different groups studied were deprived of food but were allowed water for 24 hours before the experiment. 50g chow (Supplied by Pfizer company Nigerian limited) was ground to powder, sieved and mixed with 200ml of water. The mixture was allowed to stand for 30 minutes and it settled into three layers namely topmost, middle

and bottom layers. Both the topmost and bottom layers were discarded. Leishman's stain (0.15g) mixed with charcoal (for effect) was prepared in 100ml of phosphate buffer. 20ml of Leishman-charcoal mixture was then mixed with the middle layer of the homogenized chow.

All the rats were fed orally with 3ml of Leishman's stained food mixture using an 8cm long metallic intubating syringe. The experiment was timed for 90 minutes to allow room for food to move from the small intestine completely. At the end of 90 minutes, the rats were sacrificed by decapitation and the abdomen cut open immediately. The location of the Leishman's stained food mixture in the intestine was measured using a meter rule. The intestinal transit was calculated as:

$$\frac{\text{Length traveled by the black marker}}{\text{Total length of the small intestine}} \quad X \quad 100$$

2.5 Statistical Analysis

All results are presented as mean + standard error of mean. Three sets of data were analyzed using one way ANOVA, followed by the least significant difference (LSD) procedure for significant F values, (P=.05) was considered significant. Computer software SPSS and Excel Analyzer was used for the analysis.

3. RESULTS

3.1 Effect of Graded Doses of Acetylcholine (ACh) on Intestinal Motility in the different Experimental Groups

The response to graded doses of acetylcholine with concentration of 10^{-8} to 10^{-1} g/ml by the isolated rat ileum of the control, diabetic control and diabetic treated group. At low doses, there was a gradual relaxation of the ileum followed by a gradual rise in contractile response of the ileum of the diabetic control with subsequent increase in Ach concentration. So, there was a biphasic effect on diabetic untreated rat ileum. On the other hand, there was an increase in contractile response corresponding to increase in Ach concentration in control and diabetic treated rat intestine. The diabetic treated rat intestine showed greater increase in contraction with increase in concentration of Ach (Fig. 1).

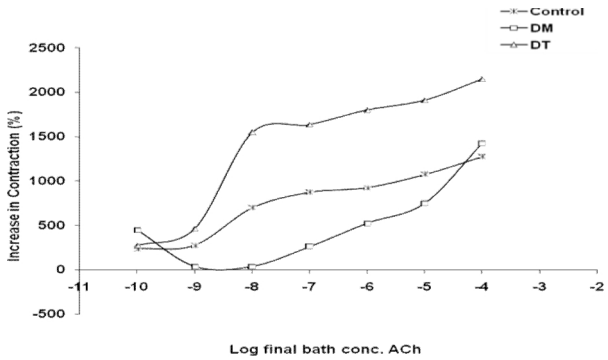

Fig. 1. Comparison of effect of graded concentrations of acetylcholine (ACh) on intestinal motility in control, DM and DMT

Mean ± S.E.M = Mean values ± Standard error of means of six experiments

3.2 Effect of Adrenaline on Intestinal Motility in the Different Groups

The administration of adrenaline showed that the ileum of the diabetic treated rat had a significantly lower (P=.001) percentage change in relaxation when compared to control or DM groups (Fig. 2). There was no significant difference between DM and control group.

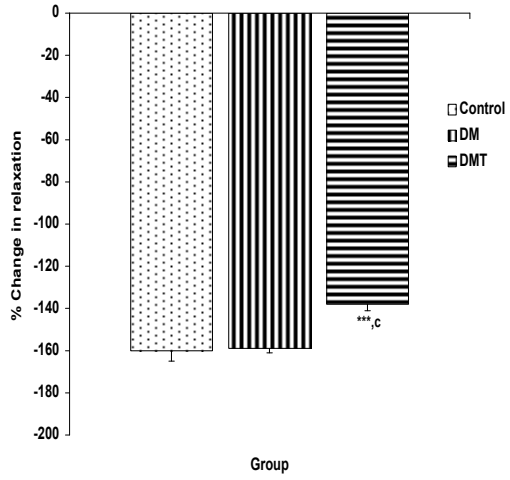

Fig. 2. Comparison of the effect of adrenaline in control, DM and DMT
Test drugs: significant from normal control, ***P<0.001 vs control, c = P<0.001 vs DM.
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

3.3 Effect of Atropine on Intestinal Motility in the Different Groups

When atropine (0.1g/ml) was administered it was observed that there was a significant increase (P=.001) in percentage change in relaxation in the DMT group when compared to control and DM groups (Fig.3). There was no significant difference between the DM and control group.

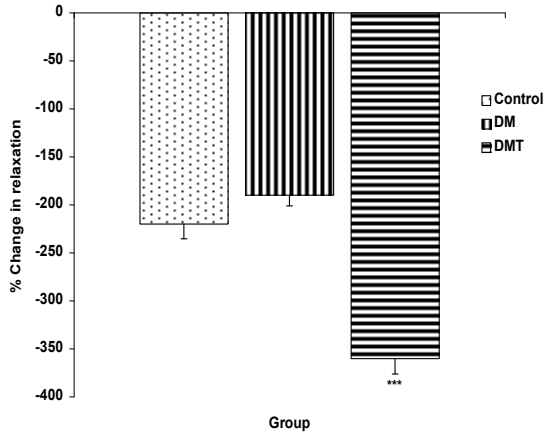

Fig. 3. Comparison of the effect of atropine in control, DM and DMT groups
Test drugs: significant from normal control, ***P<0.001 vs control, c = P<0.001 vs DM.
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

3.4 Intestinal Transits in the Different Experimental Groups of Rats

The mean values of intestinal transits were: 46.813 ± 3.577, 57.529 ± 2.043 and 64.821 ± 3.486per cent for the control, DM and DMT groups respectively. The DM and the DMT group had significantly higher (P=.05) percentage transit than the control group. There were no significant differences between DM and DMT groups, as shown in Fig. 4.

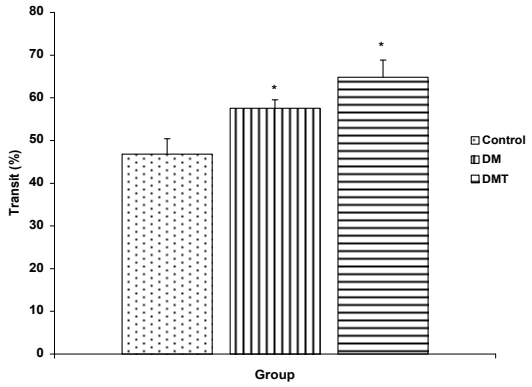

Fig. 4. Comparison of intestinal transit (as percentage of the total length) in the different experimental groups

*Test drugs: significant from normal control, * P < 0.05*
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

3.5 Fasting Blood Glucose in the Different Experimental Groups of Rats

The mean values of fasting blood glucose in the control, DM and DMT experimental groups were 2.46 ± 0.192, 28.2 ± 1.52 and 16.5 ± 1.21mmol/l for control, DM and DMT groups respectively. All the groups were significantly different. The DM and DMT groups were significantly higher ($p < 0.001$) than the control. The DMT group was signifi-cantly lower ($p < 0.01$) than the DM group Fig. 5.

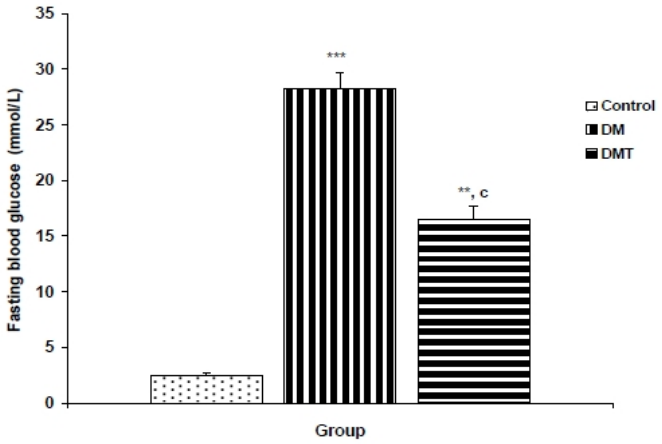

Fig. 5. Fasting Blood Glucose In The Control, DM And DMT Experimental Groups Of Rat

Test drugs: ***P<0.001, **P<0.01 VS CONTROL; C = P<0.001 VS DM
Mean ± S.E.M = Mean values ± Standard error of means of six experiments

4. DISCUSSION

Estimation of the blood glucose levels for the control, diabetic (DM) and Diabetic treated (DMT) experimental groups confirmed hyperglycemia in the test groups (i.e. DM and DMT), thus suggesting that the insulin – producing pancreatic beta cells were destroyed by streptozotocin (STZ) administered for the induction of DM in these groups. Other studies had also reported the hypoglycaemic effect of OG. Aguiji et al. [21] and Egesie et al. [27] have both re-ported the efficacy of OG in lowering the blood glucose level in STZ – induced diabetic animals [17,9]. Though treatment with the aqueous extract of OG did not return the blood glucose level to normal when compared to the control group, the level of reduction was significant when compared with the diabetic control group [28].

Studies that have investigated small intestinal motility in diabetes mellitus have revealed a wide spectrum of motor patterns, ranging from normal to grossly abnormal motility, as observed in patients with chronic intestinal pseudo-obstruction syndrome secondary to DM. Camilleri and Malagelada [12] reported that small intestinal motility was abnormal in 80 per cent of patients with long-standing DM who had delayed gastric emptying. While these observations suggest that small intestinal dysmotility is also evident in some patients who have normal gastric emptying [13], indicating that delayed gastric emptying is not a reliable predictor of small intestinal dysmotility.

Different chemical agents known to influence intestinal motor function were employed in this study. Application of increasing concentrations of acetylcholine (Ach) was found to increase the tone of contraction, with the DMT group showing higher responses than the control and DM groups. There was a higher percentage change in relaxation of the ileum of the DMT group when compared to the control and DM groups on application of atropine – a cholinergic blocker. Addition of adrenaline effected a significantly lower percentage change in relaxation in the DMT group. The control and DM group had a higher percentage change with no significant change between the two.

Many studies have shown that the gastrointestinal motor responses to various stimuli are affected by acute hyperglycemia in both healthy subjects and diabetic patients. The exact mechanism through which glucose influence motor and sensory function of the intestine is still unresolved. Both stimulatory and inhibitory effects occur during hyperglycemia, indicating that the effects are likely to be mediated by neural or humoral mechanisms, rather than a direct effect on the smooth muscle of the gut.

Both peripheral and autonomic neuropathies are frequent complications of DM. Since the autonomic nervous system (ANS) plays a prominent role in the regulation of gut motility, a prevailing hypothesis has been that autonomic neuropathic dysfunction could account for much of this disturbance. Hyperglycaemia by promoting increased intraneuronal glucose, results in an increase in production of sorbitol from glucose by aldose reductase. The sorbitol accumulation leads to decrease myo-inositol, reduced Na^+/K^+ - ATPase and impaired nerve conduction [29].

The greater increase in intestinal contraction seen in the DMT group compared to the DM group on addition of graded doses of Ach could be secondary to the hypoglycemic activity of OG which in turn probably increases myo-inositol and Na^+/K^+ - ATPase to enhance nerve conduction in line with the report of Schmidt et al. [29]. This is further strengthened by the observation that the Ach-like action of OG does appear to be mediated by M_3 receptors since application of atropine (an M_3 receptor blocker) showed higher percentage change in

relaxation in the DMT group. Adrenaline is known to inhibit spontaneous movement by direct effect on the smooth muscle through α and β receptors. Addition of adrenaline gave lower percentage change in relaxation in the DMT group; showing that OG may likely oppose its effects by blocking its receptors.

The highest percentage transit (lowest transit time) occurred in the DMT group followed by the DM group. The transit time is a function of the rate and force of smooth muscular contraction of the gut. This is demonstrated by the frequency and amplitude of spontaneous contraction. The increase in gastrointestinal transit (reduced transit time) in the DM group in this study agrees with the findings of Rosa-e-Silva et al. [14] who in a study using radio-labeled isotopes, small intestinal transit was accelerated in diabetic patients with diabetic neuropathy. Increased levels of the gastrointestinal hormones, namely; motilin and gastrin have been found in diabetic patient [15,30]. Whether these hormones are involved in the differences between the DM and DMT groups transit time is uncertain. Further studies will be required to explain this.

The reduction in the transit time in the DMT group shows that OG increase intestinal smooth muscle contraction, thus, potentiating the action of Ach. The result here is consistent with the intestinal motility findings above. This further demonstrates the efficacy of OG in reversing the autonomic neuropathic defects in DM.

5. CONCLUSION

Previous studies had reported complications of autonomic neuropathy secondary to hyperglycemia of DM. Autonomic neuropathy is implicated in impaired intestinal motor activity in DM. Our results have demonstrated that impaired intestinal motor activity in Type I STZ- induced diabetic rats is enhanced by treatment with OG. This may possibly be due to its hypoglycemic properties and its concomitant impact on related biochemical and neuroendocrine interplay affecting GIT motor function.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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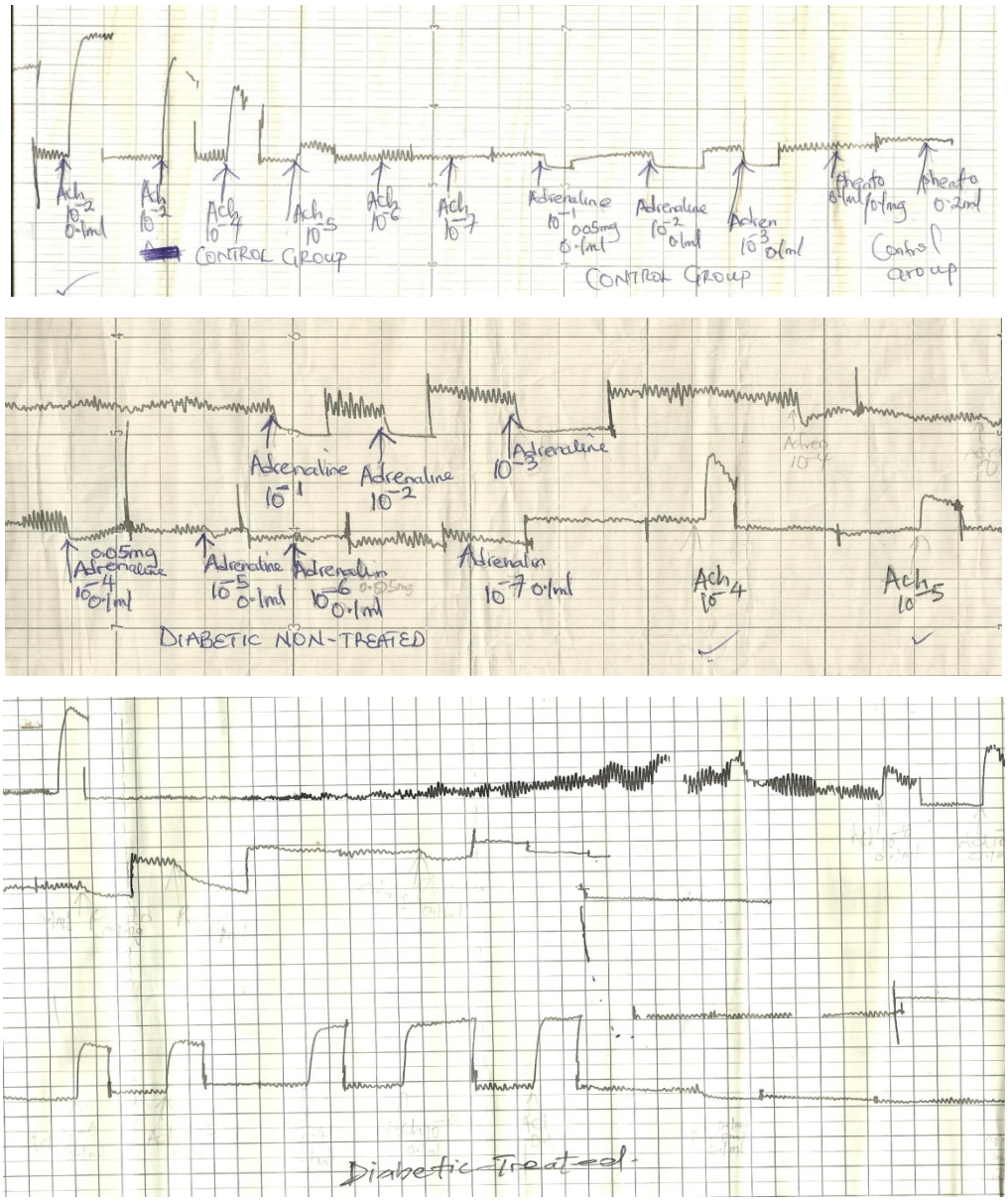
Sample Tracing of Intestinal Motility Experiment



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