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REVIEW ARTICLE

HAEMONCHUS CONTORTUS AND OVINE HOST: A RETROSPECTIVE REVIEW.

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Abstract

Gastrointestinal (GI) parasitic infections are a world-wide problem for both small- and large-scale farmers. Infection by GI parasites in ruminants, including sheep and goat can result in harsh economic losses in a variety of ways: reproductive inefficiency, decreased work capacity, involuntary culling, diminished food intake, poor animal growth rates and lower weight gains, treatment and management costs, and mortality in heavily parasitized animals. Among the GI parasites that cause losses to the farming industry, the barber's pole worm *Haemonchus contortus* is the predominant, blood- sucking, highly pathogenic, and economically important nematode that infects small ruminants. Here, we review the historical and recent literature on the ovine-parasite-environment interaction for *H. contortus* to bring avenues where advances in the understanding of these interactions is an indispensible to develop a cost effective control strategies as potential options for the haemonchosis control in sheep and the proper management of sheep in various production systems.

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History of Parasitology:-

The Egyptian Ebers papyrus of 1500 BC illustrates parasitic disease descriptions, which have been proven by the calcified helminth egg disclosure in mummies dating back to 1200 BC. Our earliest ancestors could be knowledgeable of the larger species, such as the roundworm *Ascaris* and tapeworm *Taenia*, which can be observed with the naked eye [1].

In the 17th century, Robert Hooke invented the microscope and our life understanding and disease increased. Further understanding of the invisible, microscopic world has been occurred after the establishment of modern microbiology in the 19th century by Louis Pasteur and Robert Koch [2]. Thanks to modern technology, there have been nearly 300 species of parasitic helminths known to be human parasite. Additionally, livestock, crops and pets are all victims of parasitic helminths, which cause extreme effects on the human population as well [3].

Helminth Classification:-

Parasitic helminths are contained in the following groups: flatworms (platyhelminthes), namely cestodes (tapeworms) and trematodes (flukes), and roundworms or nemathelminths (nematodes). The name helminth was mainly used to stand for worms of the phyla platyhelminthes and nemathelminths; however, it has acquired an extensive sense, being now commonly employed for all worm parasites mentioned above. Below is a simple flow chart to aid in parasitic helminth classification of [4; 5](Fig. 1).

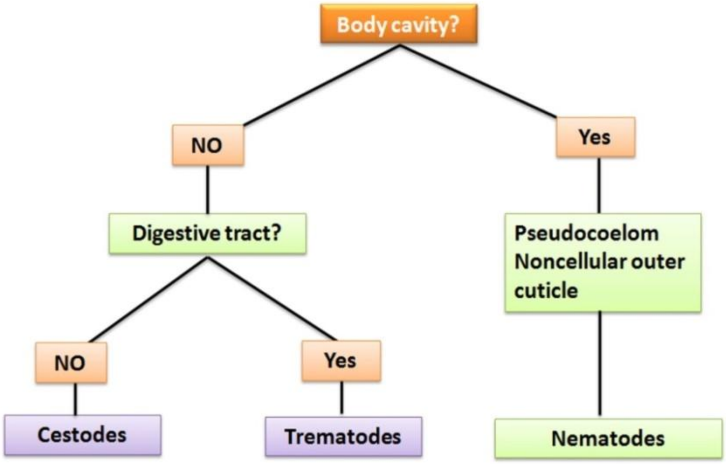

Figure 1:- A simple algorithm for the identification of parasitic helminths.

Nematodes are one of the most diverse groups of organisms on the planet (Fig. 2). Within the animal kingdom, nematodes are second only to the arthropods both in the species numbers and in the individual numbers present. Some are free-living, and many are parasitic, causing devastating diseases and socioeconomic problems world-wide [6].

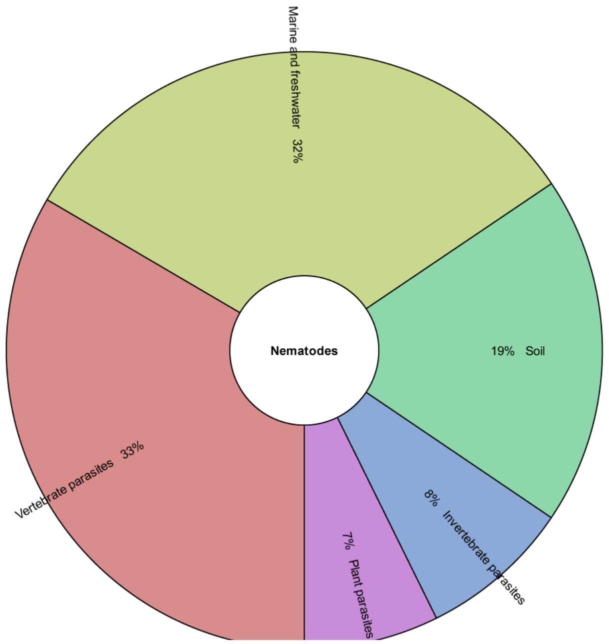

Figure 2:- An approximate percentage of nematode genera in various habitats.

Gastrointestinal nematode (GIN):-

Livestock are an exceedingly valuable agricultural commodity in developing countries worldwide. They are raised under diverse husbandry systems ranging from large-scale intensive commercial programs to conventional small-holder and village production systems. When ruminants graze on natural pastures, which are common aspect of approximately all production systems, climate plays an essential role in the gastrointestinal nematode (GIN) transmission. GINs are dominant contributors to diminished yield and can reduce the meat, milk and wool production. All grazing ruminants are vulnerable to GIN infections at pasture and any future intensification of pasture-based systems will likely augment the risk of GIN diseases. The restricting environmental variable controlling the worm egg development to infective larvae is rainfall; because temperatures are always warm (i.e. tropical and subtropical regions) enough to facilitate this process. Therefore, there is a direct correlation between the harshness of GIN problems and rainfall in these regions during the wet periods of the year where livestock are raised in the developing countries. They have direct life-cycles with the following patterns: nematode eggs are passed out with faeces of affected animals. The nematode eggs develop into 3rd stage larvae on the pasture. These infective larvae migrate onto the surrounding herbage to facilitate larval pick-up and are ingestion by the grazing ruminants for the parasitic phase initiation of the life-cycle. The infective larval-stage numbers present in the host environment at any given period is related to nematode egg numbers passed by the grazing animal, and this widely determines the parasite numbers potentially established in a susceptible grazing host owing to the absence of pre-parasitic and their infective stage multiplication [7]. Moreover, some of these GINs have diverse development times and stages outside and inside the definitive host; knowledge of which is crucial for effective control measures. Nevertheless, factors such as age, breed, and nutritional status of the animal as well as characteristics of the environment also have a reasonable impact on the GINs and their capacity to infect and inflict deterioration to the grazing host [8; 9]. Grazing sheep are perpetually infected with a wide-range of nematode species, which have been the subject of several reviews [10; 11; 12; 13; 14]. The most important GINs found in sheep and goats are the tricho-strongylids *H. contortus, Trichostrongylus axei, T. colubriformis, T. vitrinus, T. capricola, Cooperia curticei, Nematodirus filicollis* and *N. spathiger*, the hookworm *Bunostomum trigonocephalum*, the strongylids *Oesophagostomum columbianum* and *Chabertia ovina*, the trichurids *Trichuris* spp. and the oxyurid *Skrjabinema ovis*. Moreover, it has been reported that the most important nematode parasite in small ruminants that are reared in warm climates is *H. contortus* [15; 16; 17], which is also important in countries with a temperate climate, including Sweden and Canada [18; 19]. One has to bear in mind that *H. contortus* and *Oe. columbianum* are of considerable clinical and economic importance on sheep and goat production. *H. contortus* and related species belong to a large order of GINs (Strongylida) of animals, including humans. Haemonchosis caused by *H. contortus* represents ~15% of all gastrointestinal diseases of small ruminants world-wide and results in extensive financial losses (http://www.fao.org). *H. contortus* is a blood-feeding worm that leads to anaemia and associated complications, causing death in extremely affected animals [20]. It causes diminished production and economic loss due to treatment costs and control measures [21; 22].

History of *H. contortus* nomenclature:-

H. contortus was first charactereized in 1803 by Rudolphi [23]. Primarily, the parasite was termed *Strongylus contortus* [24] and It was however, not until the 1900s that *H. contortus* became the approved nomenclature [25; 26]. There have been different common names associated with *H. contortus,* including barber's pole worm, twisted stomach worm, and wire worm [27; 28; 29].

Taxonomy:-

Haemonchus contortus belongs to the family Trichostrongylidae as outlined below[30]:
Class: Secernentea
Subclass: Rhabditia
Order: Strongylida
Superfamily: Trichostronglyloidea
Family: Trichostrongylidae
Scientific name: *Haemonchus contortus*
Common name: Barber pole worm

Haemonchus contortus life cycle:-

H. contortus is an abomasal [31] and compartment 3 (C-3) blood feeding nematode of small ruminants (a four-chambered stomach/sheep) and pseudo-ruminants (a three-chambered stomach/ camelids) [32], respectively. The common parasite name is the barber-pole worm on account of the white reproductive tract is wrapped around the red blood-filled intestine give a twisted or barberpole appearance [33](Fig. 3).

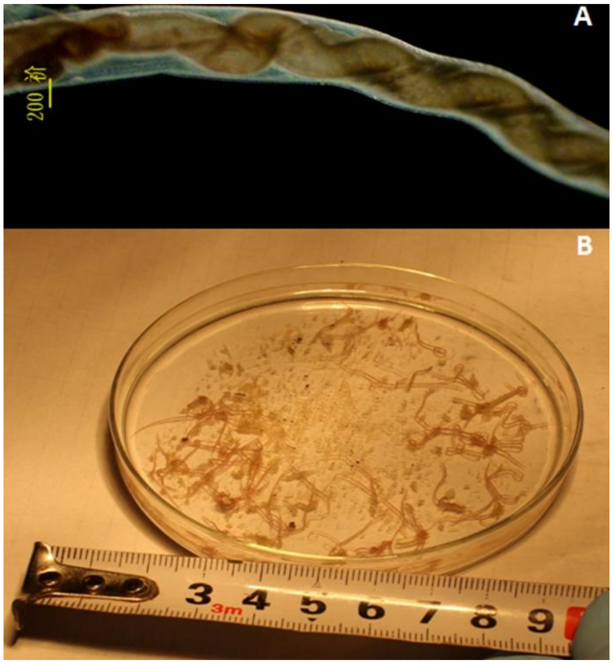

Figure 3:- *H. contortus* showing barber-pole appearance with white ovaries twisted around red, blood-filled intestine (A), and male and female *H. contortus* adult recovered after necropsy (B).

As shown in Figure 4, the parasite has a small buccal cavity with a single tooth, called the lancet, which is made of cuticle and is used for feeding by slicing the ovine mucosa [31].

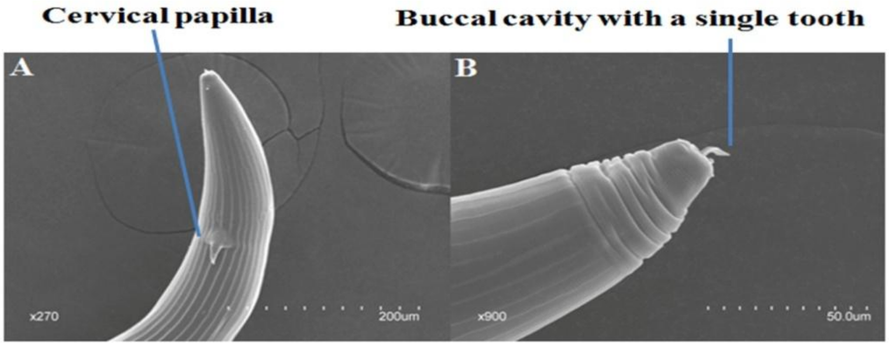

Figure 4:- Scanning electron micrographs (SEMs) of *H. contortus* -anterior end with cervical papilla and lancet tooth, which is used to initiate blood flow for feeding.

H. contortus has separate sexes and adults can be visualized with the naked eye. Adult females are 20 to 30 mm in length, tapered at both ends, and usually have a vulvar flap. Males are 10 to 20 mm in length and are tapered at the anterior end. The posterior end of the male has a copulatory bursa and spicules with a barb at the end used to hold open the female's genital opening during mating[31]. The adult males possess a peculiar three-lobed copulatory bursa involving two symmetrical lateral lobes and one asymmetrical dorsal lobe [29]. The *H. contortus* life cycle is direct, and the prepatent period is 16-21 days in small ruminants. The life cycle pattern can be categorized into four stages; these are: the parasitic stage (the interaction between the sheep and the parasite); the contamination stage (eggs are passed in the faeces during defecation); the free-living stage (larval-stages develop and survive); and the infection stage (infective larvae are consumed during grazing). Adult worms only live for a few months and reproduce sexually in the host. Females may lay thousands of eggs per day that pass out in the host faeces. *H. contortus* egg are regular, large, ellipsoidal, slightly flattened at the poles and morula not fully filled cavity of the egg with an average size range of 76-81 x 44–46 µm [34; 35]. Under ideal conditions (temperature:31°C-34°C and relative humidity: above 85%), larvae hatch from eggs in the faeces [36]. As mentioned above, the first-stage larvae (L_1) develop further and molt to become the second-stage larvae (L_2), which occur within the manure where the larvae feed on bacteria. After a second molt, larvae become the infective third-stage (L_3) about 5 days after passing out in the faeces. These larvae maintain the cuticle of the second stage as a protective sheath, which protects the L_3 from harsh environmental conditions and prevents it from feeding [37] (Figure 5).

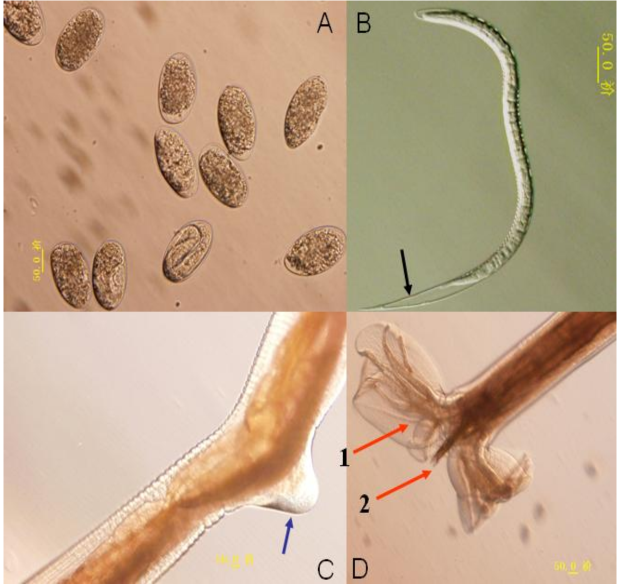

Figure 5:- *H. contortus* life-cycle stages [38].

(A) *H. contortus* egg. (B) *H. contortus* L3 larva. Slender larva, tail sheath medium length (> 50µm < 100 µm), tapering to point and often kinked. (C) *H. contortus* adult female vulval flap. The blue arrow is pointing to the vulval flap. (D) *H. contortus* adult male bursa. The red arrows are pointing to the capulatory bursa (1) spicules used to hold open the female worms genital opening (2).

Infective L_3s rely on stored energy as they travel from the faecal mass to the vegetation to be swallowed by sheep [33]. In supportive warm and humid climates, transmission can occur year round. L_3s can survive in the pasture up to one year under these conditions. Nevertheless, survival is usually weeks to a few months in cold climates. Infective L_3s undergo an exsheathment process in the forestomach and the exsheathed L_3s penetrate the abomasal mucosa and molt to the fourth-stage larvae (L_4), which return to the abomasal lumen and develop to dioecious haematophagous adults within ∼3 weeks following the ingestion of L_3s [39]. The L_4s are distributed widely in the anterior fundic area and are almost completely absent in the pyloric region; however, adult worms are distributed in the posterior fundic region of the abomasum closer to the pyloric area, which may be a selection by adult worms of a more supportive feeding site, or an avoidance of the host reaction in the area parasitized by earlier larval-stages [40]. Between 9 and 12 days after infection, the L_4s migrates back out into the lumen and molt one final time to the pre-adult stage (L_5s) under normal development conditions), which then develop into the reproductive mature adult to finalize the life cycle.

Hypobiosis:-

Haemonchus, *Trichostrongylus* and *Teladorsagia* have developed an extraordinary adaptive mechanism, referred to as hypobiosis or arrested larval development, to survive during harsh environmental conditions and ensure persistence (winter cold or summer heat)[41]. Hypobiosis [42] can be defined as "the temporary cessation of development of nematodes at a precise point in early parasitic development, where such an interruption contains a facultative element, occurring only in certain hosts, certain circumstances, or at certain times of the year and often affecting only a portion of the worms." There are two types of arrested development that occur in GIN parasites. The first is designated immune-mediated arrest (non-specific). It is elicited by either host-related or parasite-related factors at any time of the year. The second is designated seasonally induced arrest and occurs at the same time each year. This type of hypobiosis is similar to diapause in insects and elicited by an external environmental stimulus [43]. The latter seems to be the prevailing form of hypobiosis in *H. contortus* [44]. Factors that may act separately or in combination with each other to provoke hypobiotic L_4s include: a) host-related factors, such as host resistance, acquired immunity, and age [45]; b) parasite-related factors, including population density and genetic predisposition[46]; and c) environmental factors, such as temperature, humidity, and photoperiod length. Environmental factors are most likely to be the triggers involved because of hypobiotic L_4s appear to be more seasonal than immunological [46; 47]. Haemonchine hypobiosis is similar to the arrested development phenomenon (diapauses) in insects. Diapause is an inhibition of development induced by environmental factors and considered to be genetically controlled. This arrest in development is temporarily irreversible and may continue until either a specific stimulus presents itself or a predetermined period of time has elapsed [48]. The L_4s of *H. contortus* is able to undergo a state of arrested development [49]. They remain in the abomasal mucosa in a dormant (metabolically inactive) for 3 to 4 months, at which time they resume development. The end of hypobiosis coincides with changes in the weather, which causes the environment to once again become conducive to development and survival of free-living parasitic stages. Hypobiosis is beneficial to the *Haemonchus* infection as it is a means of delaying egg production until the external environment is likely to permit larval development in spring, or when moist conditions return; therefore, it is a forceful element in the condition known as spring rise in egg counts. The resumed development of the hypobiotic larvae often results in the events known as "spring rise" and "periparturient rise." A sudden pronounced surge in nematode egg counts is the characteristic features of these events as a result of the arrested larvae massively reach the reproductive adult stage [50].Spring rise occurs during the spring and although it is commonly associated with parturition, it is also seen in non-reproducing hosts [51]. On the other hand, periparturient rise harmonize with parturition during the spring lambing/kidding season but may also occur at other times of the year.

Spring lambing (i.e. ewes typically breed in fall and lamb in spring) occurs concurrently with the spring rise (periparturient rise/first rise). Therefore, the rise in the population of L_3s concurs with the augmented availability of susceptible neonates, thus ensuring transmission. During winter months, most L_3s on pasture will die and adult worms inside of the host will senesce, leaving the only surviving parasites as hypobiotic L_4s, which contribute to parasite burdens in the spring. Peri-parturient ewes will begin to produce eggs in faeces. About one month after introduction to pasture, the ewes, and more importantly lambs will begin to have high fecal egg output as a result of hypobiotic larvae emerging from the ewes and acting as a source of infection for the lambs [52]. Infected lambs can in turn serve to establish a second rise in eggs and larvae in late summer and fall. The seasonality of *Haemonchus* parasite load (i.e. generally heavier following these peaks) provides intervention points for treatment of sheep flocks with anti-parasitic drugs during these crucial times. Environmental conditions, including season and climate, host immunity, and genetics have been implicated [53]. Furthermore, the photoperiod, temperature, humidity, and host immune system relaxation due to periparturition and/or lactation are the triggers for hypobiotic larval emergence. Immunity relaxation in late gestation or immunity suppression by reproductive endocrine activity are hypothesized to play a role in larval emergence from hypobiosis [54]. However, the larval development may also reinitiate spontaneously without the influence of a stimulus after a predetermined length of time [46; 47]. This aspect further exposes the resemblance between haemonchine hypobiosis and insect diapauses [55]. Winter hypobiosis of *H. contortus* has been reported in the northern U.S.A. as an obligatory survival mechanism [53]; however, adult worms would be likely to survive during the unfavorable dry season (November to March) as adults with no serious hypobiosis [56]. Hypobiotic parasites are more resistant to drugs intended for their destruction; nevertheless, macrolide anthelmintics are the only class anthelmintics that is effective against hypobiotic L_4s [41]. The anthelmintic resistance emergence in worm populations reduces the control level of hypobiotic L_4s during the extreme environmental condition. The short life cycle and the survivability of the larvae have implemented *H. contortus* to be a highly infective GIN parasite able to cause a reasonable amount of damage to an entire ovine population. Knowledge of the lifecycle and environmental conditions provide producers with a number of tools to manage GIN parasite infection in their lambs and ewes.

Pathogenesis:-

Haemonchosis is the disease associated with severe *H. contortus* infections of the ruminant abomasum world-wide [57]. Clinical signs of disease may become more frequent following these peaks owing to higher worm burdens. They include severe anemia, seen as pale mucous membranes, periorbital and submandibular edema resulting from hypoproteinemia caused by the *Haemonchus* bloodsucking activity, lethargy, emaciation, weakness, wool loss, and even death [58]. The adult worms feed on host blood and move from one feeding site to another, leaving behind wounds that continue to hemorrhage and resulting in anemia, which is the most common clinical sign. The volume of blood that is lost and consumed with a heavy worm burden may result in the host death [29]. The degree of anemia relies on the abomasal worm numbers. Clinically, haemonchosis can be categorized into three types; hyperacute, acute and chronic. The hyperacute form occurs in young and /or unhealthy lambs exposed over a short period of time to heavy infection(ingested a massive number of L3s > 10,000), and is rare and results in lamb death[59]. The faecal color from these animals usually becomes dark due to digested blood and sudden death may occur owing to tremendous blood loss. Acute cases usually occur in young lambs that get heavily infected with or without diarrhea, but the host mounts an erythropoietic response resulting in the partially compensation for the blood loss. The parasite burden is mild, 1,000-10,000 individuals, and all ages of sheep are affected, regardless of present health status. Furthermore, anemia is accompanied by hypoproteinemia and edema, which may contribute to death. A common remark in these cases is sub-mandibular edema designated “bottle-jaw” [60]. The L_4s and L_5s larvae and adult worms are the robust blood-sucking GIN parasite; movement of the worm causes wounds and secretion of anti-coagulants resulting in a continuous haemorrhage from the abomasal wall[61]. A 2-month-old male lamb was identified with the history of anorexia, weight loss and dark color diarrheic faeces from a local farm in Jin Zhan village, Chaoyang, Beijing, China (Fig. 6). Clinical examination revealed severe emaciation, lateral recumbent position, and pale and anaemic mucous membranes. Parasitological examination showed numerous *H. contortus* eggs. The animal was died one week after treatment with with single dose of ivermectin (Shijiazhuang Fengqiang Animal Pharmaceutical Co., Ltd), and levamisole (Hebei New Century Pharmaceutical Co., Ltd). Post-mortem examination disclosed serious congestion, pinpoint petechial haemorrhages, and watery bloody contents with diverse minute hair like *H. contortus* worms in the abomasum. Gross lesions, such as petechial haemorrhages on account of the *Haemonchus* parasite attachment and feeding behavior, and severe congestion in the abomasal mucosa were corresponded with the earlier observations [62].

Figure 6:- Two-month old lamb died after treatment and post-mortem examination gross anatomy.

Bloated appearance face (bilateral periorbital oedema) and ovine hind-quarter is soiled with faeces due to diarrhea (A); Abomasal mucosa was severely congested; pin point petechial haemorrhages (B).

The possible pathogenic mechanism, which is responsible for cause of death in haemonchosis is hemorrhagic anaemia, hypoproteinemia and oedema due to vital blood sucking by both L_4s and adults. Moreover, diarrhoea causes fluid loss and dehydration resulting in hypovolaemic shock [63]. Chronic haemonchosis is noticed in lambs infected with comparatively few worms (100-1,000 individuals), and distinguished by high morbidity and low mortality. Infected lambs are unthrifty, weak and emaciated with or without anemia relying upon the ovine erythropoietic status. Pregnant ewes and does have elevated faecal egg counts (FEC) around the parturition time known as the periparturient rise. Immune response against parasitic infection shortly before and after parturition appears to be compromised owing to reasons yet to be validated [64]. Haemonchosis early diagnosis is fundamental for the infected flock or herd treatment. Generally, clinical signs as well as history are essential for the diagnosis for the acute and chronic forms of this disease. Furthermore, faecal examination can also be conducted to confirm the diagnosis. However, necropsy and looking for adult worms in the deceased animal abomasum for the diagnosis of hyperacute haemonchosis [65].

Common diagnostic techniques-determining how "wormy" sheep are!

Many diagnostic techniques have been currently made available, particularly in the field of molecular biology, biochemistry and immunology. Nonetheless, they are still expensive and not applicable in conventional practice [66]. Parasitized animals can demonstrate several infection signs depending on the GIN parasites present. The general signs include rough hair coat, diarrhea, depression, weight loss, bottle jaw and anorexia. Laboratory diagnostic findings may involve anemia (low packed cell volume), elevated faecal egg count (FEC) and loss of plasma protein.

FAMACHA© eye color chart system

The FAMACHA card was named FAMACHA© after its originator Professor Francois ‘Fafa’ Malan’s Chart. The FAMACHA chart, which depicts five illustrations of ocular membrane colors: 1: deep red (nonanemic), 2: red-pink (nonanemic), 3: pink (mild anemia), 4: white-pink (anemic), and 5: white (severely anemic) [67; 68]. The FAMACHA test is a shee*P*- side test that allows approximation of the animal’s PCV. It is performed by everting the lower lid of the eye and examining the color of the conjunctival mucosa (mucous membrane). Level of anemia can be roughly evaluated by observing the color of mucous membranes which are areas where there are a lot of capillaries (very small blood vessels) close to the surface so that tissue color reflects blood color. In general, pale or white membranes correlate with varying degrees of anemia, which correlate well with the burden of blood - sucking parasites (Fig. 7). These observations are part of a minimal database that will be an important aid in establishing the nature of disease. These measurements should be made repetitively and recorded, which over time will allow determination of improvement or exacerbation of the underlying condition. In settings in which anemia causing nematodes (mainly *H. contortus*) are predominant, blood PCV and FAMACHA score both are good indicators of the level of blood loss and associated problems. The FAMACHA © system is a selective program for managing haemonchosis n sheep and goats [69]. This system was developed in South Africa and allows owners and producers to rank an animal’s level of anemia [70; 71]. The FAMACHA card depicts five colors from red (healthy) to white (very anemic), which is then matched to the color of the inside of the lower eyelid of the affected animal. The score correlates well with PCV and can be used easily in the field [70]. The FAMACHA © system works by scoring animals on a scale of A to E and is performed by looking at the conjunctival membranes. A score of A or B is indicated as normal, while a score of D or E is anemic. The membranes of the eye are very pale at a score of E. It has been shown to be an effective way of determining, which animals need deworming for haemonchosis [69; 70; 72]. Employing this method diminishes the necessity to deworm all animals in a herd [71]. It is best to establish routine parasite evaluations, including FEC, PCV, FAMACHA, or weight gain at specified intervals (mostly 2 to 4 weeks, depending on expected severity of problems) from parturition throughout the grazing season. Because *Haemonchus* is the only parasite monitored with FAMACHA, attention should be paid to identifying and controlling other parasites when needed (e.g., by faecal egg count [FEC] or fecal culture). Recently, strong correlation among FAMACHA© eye scoring, PCV, and faecal culture positivity has been observed. Additionally, the FAMACHA© anaemia scoring guide can be employed to treat only severely anemic sheep reducing mass treatment and chance of drug resistance[73].

Figure 7:- FAMACHA© eye color chart being used to check level of anemia.

In this sheep the conjunctiva of the eye is being evaluated for color (A), on a scale of A to E (with 1 = normally pink and 5 = very pale) (B).

Body condition scores:-

Determination of body condition score (BCS) is an effective tool for managing both individual animals and herds. In an individual animal, low BCS may indicate disease or poor access to feed. In a flock or herd, a trend toward low BCSs may be indicative of inadequate feed quantity or quality or of management-related diseases, for example internal parasitism. Hands-on examination can be conducted to determine BCSs. BCSs were measured by palpating (physical feeling) the level of muscling and fat deposition over and around the vertebrae in the loin area behind the ribs and in front of the pelvis, and assigning a score of A-E, where a score of A is considered emaciated and E is considered grossly obese [74] (Fig. 8; Fig. 9; Table 1). It has been reported that changing in the body scores are good indicators of the intensity of GIN infection in the Nigerian WAD sheep [75].

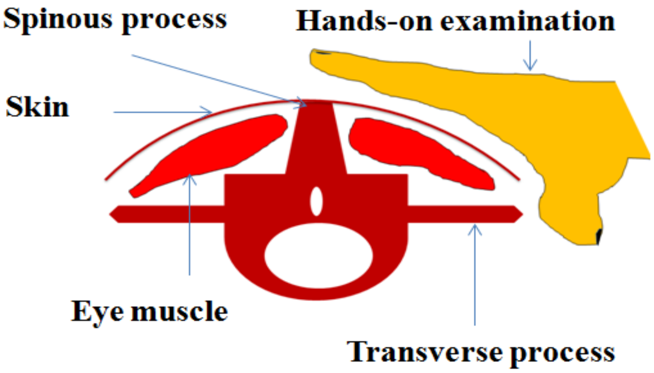

Figure 8:- Assessing body condition score by physical feeling.

Table 1:- Body condition scoring in sheep [76; 77; 78].

		Physical Finding			
Assigned score	Condition	Spinous processes	Transverse processes	Loin eye muscle	Fat cover over loin eye muscle
Condition A	Emaciated	Sharp and prominent	Sharp	Shallow	None
Condition B	Thin	Sharp and prominent	Smooth, slightly rounded	Medium depth	Little
Condition C	Ideal	Smooth and rounded	Smooth, well covered	Full	Medium
Condition D	Fat	Palpable as firm line with pressure	Not palpable	Full	Thick
Condition E	Overly fat	Not palpable	Not palpable	Very full	Very thick

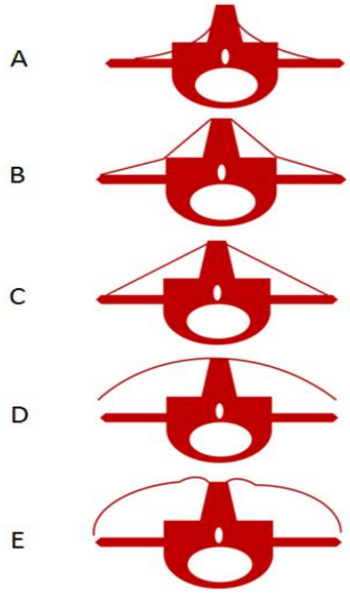

Figure 9:- Body condition scores (BCSs) for sheep. These drawings demonstrate a cross-section through the lumbar region and characterize the fat covering.

Modified McMaster egg counting for nematode egg quantitation:-

The coprological approach is the most extensively utilized method to detect helminth eggs and larvae, protozoan oocysts and cysts [79; 80; 81]. FEC plays an essential role in monitoring helminth burdens in herds and flocks, determining the pasture contamination degree and identifying anthelmintic resistance [81; 82; 83]. The McMaster method, which developed at the McMaster laboratory of the University of Sydney, is the most world-wide utilized FEC technique in veterinary and medical parasitology, and is supported by the World Association for the Advancement of Veterinary Parasitology for assessing the anthelmintic drug efficacy in ruminants [84], as well as for the anthelmintic resistance detection [82]. This method has improved diagnostic parasitology, both animal [85; 86; 87; 88; 89] and human [90; 91]. Several McMaster method modifications, including faecal weight and volume and flotation solution type, sample dilution, flotation times, an additional centrifugal application, centrifugal duration and speed, numbers of chambers of the McMaster slide counted and different coefficients for interpretation have introduced [88; 92; 93]. Three selected modifications of the McMaster counting technique, namely the McMaster method modified by Wetzel (W) and Zajíček (Z), as well as the concentration McMaster technique according to Roepstorff and Nansen (R&N) have been chosen to compare their sensitivity and reliability by [94], however the method reported by Roepstorff and Nansen proved to be the more sensitive and reliabile technique (Table 2).

Table 2:- Evaluation parameters of McMaster egg counting technique modifications [94].

	McMaster technique modifications		
	Wetzel (W)	Zajíček (Z)	Roepstorff and Nansen(R&N)
Amount of faeces (g)	2	1	4
Flotation solution type	NaCl	$MgSO_4 + Na_2S_2O_3$	NaCl + glucose
Solution specific gravity	1.2	1.28	1.3
Centrifugation (RPM)	None	2,000	1,200
Centrifugation time (min)	None	2/1	5
Flotation time in chamber (min)	2–3	5	3–5
McMaster counting chamber	3	2	2
Multiplication factor	67	33	20

Packed cell volume:-

The packed cell volume (hematocrit) is the ratio of the red blood cell volume (A) to the total blood volume (B) (Fig.10). PCV is an essential indicator of resistance of sheep to *Haemonchus* infection, and is negatively correlated with FEC in sheep (Shakya et al. 2011).

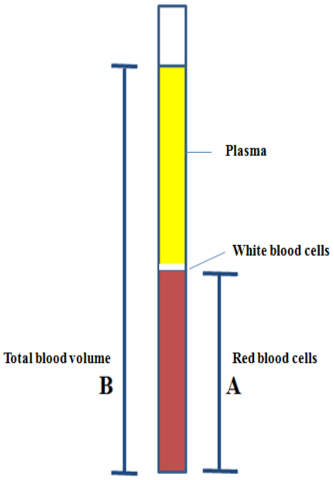

Figure 10:- Packed cell volume diagram

Immune response to GIN parasites:-

Ovine immunity:-

It has been reported nearly 10-35% of neonatal lamb mortality within the first 6 months of life, a mortality rate nearly duplicated that of mature sheep [95] owing to their naïve immune system. Neonatal-lambs are almost completely reliant upon passive transfer of maternal antibodies through colostrum in the first 3-4 months of life. Even though maternally-derived antibodies provide protection, they synchronously hamper the newborns from mounting their antibody response [96], due to this inhibition, newborns are not immunized against infectious diseases until they are at least 3-4 month old [97]. Neonatal lambs are especially vulnerable to infection when maternal antibodies are no longer present and have not yet begun to adequately mount their own immune response. The immune system consists of a wide range of diverse effector cells, tissues and organs with complex interactions that allow a rapid response to any foreign invaders [97]. The production of cytokines, and low weight signaling proteins involved in immune cell communication by activated CD4+ T helper cells in response to intracellular or extracellular pathogens resulting in the differentiation of naïve T helper lymphocytes into two subsets, T-helper type 1 (Th1) and type 2 (Th2) [98]. Th1-type cells are responsible for the cellular immunity activation, and a Th1-type response is generally noticed in response to viral infection, intracellular pathogens, and the delayed-type hypersensitivity activation. A Th1-type response usually responds to viruses and vaccinations, and is characterized by the cytokines IL-2, tumor necrosis factor (TNF), and interferon- γ (IFNγ) resulting in the mobilization of macrophages, T cells, and natural killer (NK) cells to promote proliferation and inflammation [99]. A Th2 response is distinguished by the elevated production of immunoglobulin (Ig) secretion by B cells, especially IgG and IgE and the cytokine IL-4, as well as enlarged eosinophils and mast cell recruitment [100]. A Th2-type response is associated with allergic reactions [98], and is also activated upon parasitic infection [101]. There is a balance between the expression of both the Th1 and Th2 responses, even though challenges with diverse pathogens may modify the type and ratio of cytokines expressed, for example the Th2-type cytokine increase during parasitic infections.

Host response to *Haemonchus* infection:-

Inflammation during parasitic infection is necessary in larval and adult stage mucosal worm expulsion [99]. It has been reported that a clear Th2-type response in lambs repeatedly exposed to *H. contortus* [102], discriminated by Th2 cytokine surges, eosinophil, mast cell and globule leucocyte (intra-epithelial mast cell) recruitment, and parasite-specific IgA, IgG1 and IgE elevated production [103; 104]. Antibodies, lymphocytes, eosinophils, globule leucocytes and mast cells act upon larval stages of *H. contortus* embedded within the mucosa and adult worms residing the gastrointestinal tract lumen upon parasitic infection. Effector cells degranulate, releasing vasoactive molecules, which physically expel GINs from the abomasal mucosa [9; 99]. Eosinophils are closely associated with GIN infection, and activated by Th2 cytokines, such as IL-3 and IL-5 [105]. Sheep elecit an early immune response to infection with *H. contortus* larvae, represented by the CD4 T-cell and B-cell activation in the draining lymph nodes and eosinophil, CD4(+) and gamma delta-TCR,WC1(+) T-cell and B-cell recruitment. However, increases in mast cell numbers prevail the local response during infection with the adult parasite [105]. Mediators released by eosinophils include major basic protein, peroxidases, and neurotoxins, and have been demonstrated to have lethal effects against GIN parasites *in vitro* [106]. Mediators act as robust vasodilators, enhancing smooth muscle contraction and subsequent abomasal parasite expulsion [107]. It has been found that sheep with low egg counts had higher numbers of circulating eosinophils, which have been also been associated with larval migration inhibition [108]. Eosinophils and other microenvironmental factors, such as globule leucocytes and IL-4 can effectively kill GIN larvae *in vivo* [109]. Infection with *H. contortus* is associated with the production of mucosal mast cells and globule leukocytes within the GI tract of the sheep [110; 111]. Sheep that are more genetically resistant to parasites have more globule leukocytes than susceptible breeds [112]. Mucosal mast cells, recruited from bone marrow by Th2 cytokines, such as IL-4, histamine release, are eventually becoming globule leukocytes after degranulation [110]. Several studies have recorded the role of mast cell degranulation in worm expulsion [113; 114]; however, quantifying mast cell numbers upon necropsy is not a precise reflection of activation status and can therefore be ambiguous [115]. On the other hand, globule leukocyte quantification has been demonstrated to contribute a more accurate measure of mast cell activity [115].

Factors affecting host response to parasitic infection:-

Age is the most substantial factor in an animal's ability to effectively fight parasitic infection. The immune system develops with age; therefore, young lambs harbor the most serious *H. contortus* infections and account for the bulkiest commercial losses among producers as a result of diminished weight gain and death in extremely infected hosts [99]. The effects of haemonchosis are also more obvious in pregnant or lactating, undernourished, diseased or stressed animals due to a compromised or underdeveloped immune system [116; 117]. Genetic factors also play a role in an animal's resistance to parasitic infection. Several tropical and subtropical breeds of sheep are documented to have more natural resistance to GIN parasites. Resistant breeds include St. Croix [118], Florida Native [119; 120], and Gulf Coast Native [8]. Resistance in these breeds is defined as diminished establishment of larvae and their subsequent development into adult stages [121]. Nutritional status is a key component of the host immune response and the host's subsequent ability to mount an effective defense against GIN infection [122]. It is well-documented that animals on diets deficient in protein or key vitamins have a weakened capacity to combat parasitic pathogenesis, and concomitantly GINs significantly restrict the host's ability to efficiently exploit nutrients [123]. Lambs fed a diet high in protein harbor less severe GIN infections owing to heightened immune response. Furthermore, Immunoglubulin (Ig) A-mediated suppression of worm growth and fecundity is influenced by the quality of the diet [124]. Several studies have shown that supplementation with protein, energy [125], and trace elements [126] enhances host resistance and resilience to GIN infection. Resilience is another concept relating to the ability of the sheep to thrive in the presence of *Haemonchus* and reflects the host response to *Haemonchus* infection (Gray and Gill 1993).

Distribution and importance:-

H. contortus is distributed world-wide in tropical and subtropical regions with concentrations in the tropics and subtropics where there are high temperatures and a lot of rainfall. The parasite can also be found in more temperate areas, such as the United States. It dominates over other GINs, such as *Teladorsagia* and *Trichostrongylus* species in the southeast U.S because of the warm and humid environment. The environmental temperatures (31°C-34°C) are optimum for *H. contortus*; however, it can be existed in temperatures as low as 10°C and as high as 36°C [37; 127]. The hot and dry summer, and relatively cool winter conditions frequently constrain *H. contortus* development to short periods of the year in Mediterranean climates [128], diminishing the risk severity and duration. *H. contortus* is of relatively lesser importance in higher latitudes, owing to shorter and cooler summers, and more severe winters in studies, including Canada [129], Sweden [18], and South Dakota [130]. On the other hand, the existence of *H. contortus* in arid and semidesert areas is likely to witness its survival capacity (hypobiosis) and potential for rapid population expansion [131]. Nearly 60 different species of both domestic and wild ruminants have been identified as hosts for this GIN parasite [58]. Cross-host transmission is possible between wild and domestic hosts, for example white-tailed deer and domestic cattle and sheep [132]. It has a wide host range, including cattle, white-tailed deer, bison, antelope, giraffes, and camels; however, sheep and goats tend to be the favored hosts [133]. Domestic sheep appear to be the most exceptionally overwhelmed, which may be due to their grazing behaviors and strong flocking [58].

Ruminants (pregastric and postgastric microbial action):-

The gastrointestinal tract (GIT) of animals enables them to digest food, absorb nutrients and excrete waste products. The GIT nature is mainly determined by the food type. The stomach of carnivorous and omnivorous animals is relatively simple (i.e. hydrochloric acid and pepsin for primary digestion). However, the simple-stomach animals have a modification of the lower tract, the caecum, which is inhabited by microbes, whose function is to degrade cellulose. Some herbivores (hind-gut fermenters) have developed especially large caeca (e.g. the horse) or have other mechanisms for maximizing microbial intervention in the fiber digestion (e.g. coprophagy in rats and rabbits). The GIT of the ruminant animals has, in addition to the caecal (postgastric) fermentation, a large organ (i.e. rumen), inhabited by complex microbial populations, whose function is to degrade fibrous feed before it reaches the true stomach. The anatomy of the ruminant stomach is well-documented and the interested reader can find detailed descriptions in diverse specialized texts [134].

Only a brief and somewhat simplified description will be presented here. Ruminants are any of the diversified cud (fermented ingesta) chewing cloven-hoofed quadrupeds of the order *Artiodactyla*, obtain their food by browsing or grazing, such as cattle, sheep, goats, buffalo, deer, elk, giraffes and camels that usually have a stomach that are divided into three or four compartments. Ruminants are even-toed animal that regurgitates and masticates its food after swallowing (rumination). A diagram of feed conversion in simple stomached animals versus ruminants is presented in Figure 11. Unlike simple-stomach animals (monogastrics), such as poultry, ruminants have a digestive system designed to ferment foodstuffs and provide energy. True ruminants, including cattle, sheep, goats, deer, and antelope, characterized by their four-chambered stomach, namely the rumen, the reticulum, the omasum, and the abomasum as viewed from outside, in Figure 5, and "cud-chewing" behavior. The reticulo-rumen chambers have a wide variety of microorganisms that are essential for the digestion of plant cell walls and the production of volatile fatty acids (VFAs). On the other hand, the omasum compartment is characterized by the presence of many folds involved in the absorption of nutrients and water. The abomasum is the “true stomach” of a ruminant, and it is comparable to the non-ruminant stomach.

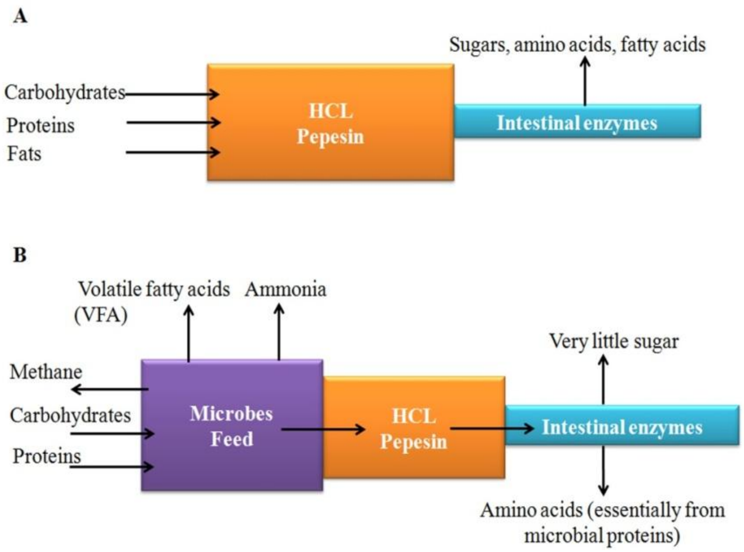

Figure 11:- Food digestion in multi- chambered stomach animals (microbial fermentation prior to digestion in ruminants) versus mono-gastric animals (non-ruminant animals)[135].

In the newborn lamb, the rumen is undeveloped and is small in comparison with the abomasum. The immature small ruminants do not have a functional rumen and reticulum, and undergo reticulorumenomasal growth. Rumen papillae (sites of nutrient absorption) lengthen and decrease in numbers as part of rumen development. The reticulum resembles a "honey comb" in appearance. Digesta mingle continually between both sections. Relatively little digestive activity occurs in the omasum (many piles) (Fig. 12; Fig. 13).

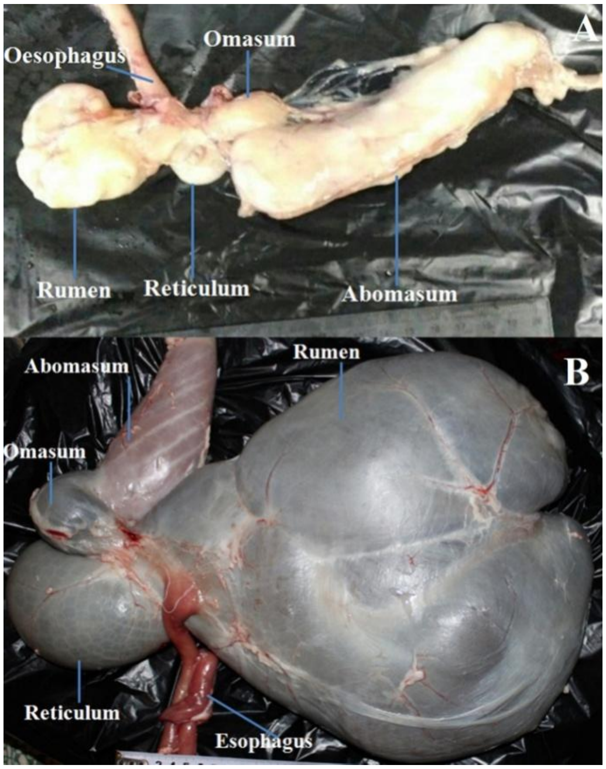

Figure 12:- Illustrating the external structure of the *rumen*, the *reticulum*, the *omasum*, and the *abomasum*, and the relative proportions of stomach compartments in sheep at different ages [7-day-old lambs (A) versus 140-day-old lambs (B)].

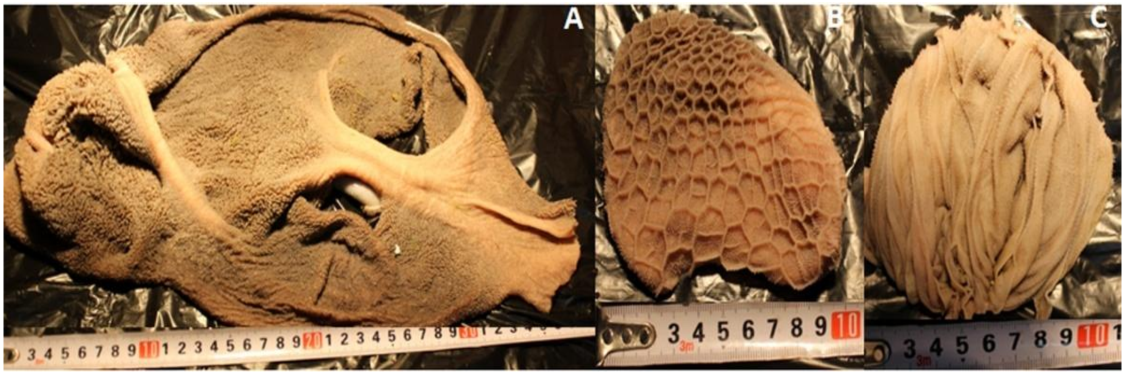

Figure 13:- Illustrating the internal structure of the *rumen* (A), the *reticulum* (B), and the *omasum*(C).

History of Sheep:-

The first livestock species to be domesticated were sheep and goats about 11,000 years ago in southwest Asia. They were primarily reared for meat; nevertheless, wool was discovered to be a beneficial product by the 4th and 5th millennium B.C. in southwest Asia and Europe [136]. Sheep then spread across Europe, Asia, and into Africa, developing into numerous breeds.

The mouflon (*Ovis orientalis orientalis* group) is a subspecies group of the wild sheep (*Ovis orientalis*). Populations of *O. orientalis* can be segregated into the mouflons (*orientalis* group) and the urials (*vignei* group). All modern domestic sheep breeds are most likely descended from the wild mouflon of Europe and Asia [137; 138; 139]. *Ovis aries* is an entirely domesticated animal that is broadly reliant on humans for its health and survival.

Characteristics of Sheep:-

Sheep belong to the order Artiodactyla with camelids, suborder Ruminantia, family Bovidae, and subfamily Caprinae [140]. Sheep have an array of sizes, colors, and breeds globally and are considered to be intermediate grazers (i.e having nutritional requirements midway between grazers and browsers).

Economic importance of sheep:-

Sheep are a crucial part of the global agricultural economy. China, Australia, India, and Iran have the bulkiest modern flocks, and serve both local and global requirements for wool and mutton. However, New Zealand has smaller flocks and retains an enormous international economic impact because of sheep product exportations. The conventional essential markets, including European Union (EU) and United States of America (USA) will be enlarged by augmenting demand from developing countries, such as China, Saudi Arabia, Jordan, United Arab Emirates, India, Turkey and Qatar [141]. According to Food and Agriculture Organization of the United Nations (FAO), the ten countries with the largest number of heads (expressed as a percentage) of sheep were: mainland China, Australia, India, Iran, Nigeria, the former Sudan, United Kingdom, Turkey, New Zealand, and Ethiopia. Interestingly, mainland China has changed dramatically from the top three producers in 1961 to the top first in 2014 (Fig. 14) (**http://www.fao.org/faostat**).

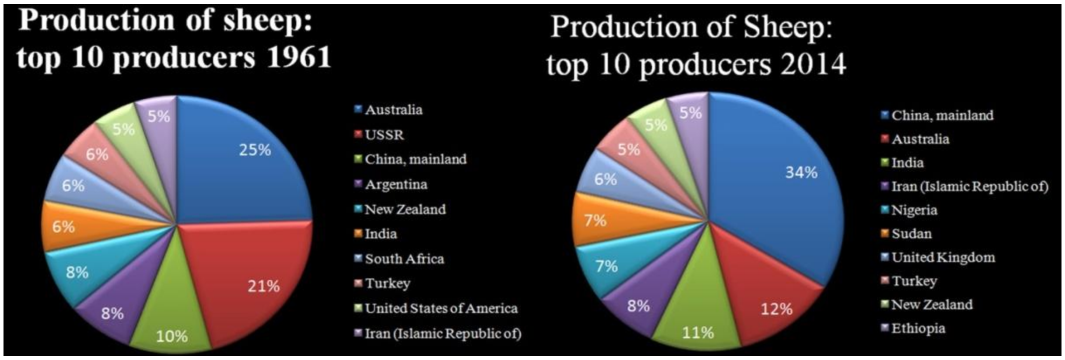

Figure 14:- Top 10 sheep producers world-wide.

Sheep versus goats:-

Goat and sheep industry have made monumental gains in productivity globally. Both species provide humans with meat, milk, wool and skins. Goats are well-known as a tough animal that can be fruitful in extreme environments that are not appropriate for other ruminants, such as sheep and cattle[142]. By comparison with sheep, goats have an exceptional ability for walking long distances, are recognized to select the most nutritive plants and can utilize bushes and shrubs [143] (Fig. 15). Several reports showed that sheep and goats share the same species of GIN parasites [144; 145]. Additionally, both sheep and goats can readily transmit GIN parasites to each other [146; 147].

Cross-infection of resistant GIN parasites between these two hosts may occur and must be a significant cause for concern in countries like China where goats and sheep may share the same farming system. Goats prefer browsing, while sheep will rely almost completely on grazing pastures. Browsing diminishes L_3 intake owing to higher numbers of infective larvae are only found very nearby the base of pastures[148]. Similarly, higher faecal egg counts were reported in the Angora goats (grazer) compared to Saanen goats (browser) due to the differences in feeding behavior [149].

Therefore, sheep are more likely to contract GIN parasite infections due to grazing behavior; however, goats do not mount the same level of immune response to the GIN parasites as sheep. Several studies have compared the level of GIN parasite infection in goats and sheep during common grazing when they placed in diverse conditions. The higher faecal strongylate egg counts of New Zealand feral goats are significantly different from those of adult Romney sheep grazing mixed grass and clover swards with no access for browsing [150]. Furthermore, other studies have reported that goats are generally more succumbed to parasitic infection than sheep under grazing systems [151; 152]. Results from another study involving Coopworth lambs and Saanen kids between 6- and 8- month-old grazing naturally infected pasture indicated that after approximately 6 months, Saanen kids had significantly higher faecal egg counts than those of the Coopworth lambs [153]. Previous research comparing sheep and goats has found that the average strongyle faecal egg counts of sheep reduced from the age of 8 months onwards whereas this only happened in goats from 12 to18 months onwards under the traditional husbandry system in peninsular Malaysia [154]. Faecal egg counts in sheep declines more rapidly due to the earlier development of an effective immune response to GINs compared to goat [155]. A similar picture documented that goats are highly susceptible to GIN infections in general and to *H. contortus* in particular compared to sheep [156]. Poorly developed immunological responses are the primary cause of their relative inability to control GIN infections, and the associated pathophysiological consequences [149].

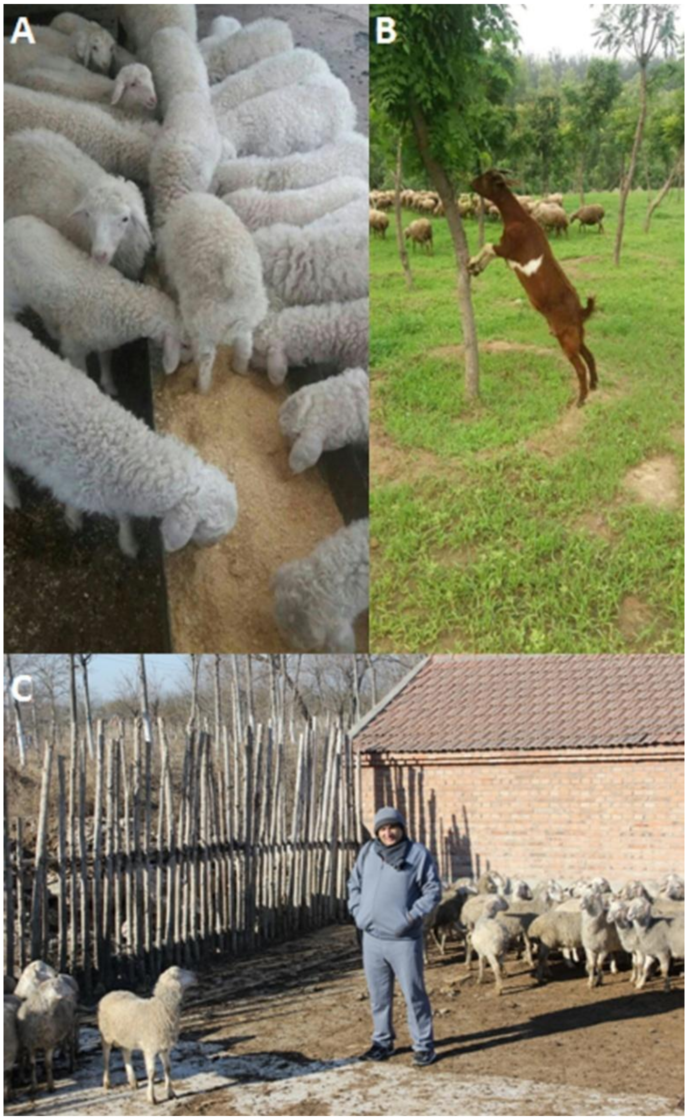

Figure 15:- Traditional method of goat and sheep housing and management.
The figure shows lambs fed concentrate diets (A), browsing goats and grazing sheep shared the same farming system on pasture in rangeland near their owner's premises at Jin Zhan village, Chaoyang, Beijing, China (B), and sheep and goats confined in their shelter (C).

Abomasal anatomy:-

The abomasum is separated into three obvious anatomical parts. These are: the cardiac region, which contains a small circular area around the omaso-abomasal junction, the fundic/corpic area, which is distinguished by luminal folds covering the major part of the abomasal surface, and the pyloric area, which is the most distal part, is marked by the existence of rugae (Fig. 16).

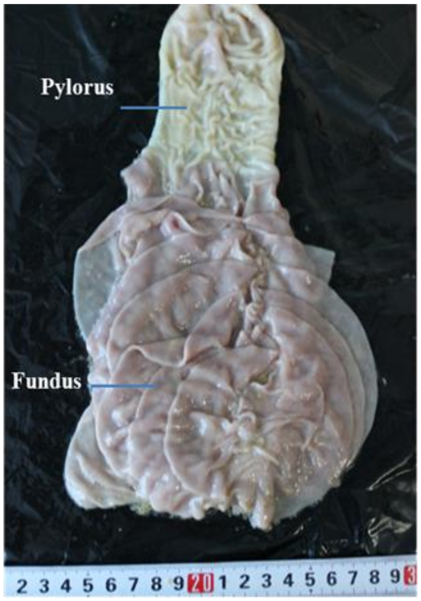

Figure 16:- Inner structure anatomy of the ovine abomasum.

Histologically, the abomasal wall, like the rest of the gastrointestinal tract, is organized into four concentric layers from the outside inward, which are: the *tunica serosa*, the *tunica muscularis*, the *tunica submucosa* and the *tunica mucosa*. The *lamina propria* has a connective matrix supporting the gastric epithelium and the feeder blood vessels. The gastric epithelium is composed of surface epithelial cells (cuboidal to columnar cells) and gastric glands. The cellular layer forms numerous invaginations, called gastric pits or foveolae serving as draining duct of adjacent glandular secretions to the lumen. The abomasum has two types of gastric glands according to their anatomical location, namely the pyloric and fundic glands (Fig. 17; Fig. 18).

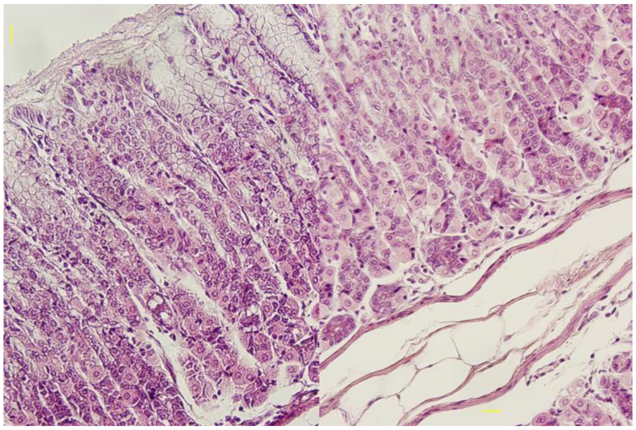

Figure 17:- Normal architectures were seen in the ovine abomasal tissue (fundic region). HE 40X. Bar = 10 um.

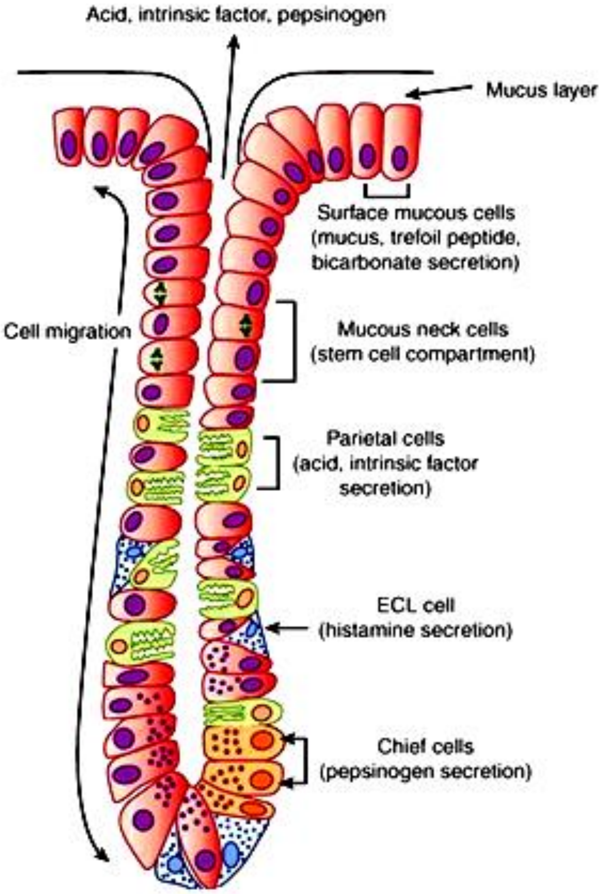

Figure 18:- Gastric gland structure from the fundic area (Adapted from [157].)

Abomasum is one of the most important sites for living bursate nematodes belonging to Trichostrongylidae family in small ruminants, because it is the site location for 3 pathogen species of GI nematodes e.g., *Haemonchus* spp., *Teladorsagia* spp., *Ostertagia* spp.and

Trichostrongylus spp. [158]. The histopathology of haemonchosis in sheep has been the subject of intense investigations during the last decades [61; 159; 160; 161]. Abomasal nematode larvae enter the gastric pits and glands, where they cause local lesions, the nodules, which have at their centre developing larvae in distended glands lined by many flat undifferentiated cells, but few secretory cells. These nodules are diverse on the abomasal folds [162; 163]. Adjoining parasitized glands demonstrate mucous cell hyperplasia with fewer parietal cells and chief cells. These changes become more broad after the L_4s or immature adults emerge [163; 164; 165; 166; 167; 168]. Luminal stages stay close to and within the superficial mucus [169]. The infected sheep abomasa are much heavier than control animals and the mucosal thickness is much greater [170; 171]. The pits are expanded and there are fewer parietal cells and chief cells, however, more mucous neck cells (MNCs) and undifferentiated cells [172]. Similar generalized histological changes are observed after adult *T. circumcincta* [168; 173] or *H. contortus* transfer [174] even though there are no damaged glands where larvae have grown. There may be an association between the pathology, histopathology and inflammatory responses to the nematode presence, especially through the parietal cell loss and inhibition. Infection provokes the release of cytokines, including IL-1β, IFN-γ and TNF-α, which are inhibitors of parietal cells [175; 176; 177]. Parietal cell loss not only results in diminished acid secretion and increased abomasal pH, although fewer chief cells, owing to parietal cells produced growth factors necessary for mucous neck cells (MNCs) to develop into chief cells [178]. In line with these findings, this occurs in other pathologies where parietal cells are lost, for example transgenic mouse models [179; 180]. The increase in mucus-producing cells in general, and MNCs in particular, in consistent with the increased mucin secretion seen in *H. contortus*-infected sheep [181].

Pathophysiology:-

H. contortus- or *T. circumcincta*-infected sheep have increased gastric pH, elevated serum concentrations of pepsinogen and gastrin, and diminished acid secretion [166; 174; 182]. The abomasal pH of uninfected sheep is approximately 2.8, nevertheless the pH may be 4 and above in *T. circumcincta* infected sheep [166; 182]. Previously challenged sheep with *Ostertagia circumcincta* may be able to acidify their abomasal fluid and maintain the pH low, while naive animals lose the ability to maintain abomasal pH [183]. Hypergastrinaemia began at the same time as abomasal pH became increased, however stayed high and continued to augment when pH had reached a maximum and had returned towards normal. Serum gastrin was depressed when abomasal pH exceeds 5.5 in *O. circumcincta*-infected sheep [166; 184].

Hyperpepsinogenaemia is frequently employed in ruminants as an indicator of abomasal parasitism [166; 174; 182; 185; 186; 187]. Serum pepsinogen usually elevates at the time of parasite emergence from the glands or a little earlier and remains increased for up to 30-60 days after a single infection while the parasites are still present in the abomasum in *O. circumcincta*- and *H. contortus*-infected sheep [166; 168; 174; 188]. The magnitude of the increased plasma pepsinogen levels in ovine gastrointestinal trichostrongyles, including *Ostertagia leptospicularis* and *O. circumcincta* varies between animals, from approximately zero [166; 174; 182; 187; 189] to remarkable increase in immune animals, even with small worm burdens [190]. After transfer of adult *H. contortus* [174], *Ostertagia ostertagi* [165], or *T. circumcincta* [164; 166; 168; 188], abomasal pH, serum gastrin and pepsinogen concentrations increase within the first day. These effects on abomasal secretion are proposed to be initiated by abomasal parasite chemicals [164; 166; 167; 168], but later also to include the host response. *H. contortus* excretory/secretory products (ES), which are released by GINs to their environment, consist of diverse bioactive components, including chemotaxins, metabolic end-products, enzymes, immunomodulators and growth factors. ES has been reported to inhibit acid secretion *in vitro* [191], as well as restrain the enterochromaffin-like cells, which may indirectly cause diminished acid secretion by parietal cells [187; 192]. Ovine gastrointestinal nematode chemotaxins recruit granulocytes *in vitro* [193], which could be another way of damaging parietal cells *in vivo* [163; 167].

Conclusion and future directions:-

We have attempted to provide a comprehensive overview about the haemonchine parasite and the ovine host as well to reveal intervention points that could be exploited to discover novel therapies, vaccine strategies and prophylactic intervention points for parasites, and to understand the parasitic disease progression and the infection consequence.

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Competing interests:-

The authors declare that they have no competing interests.

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