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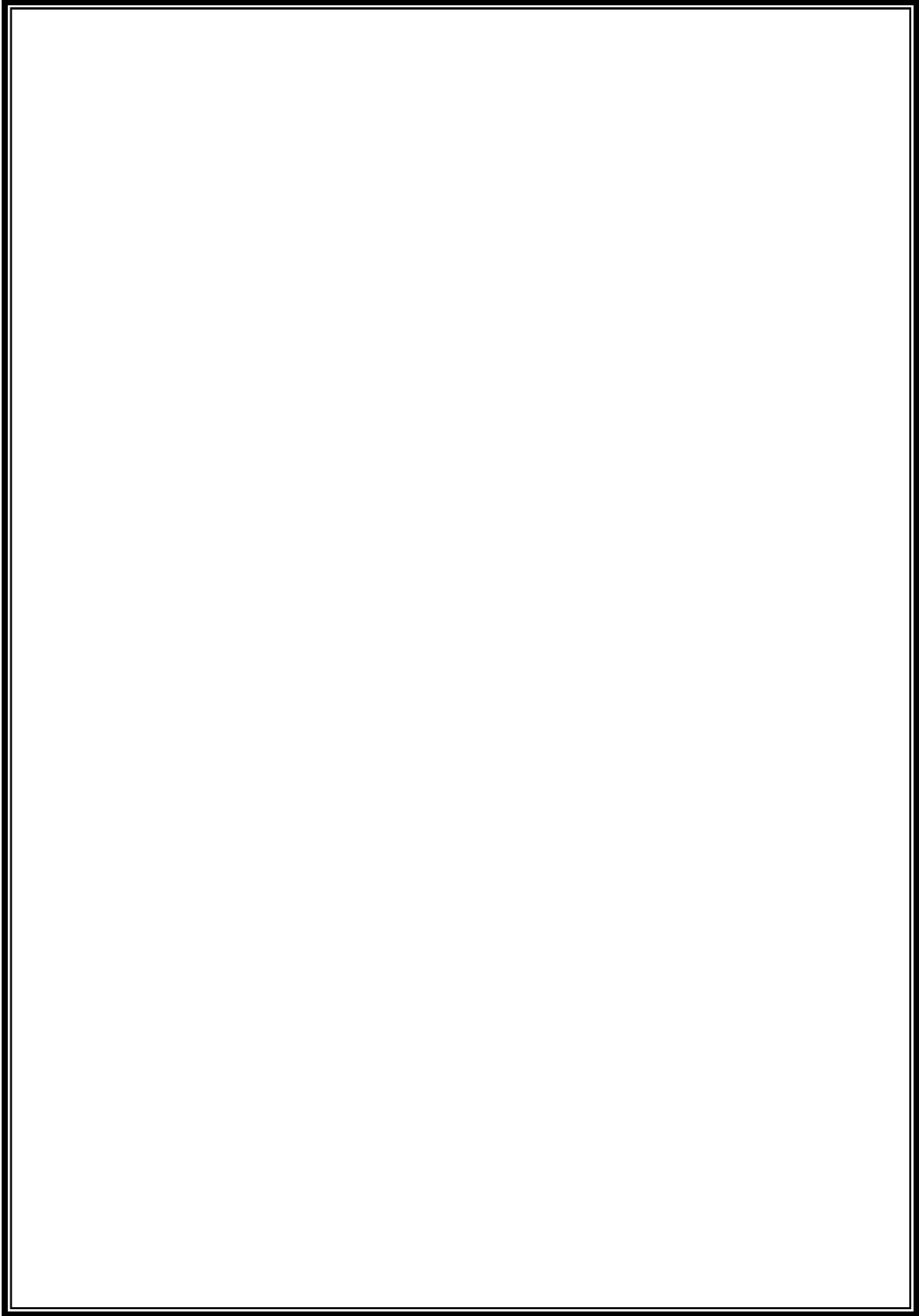
Elimination of Visceral Leishmaniases

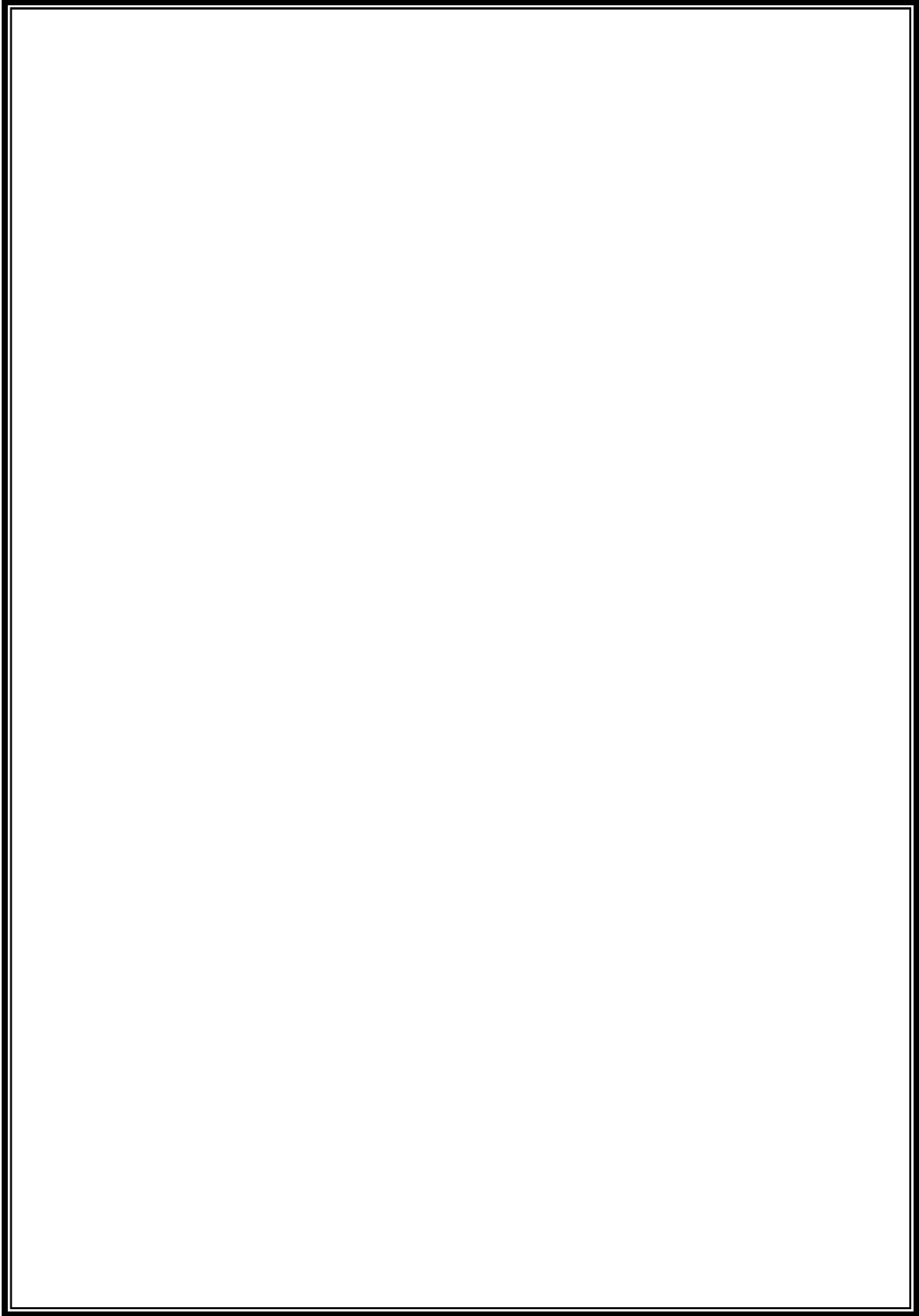
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Varanasi, India, 10-14 November 2003*

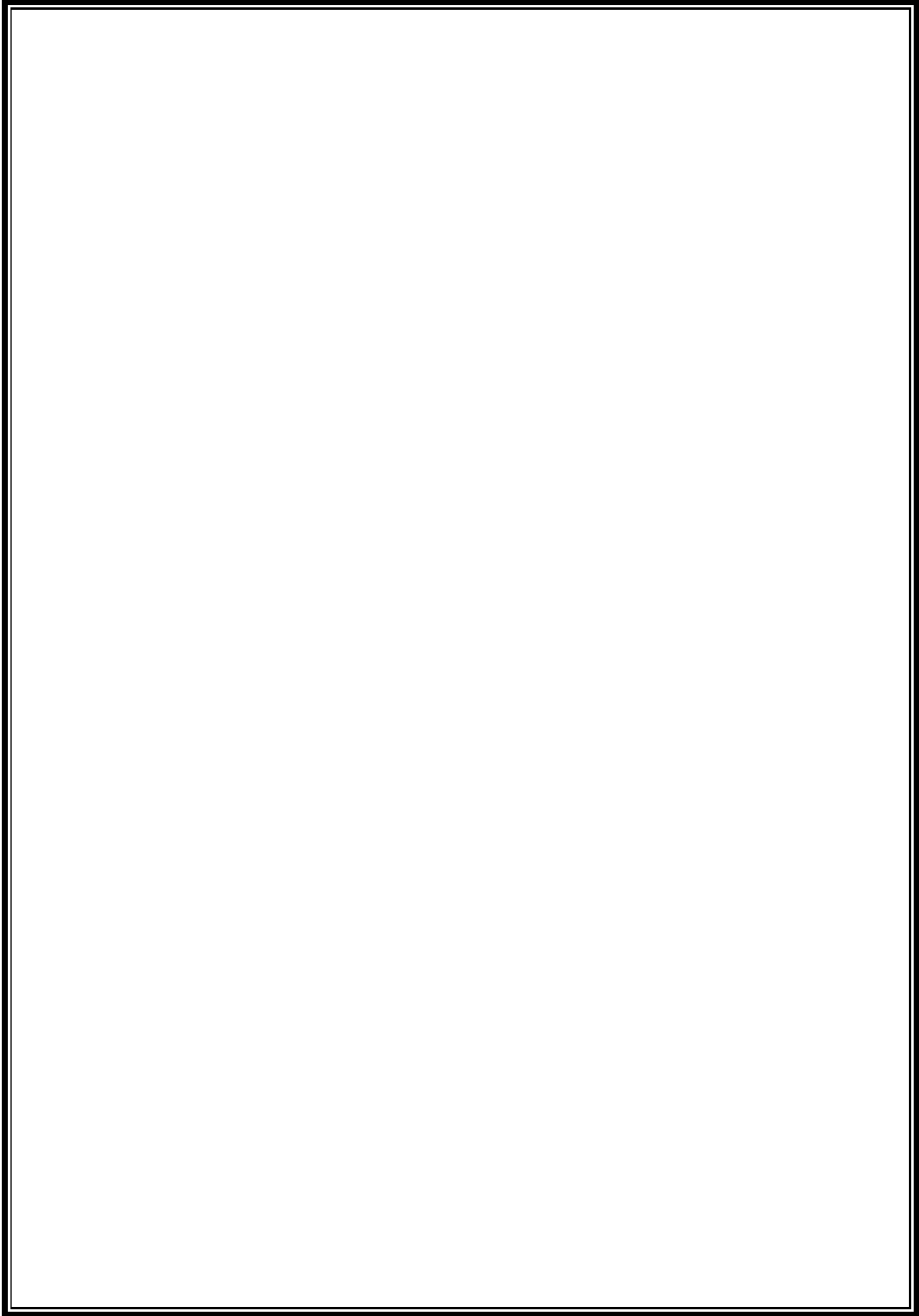
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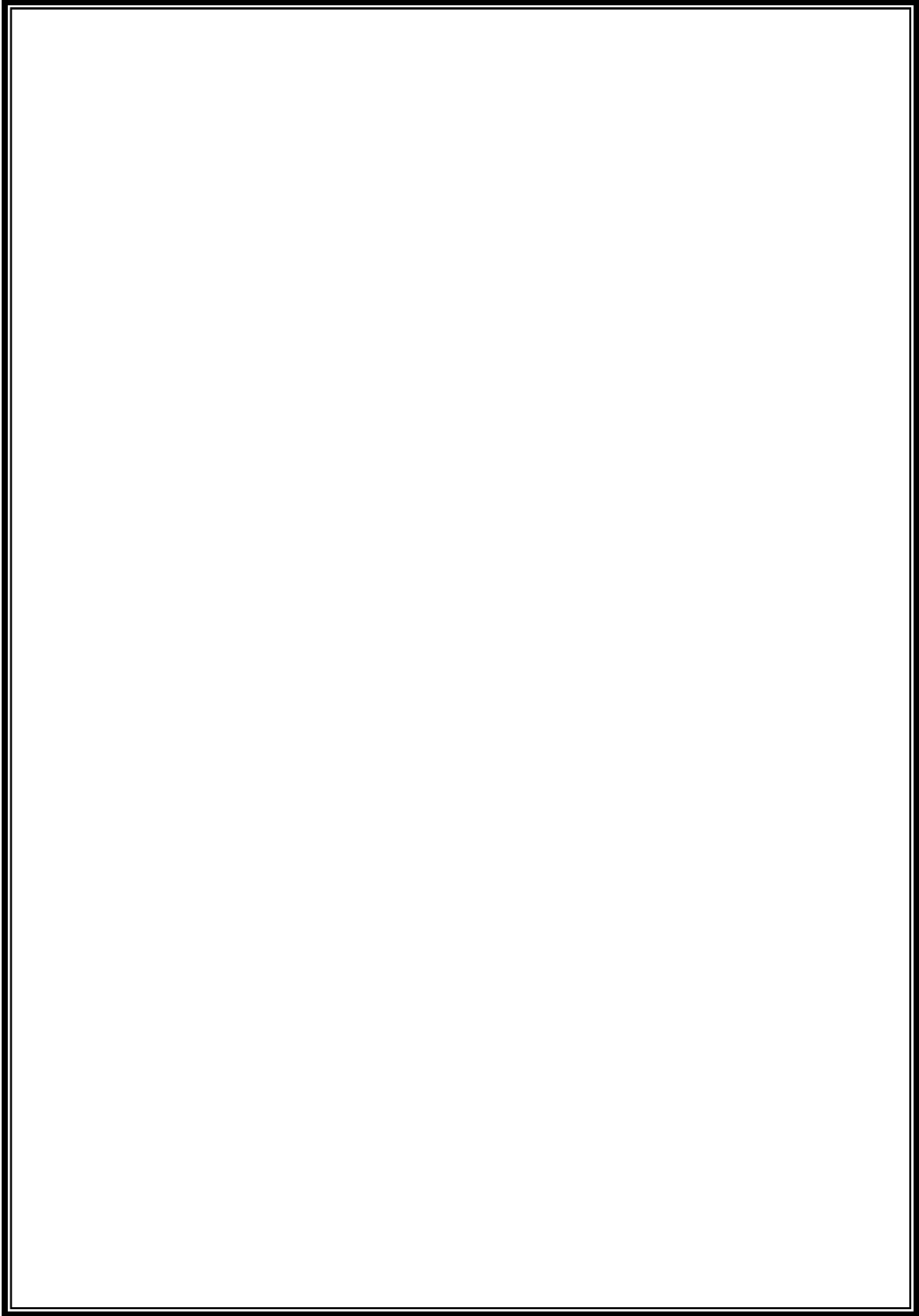


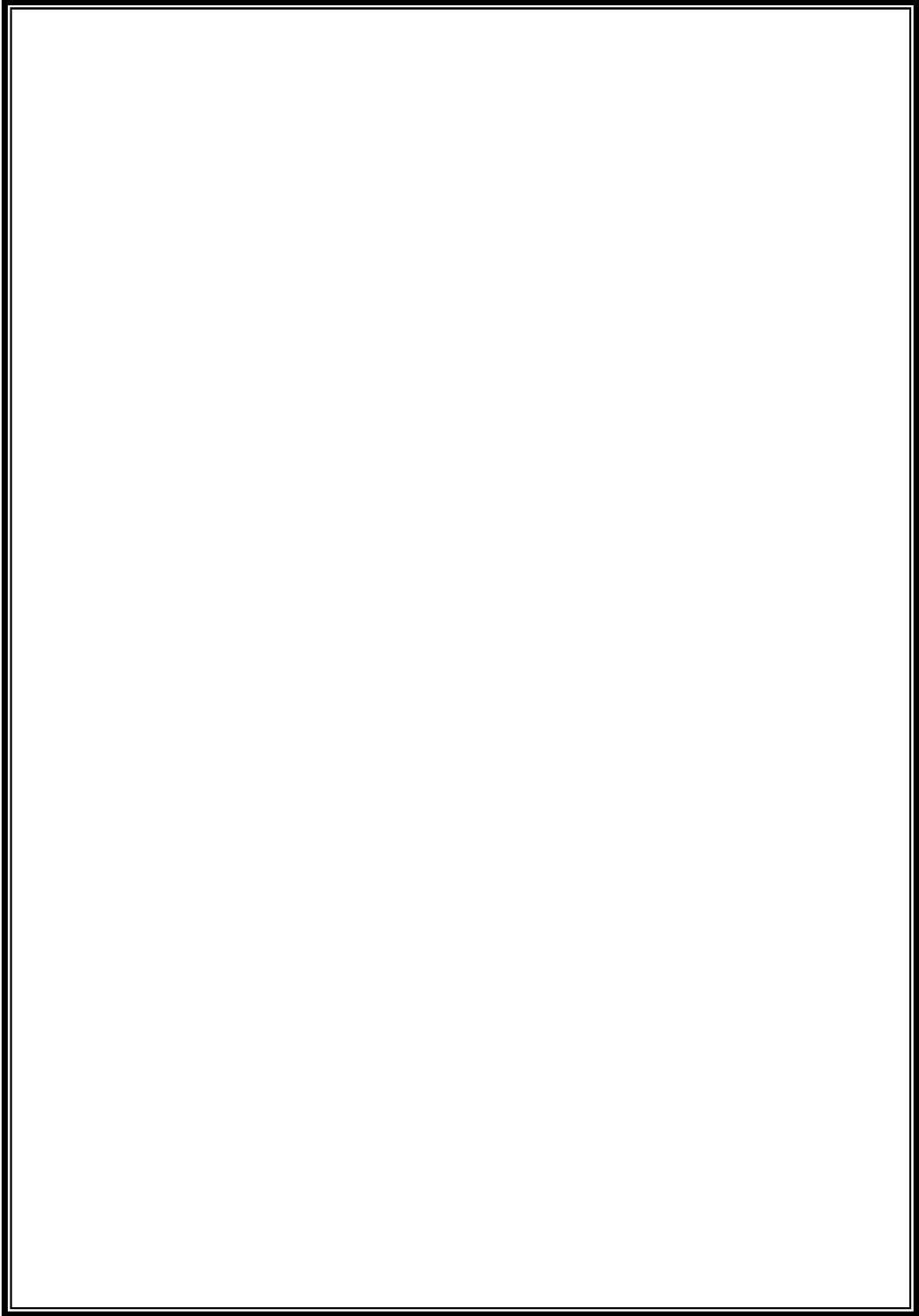
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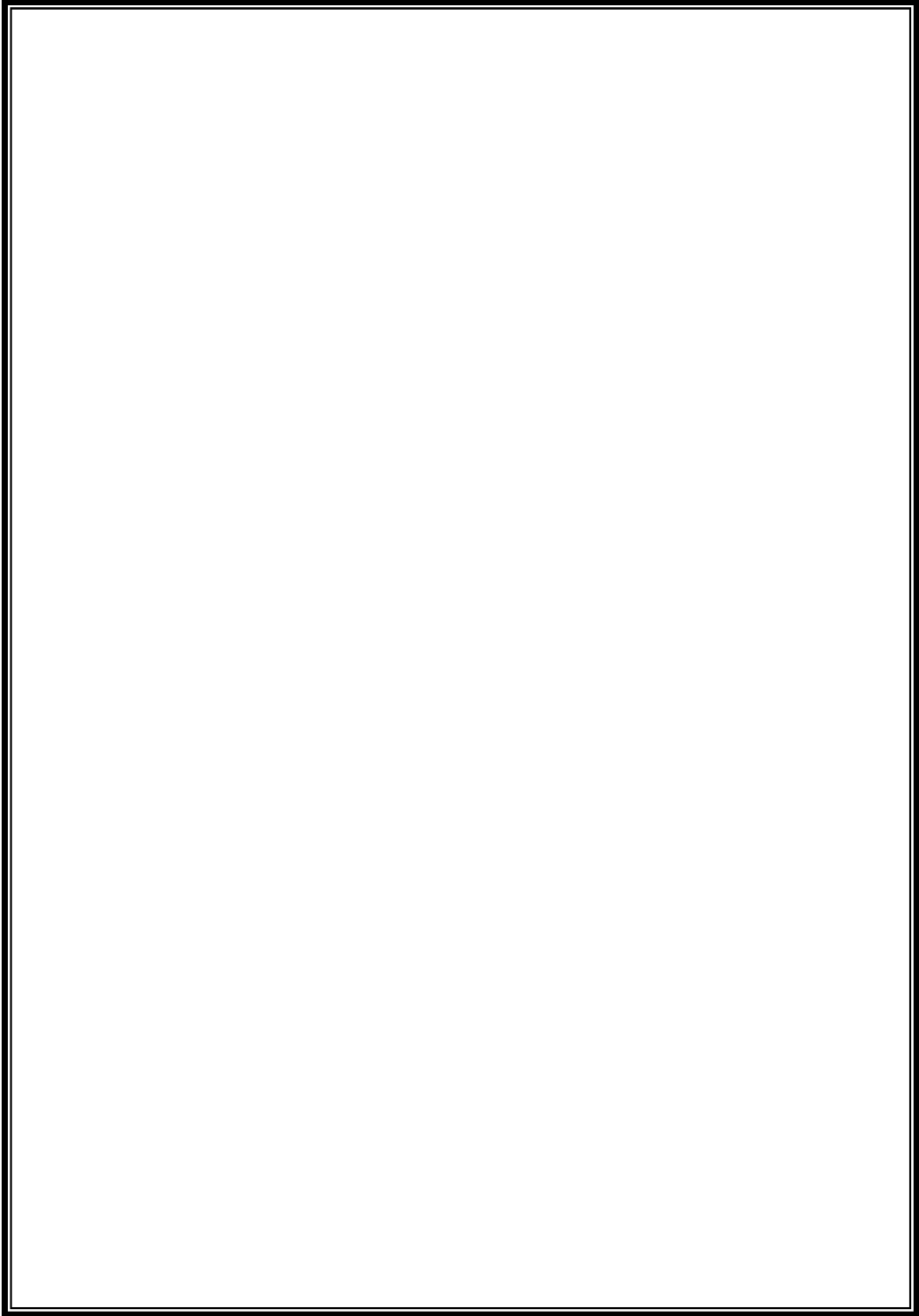


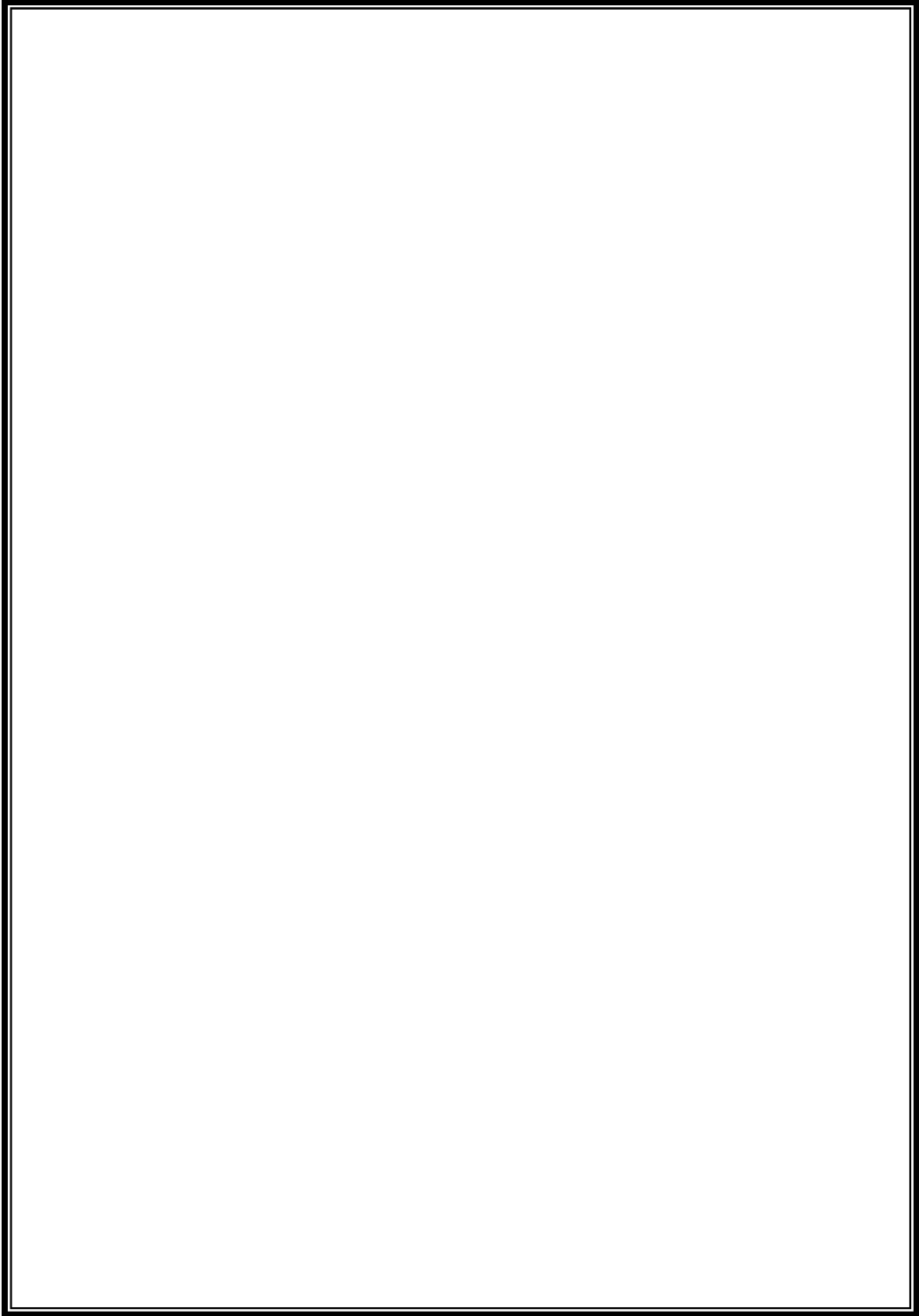


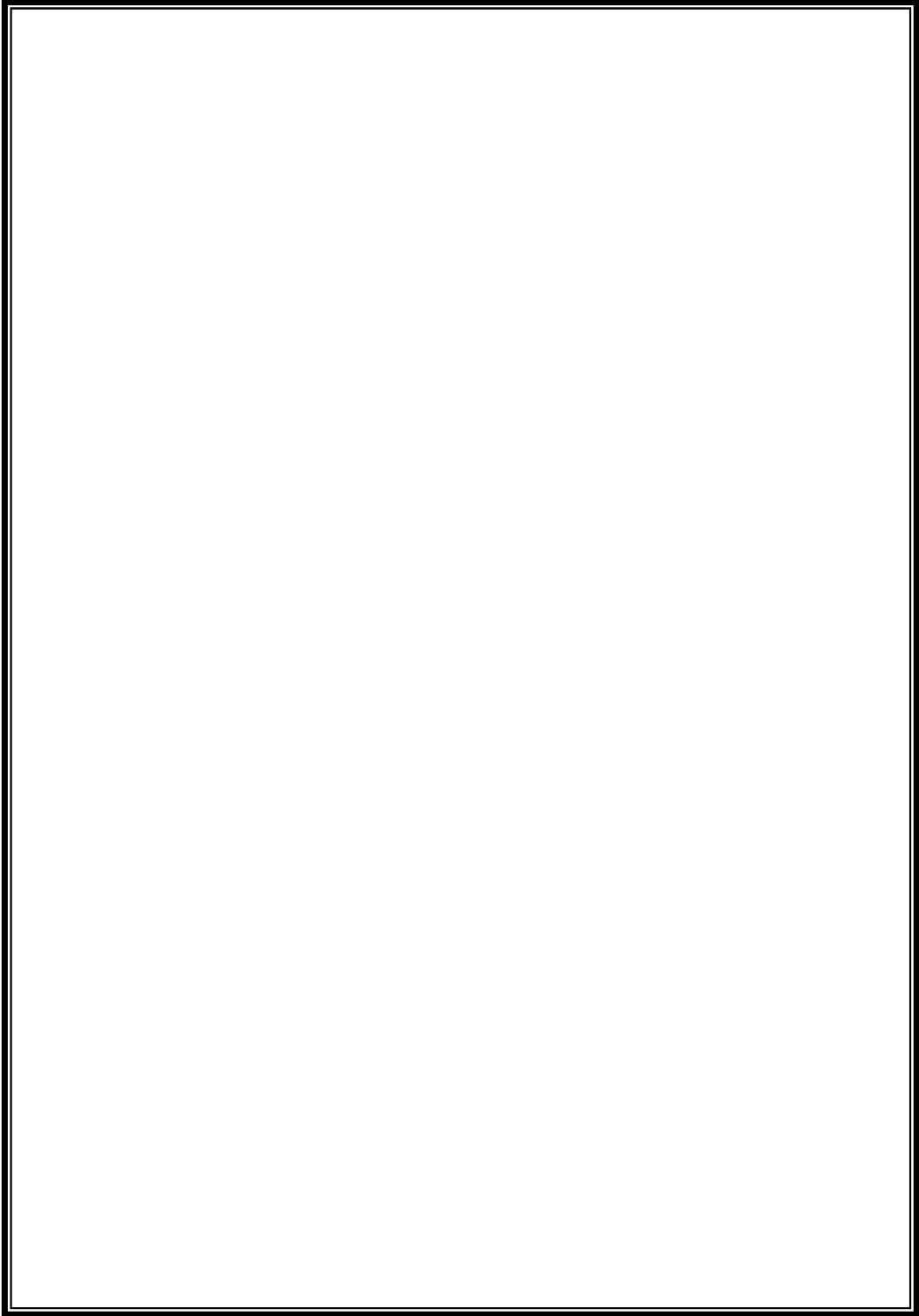


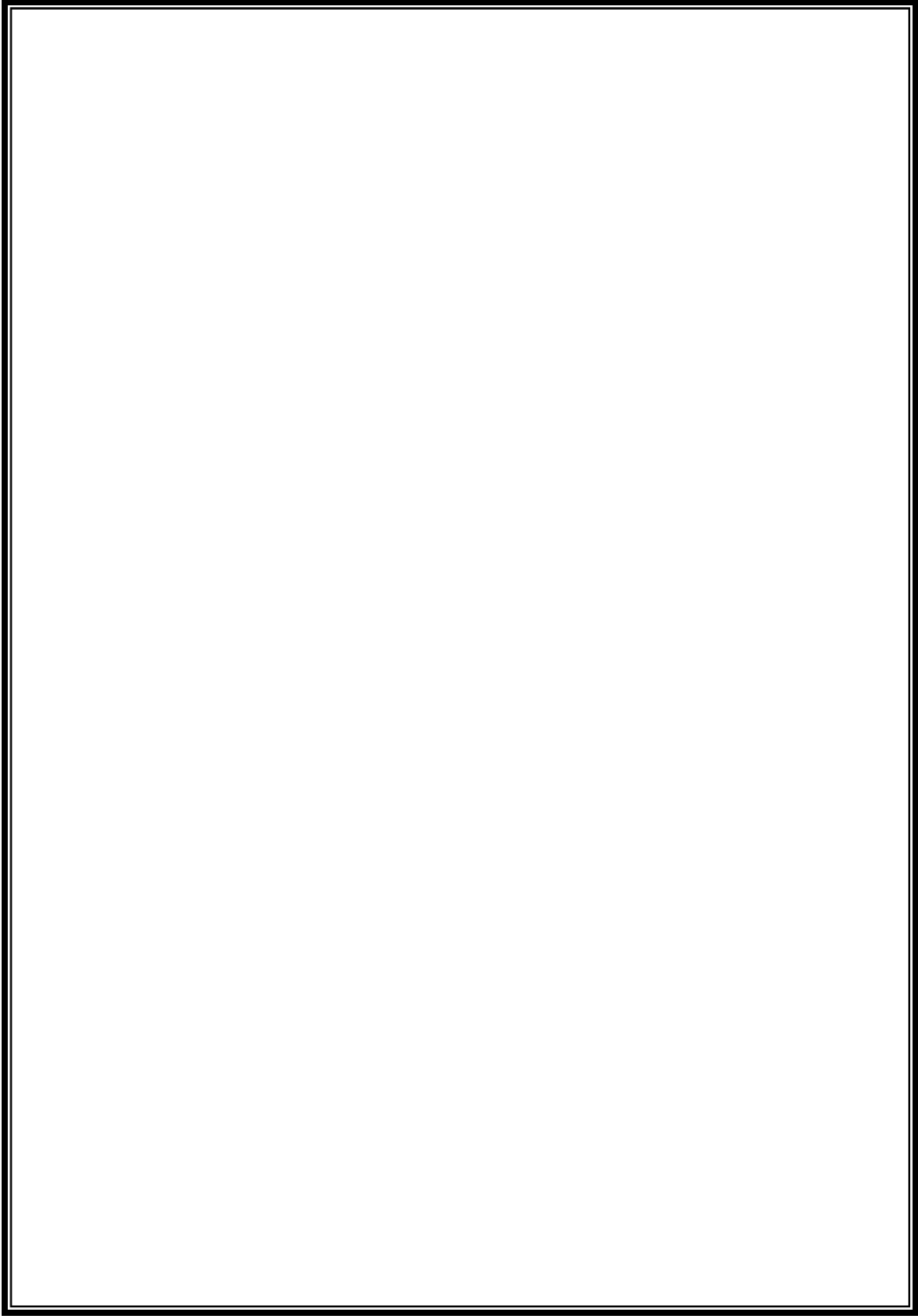


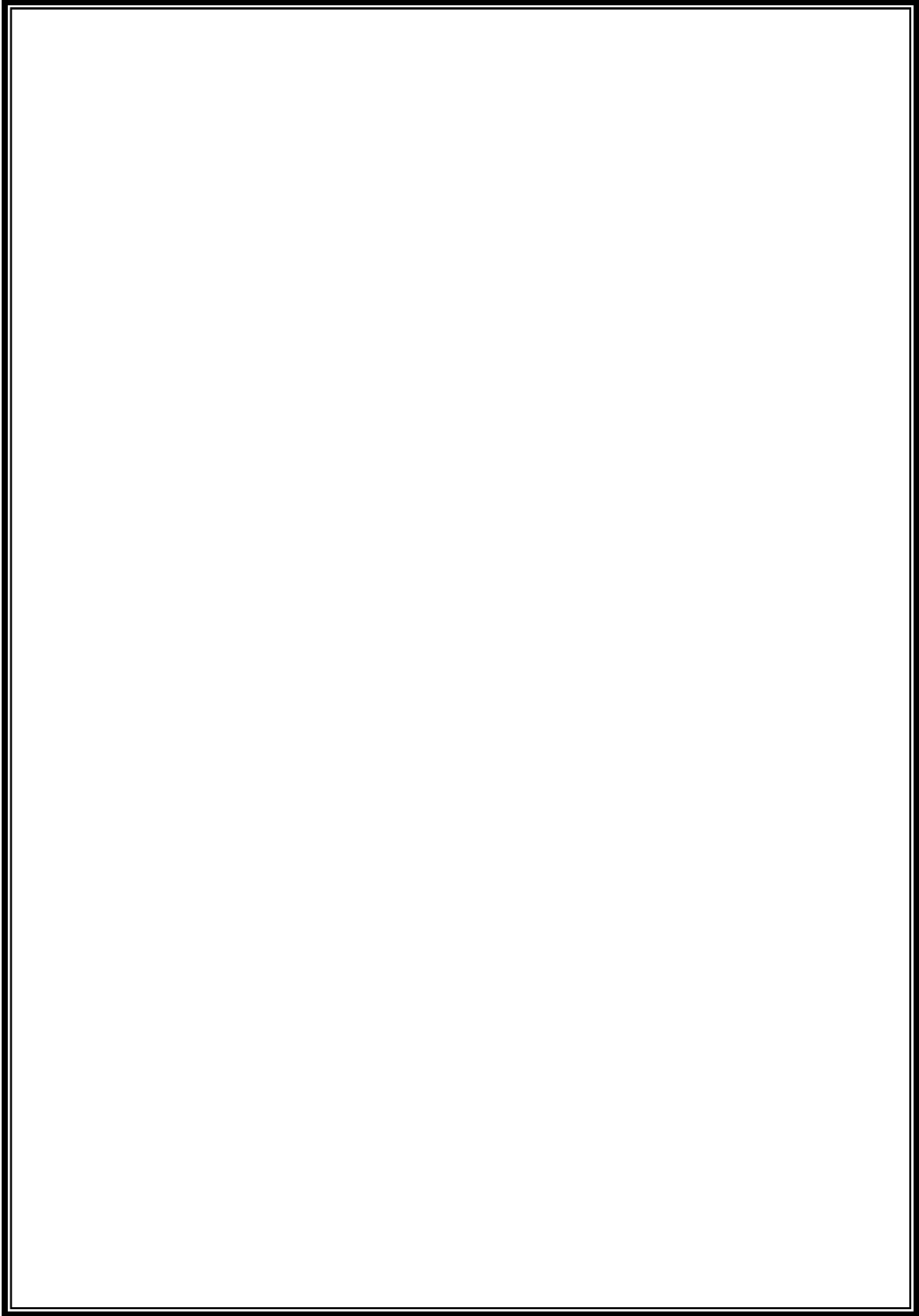


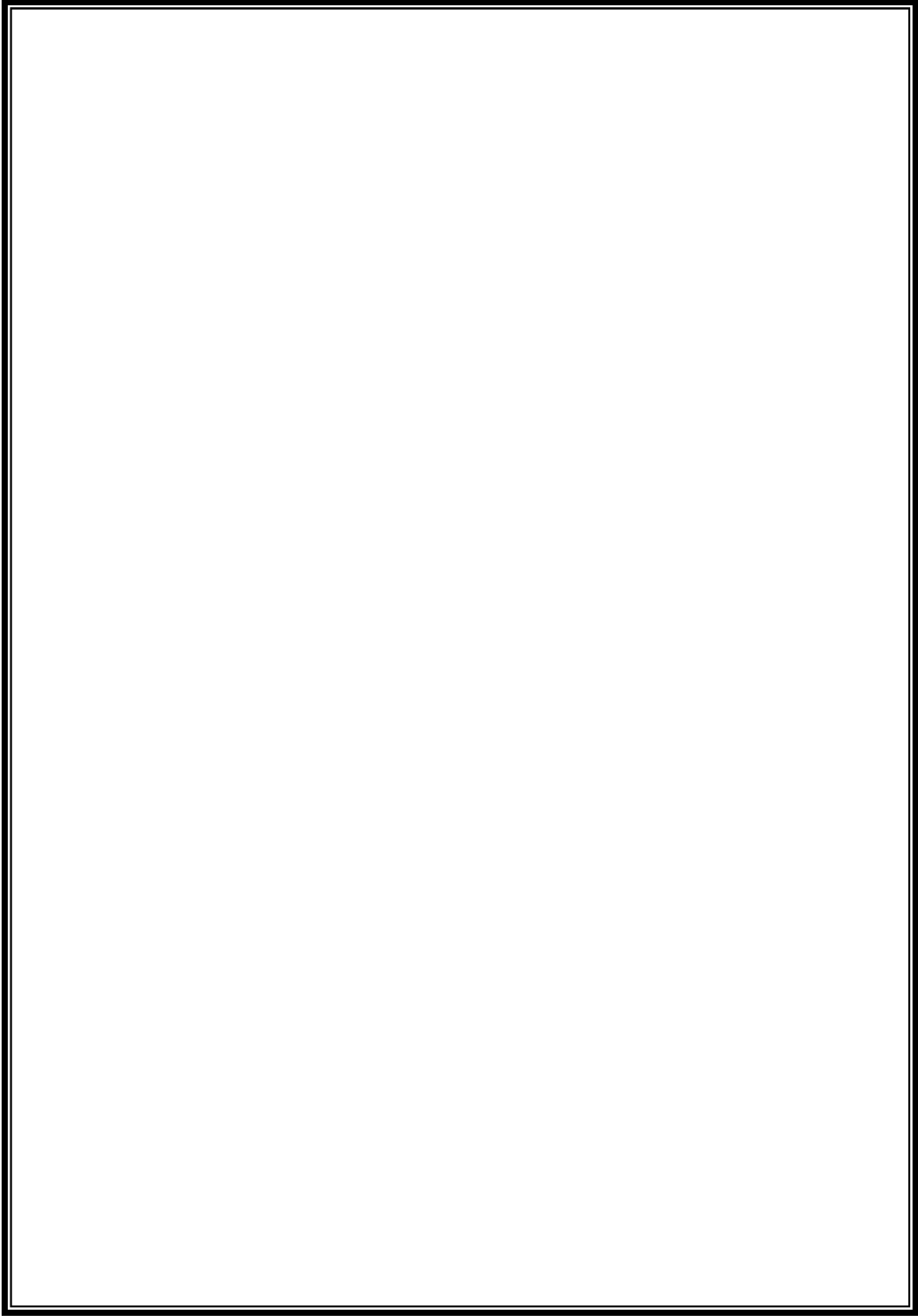


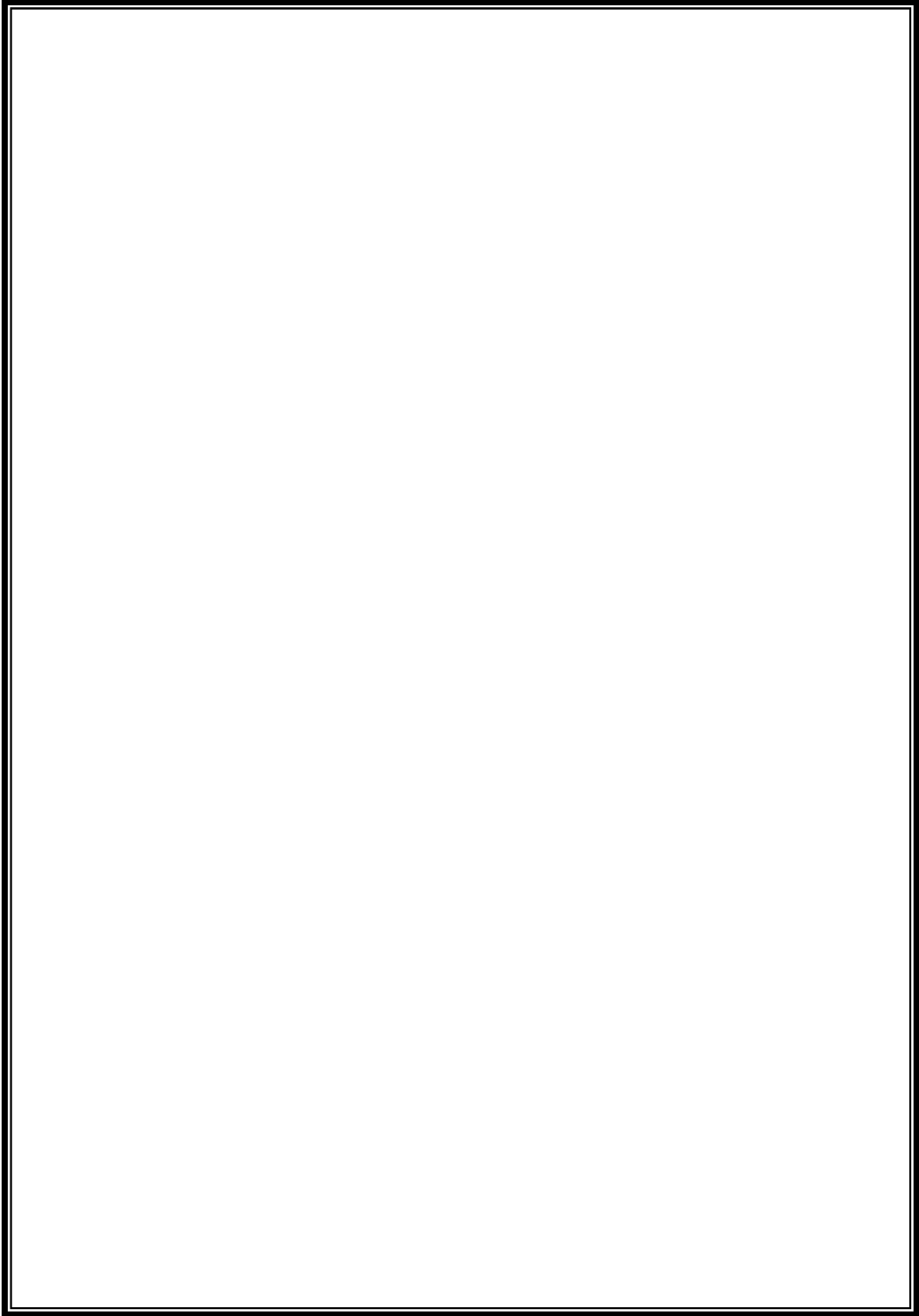


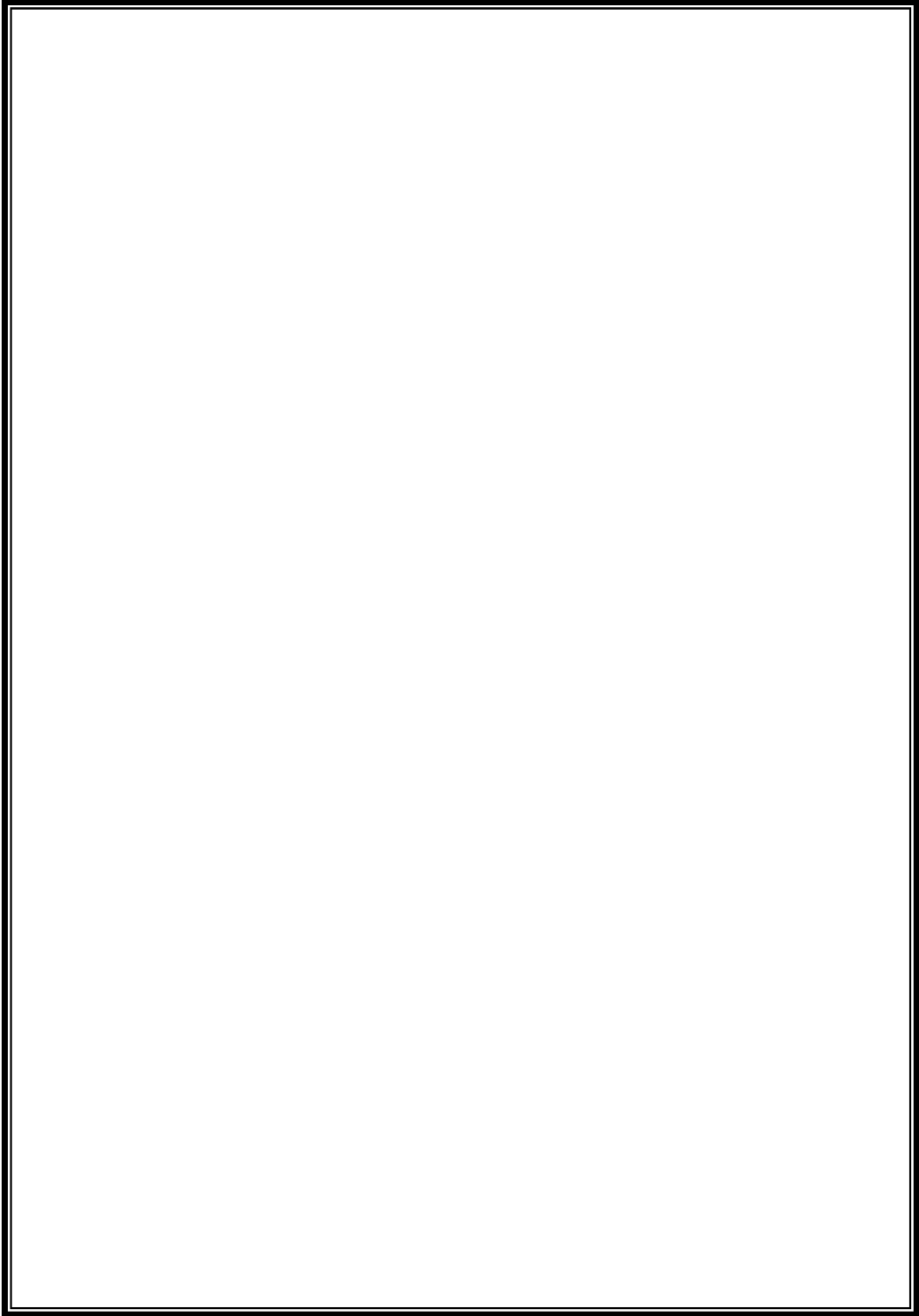


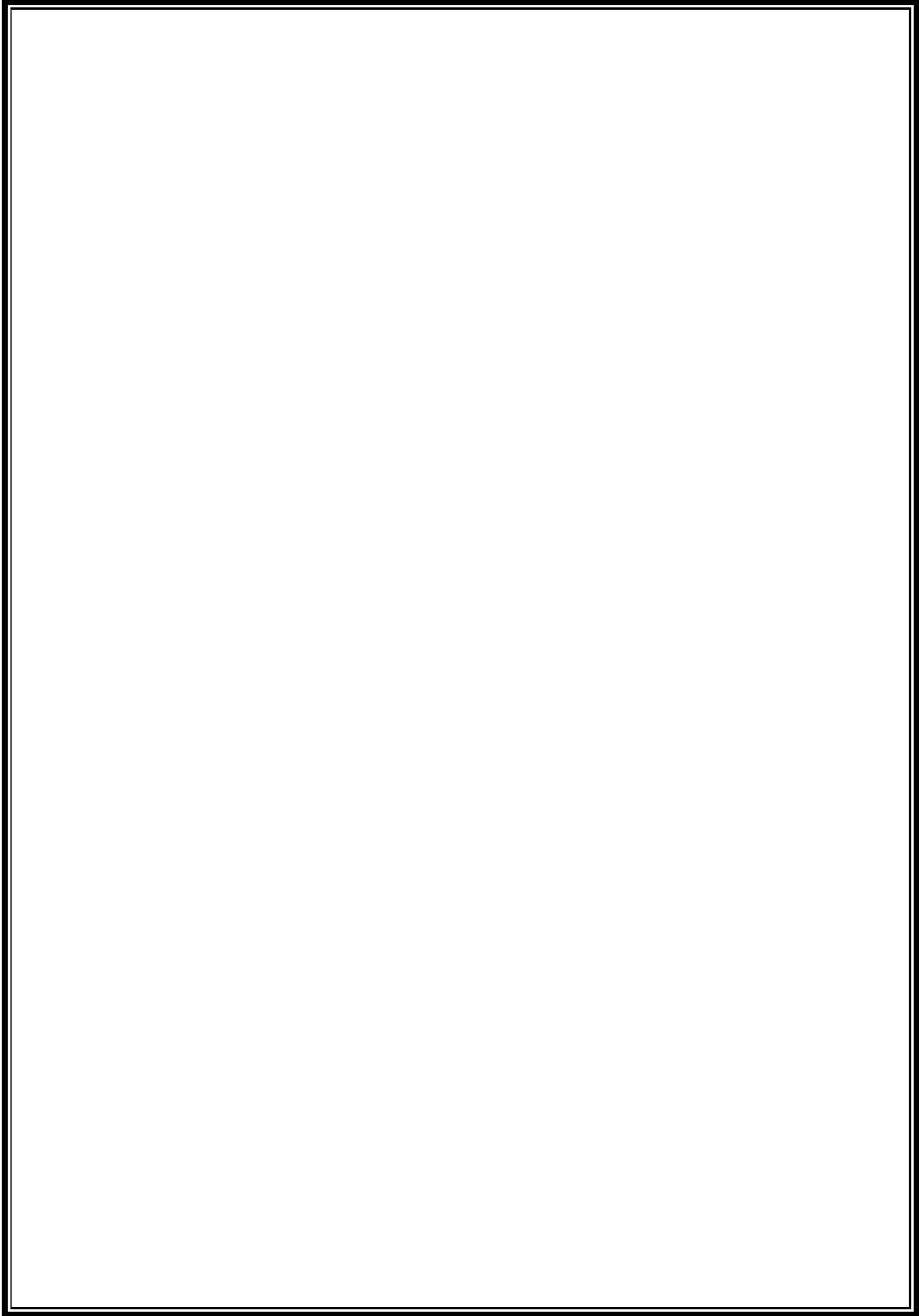


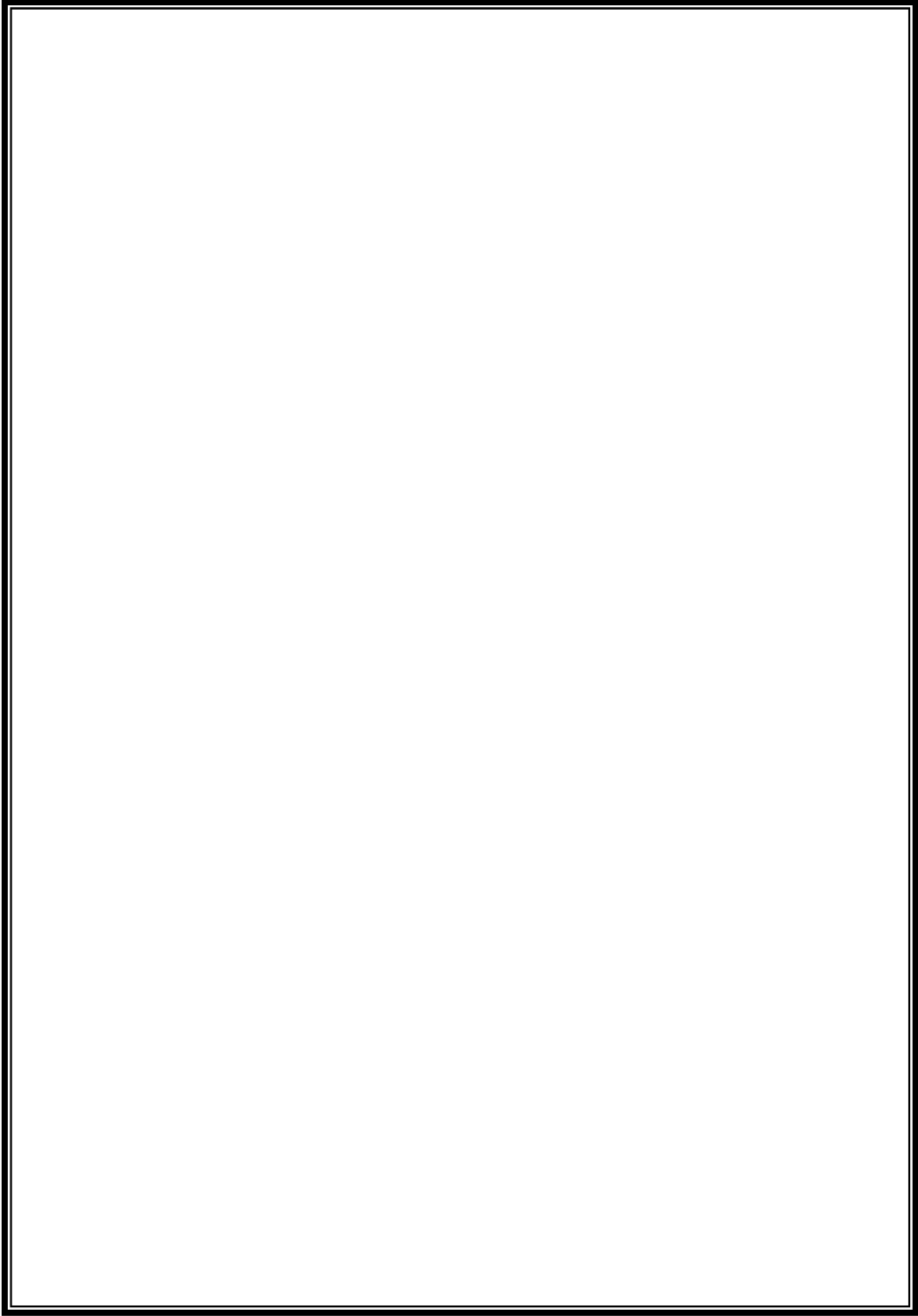


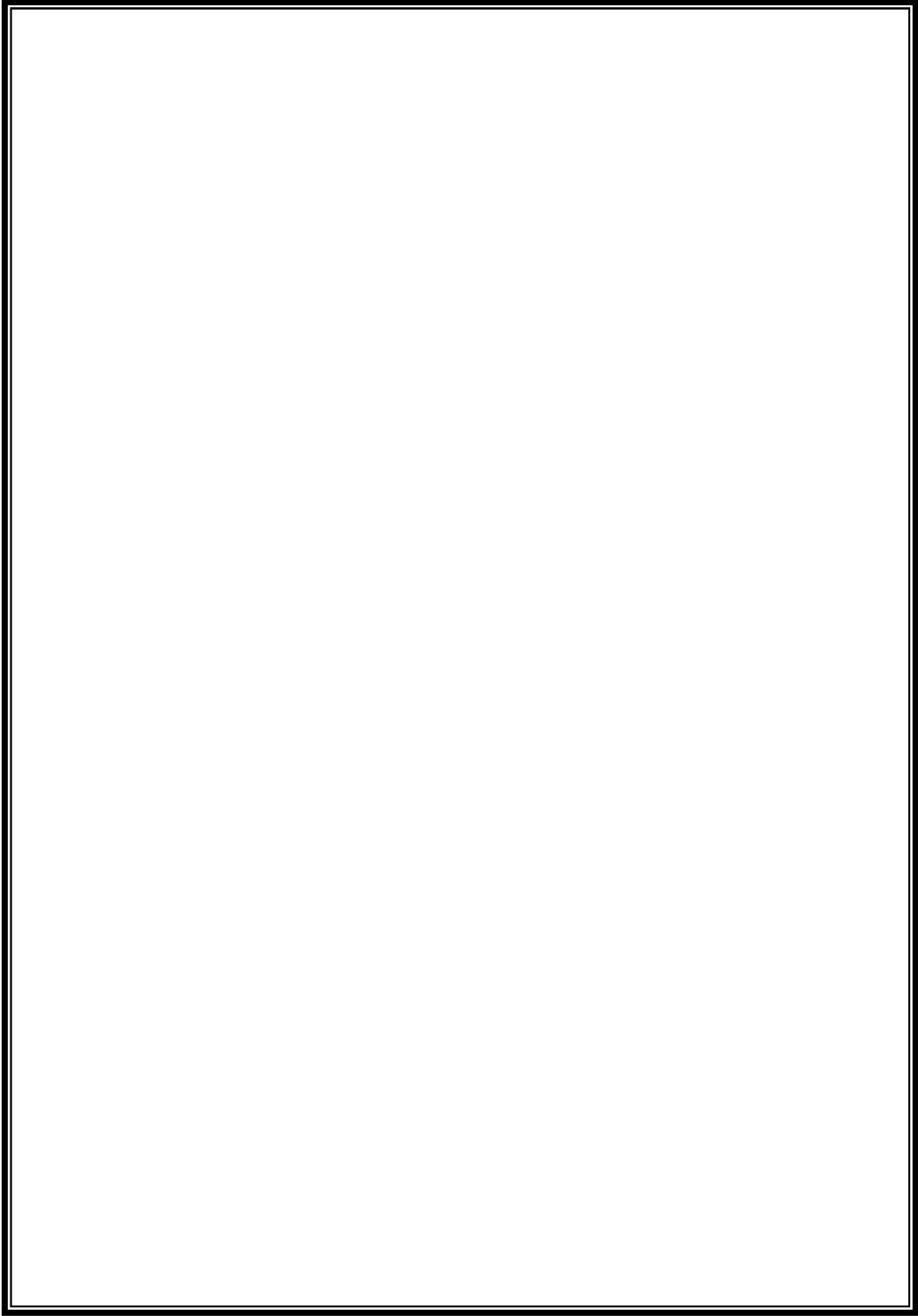


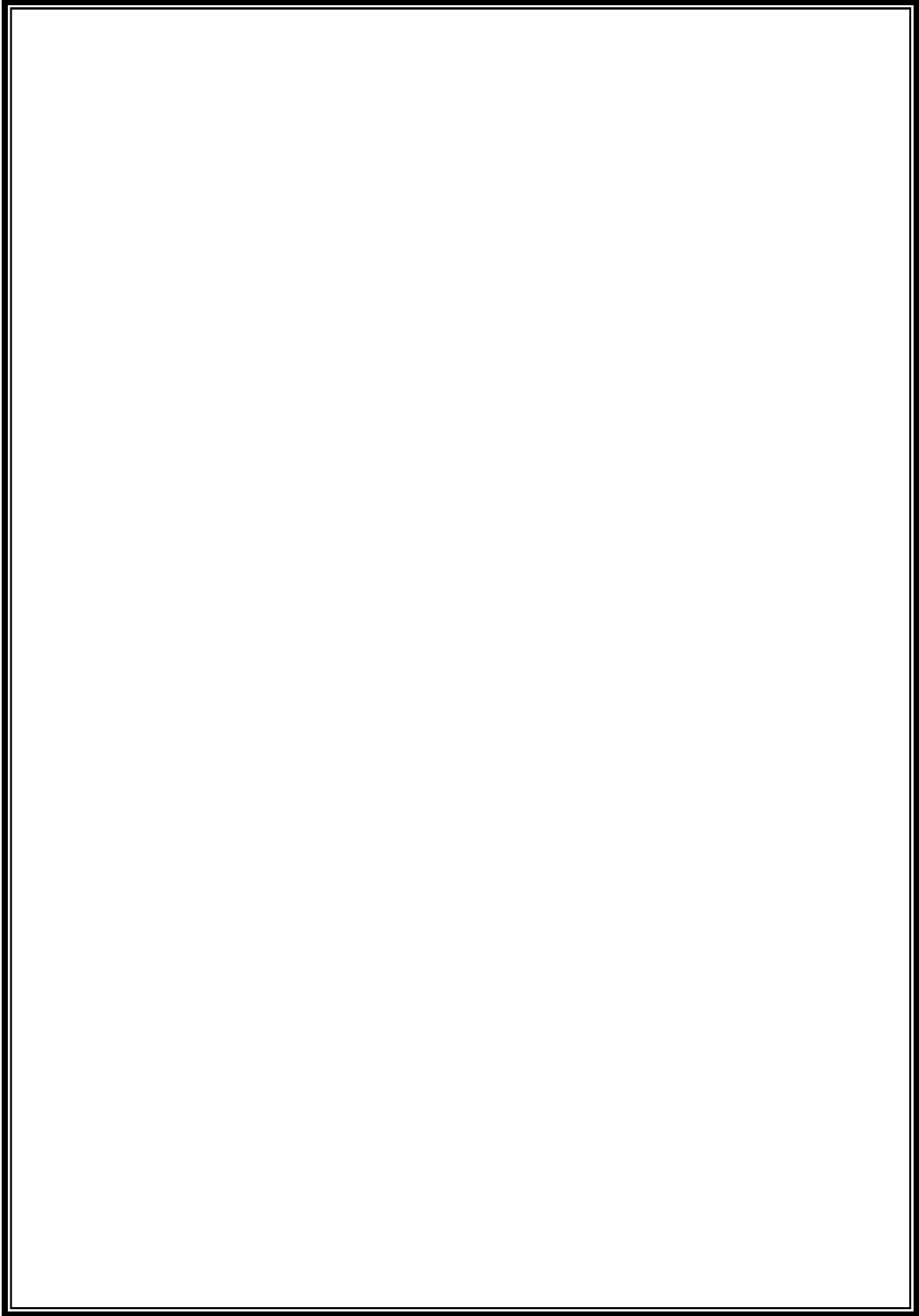


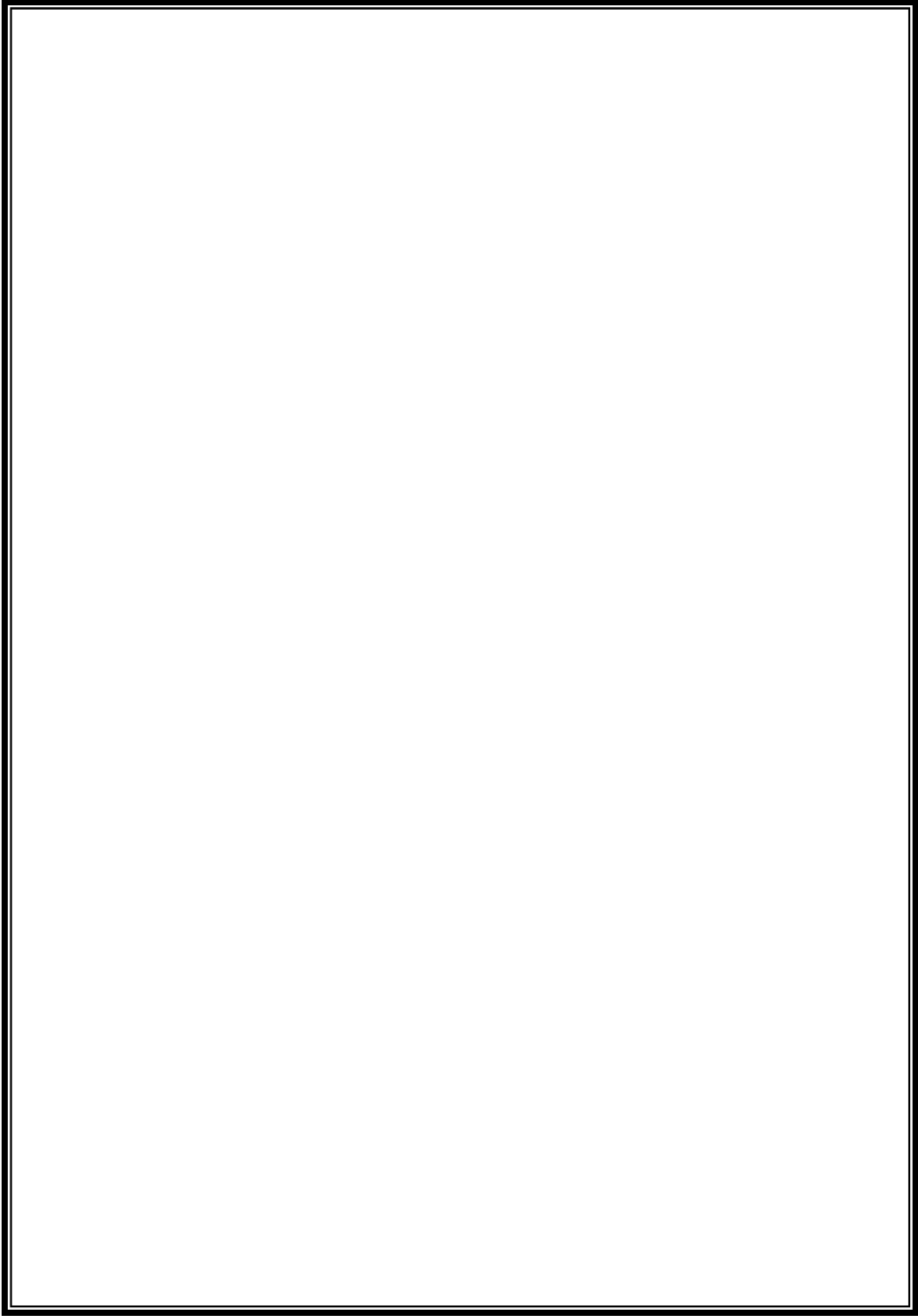


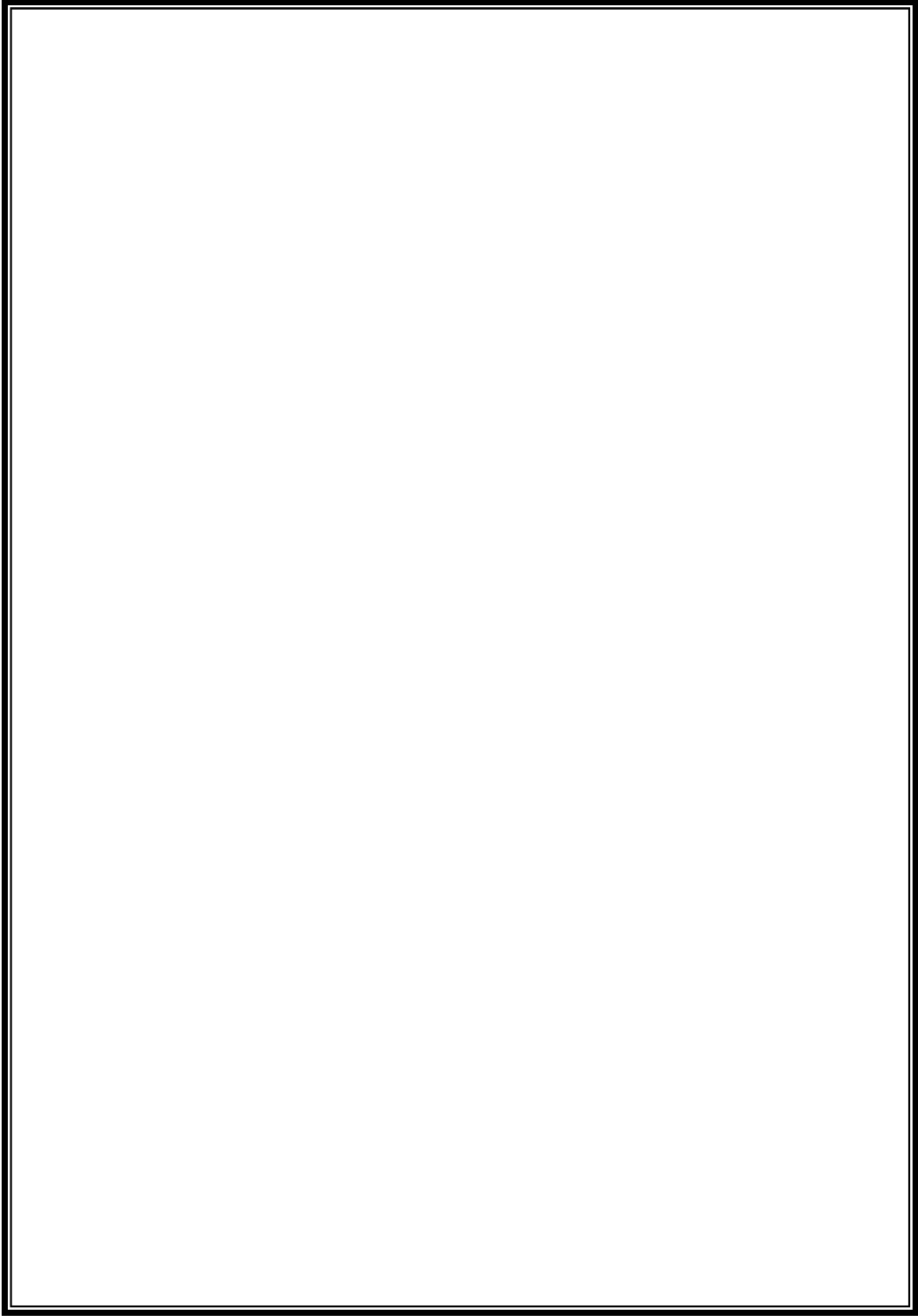


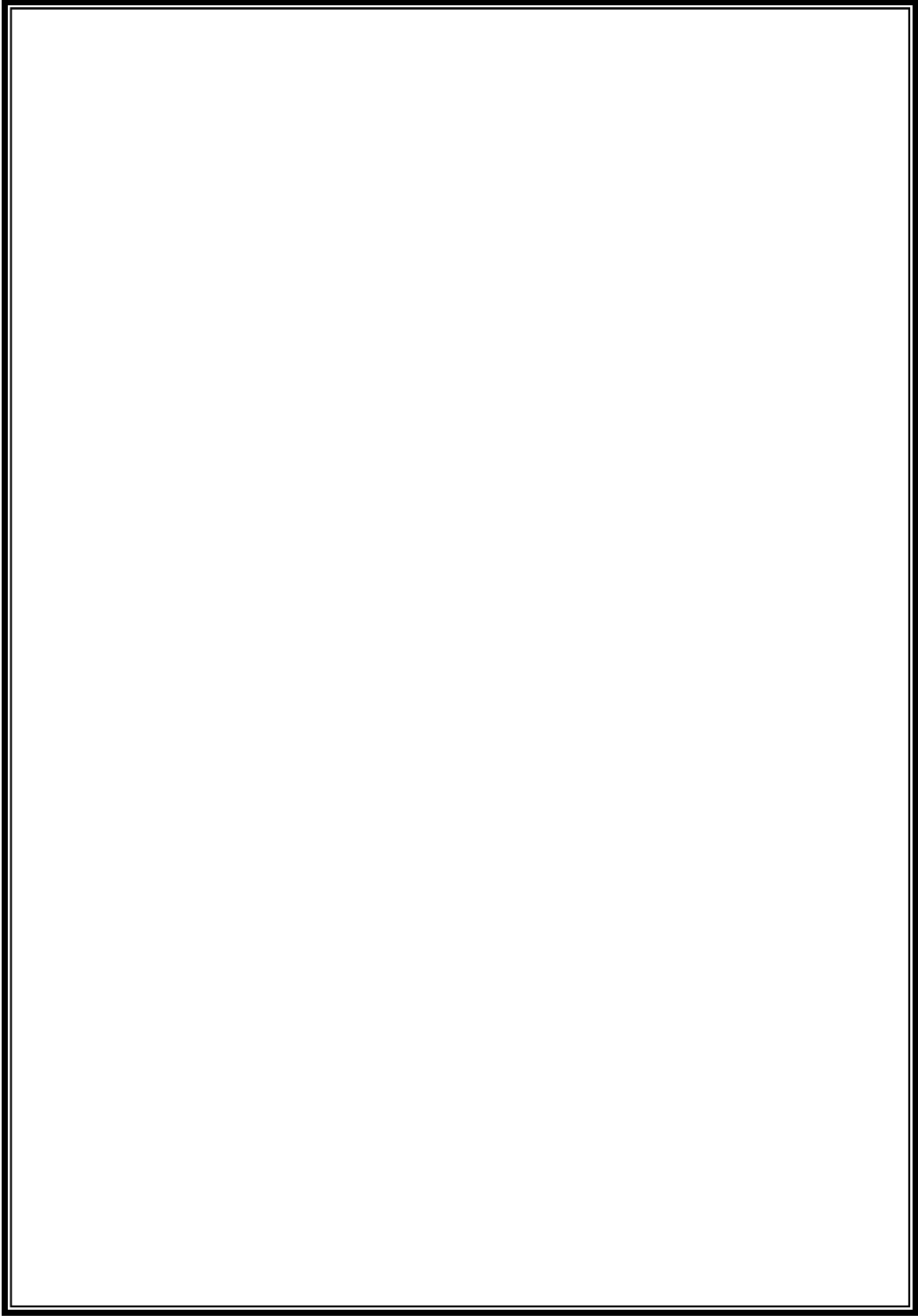


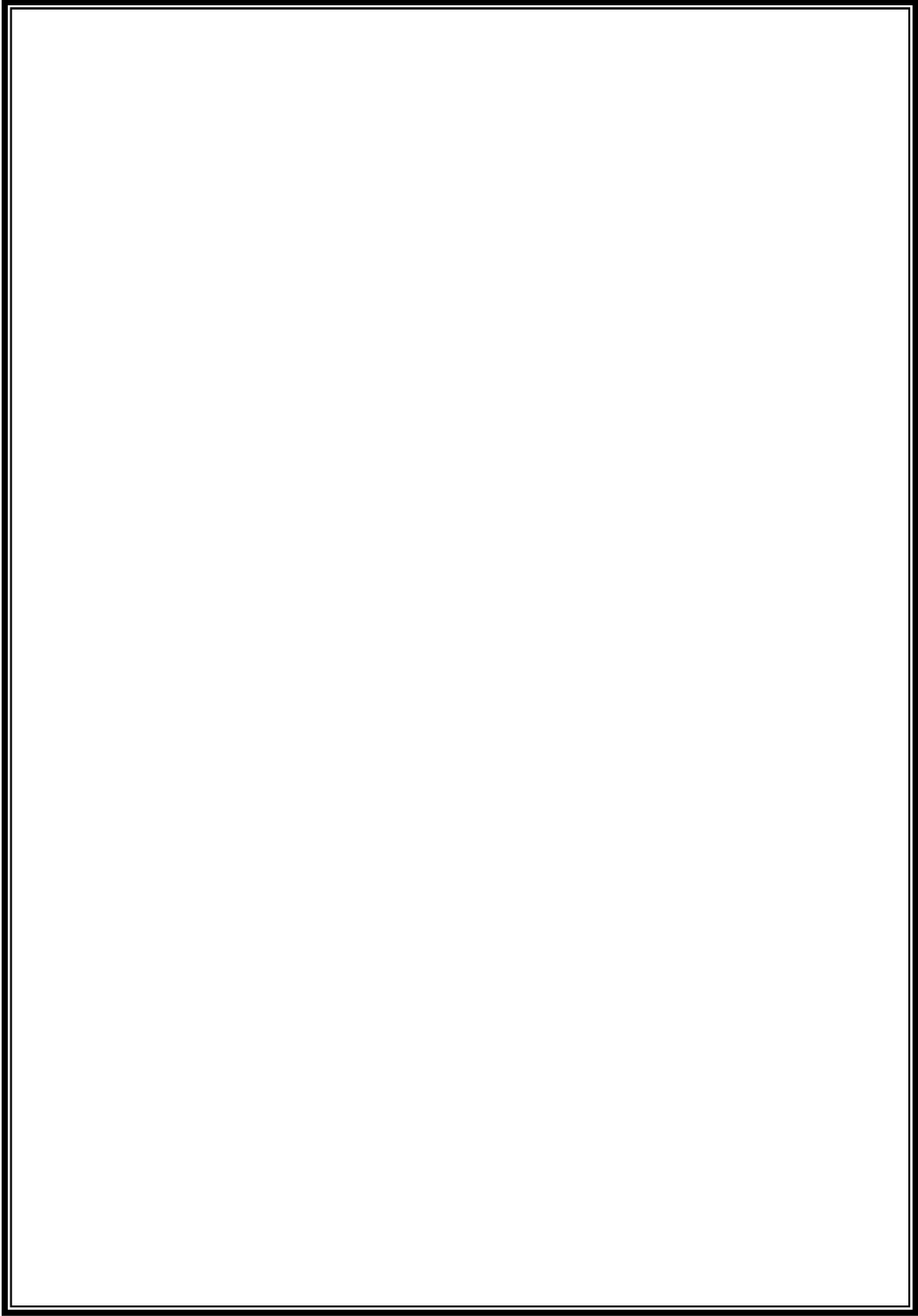


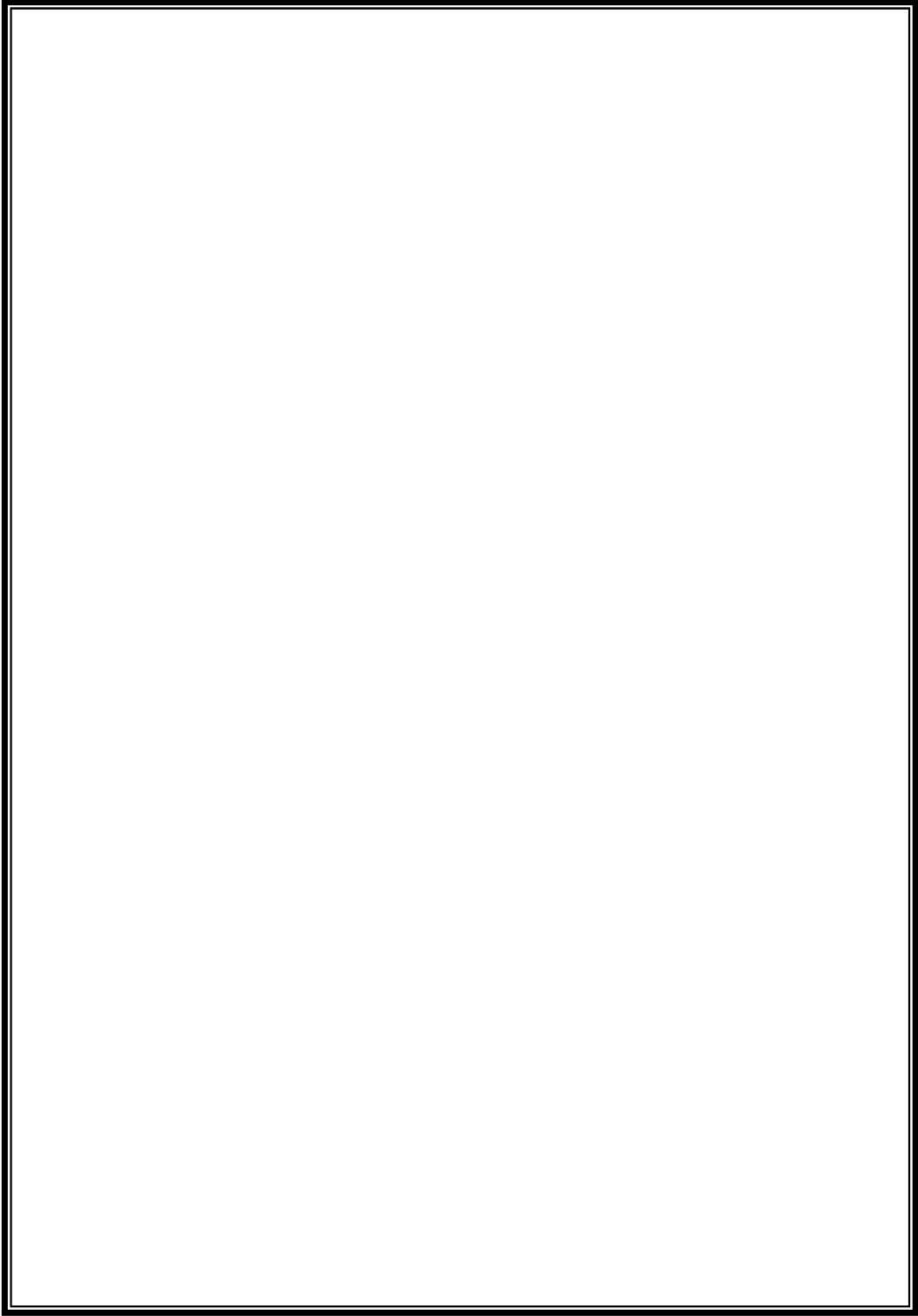


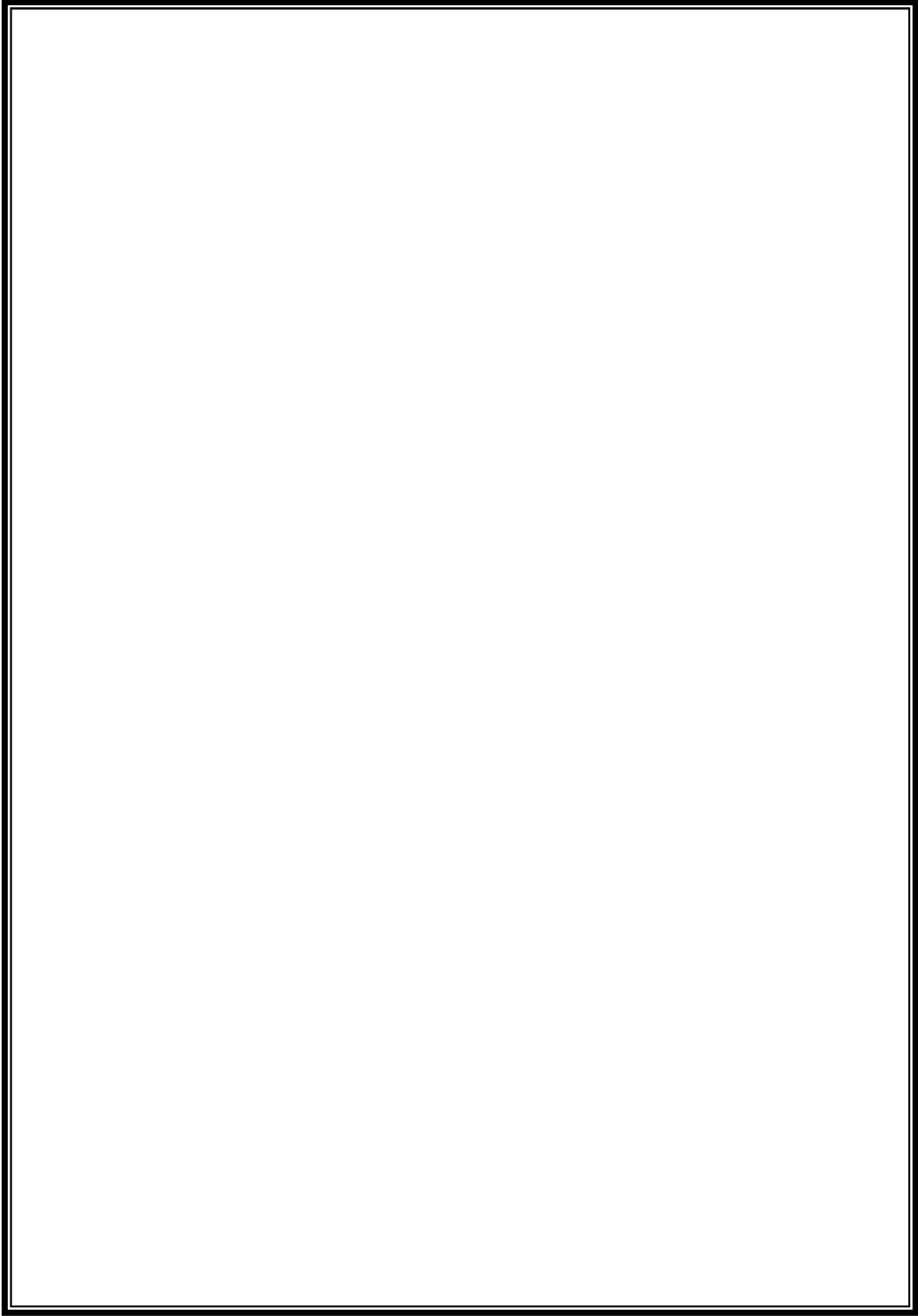


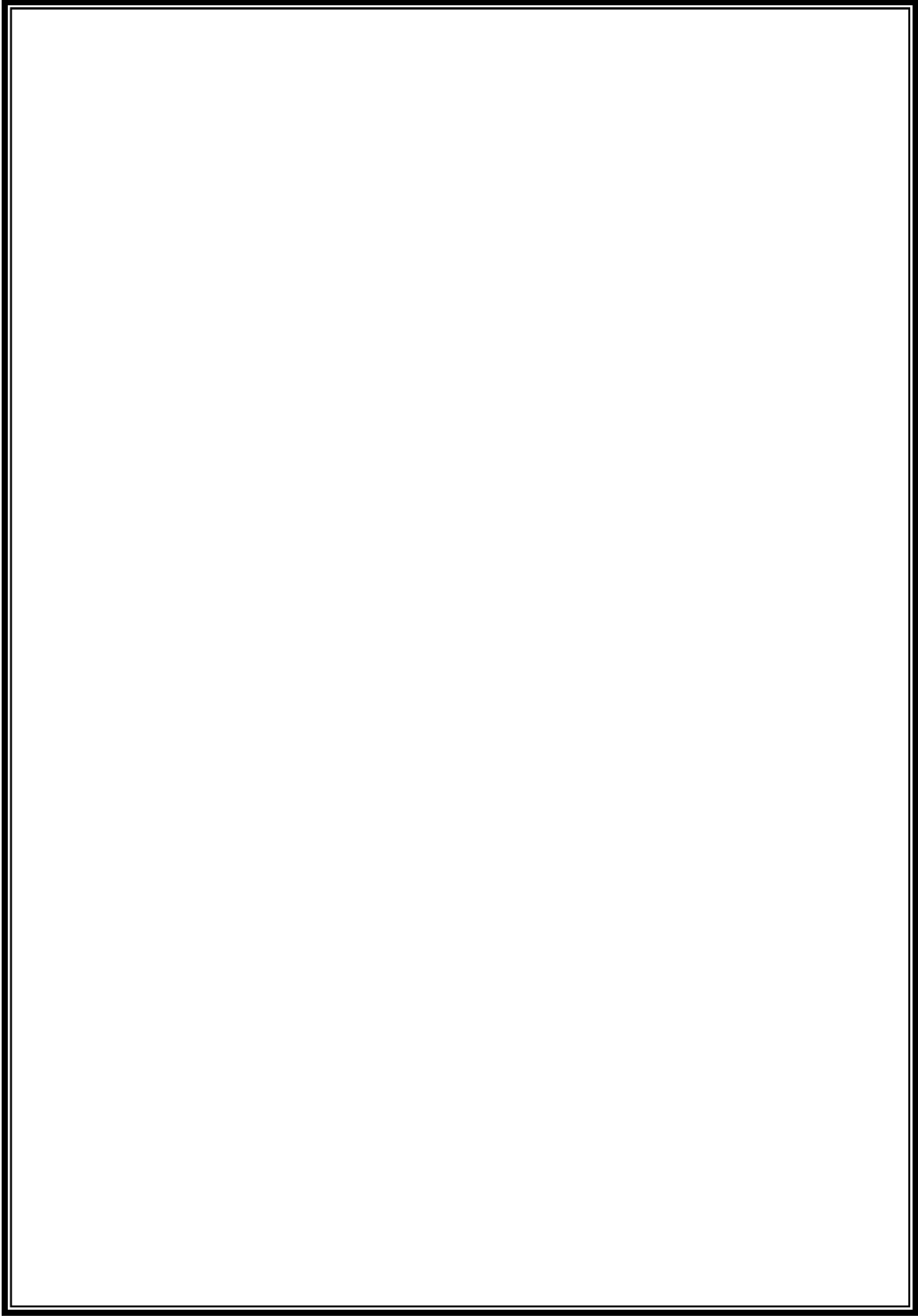


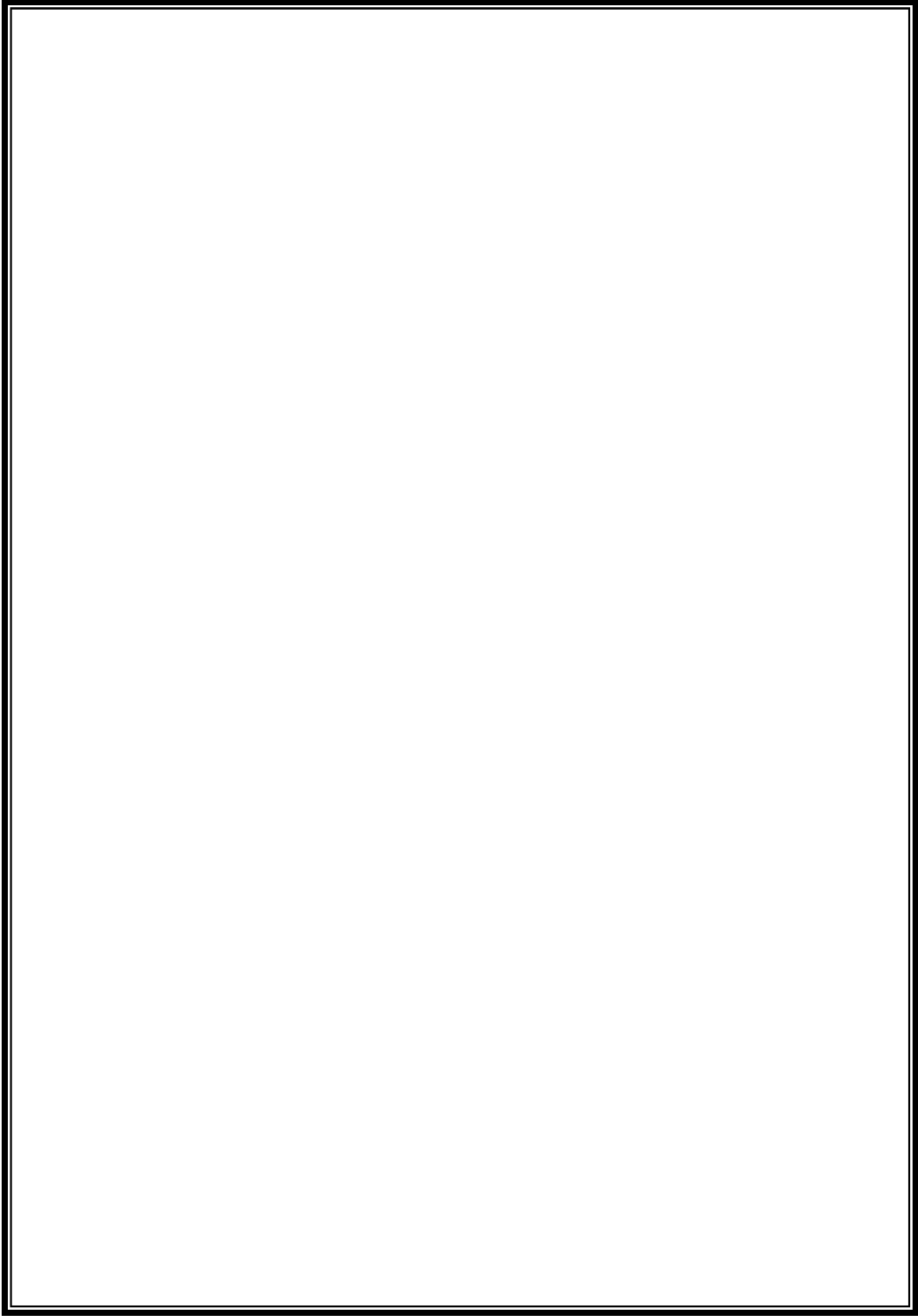


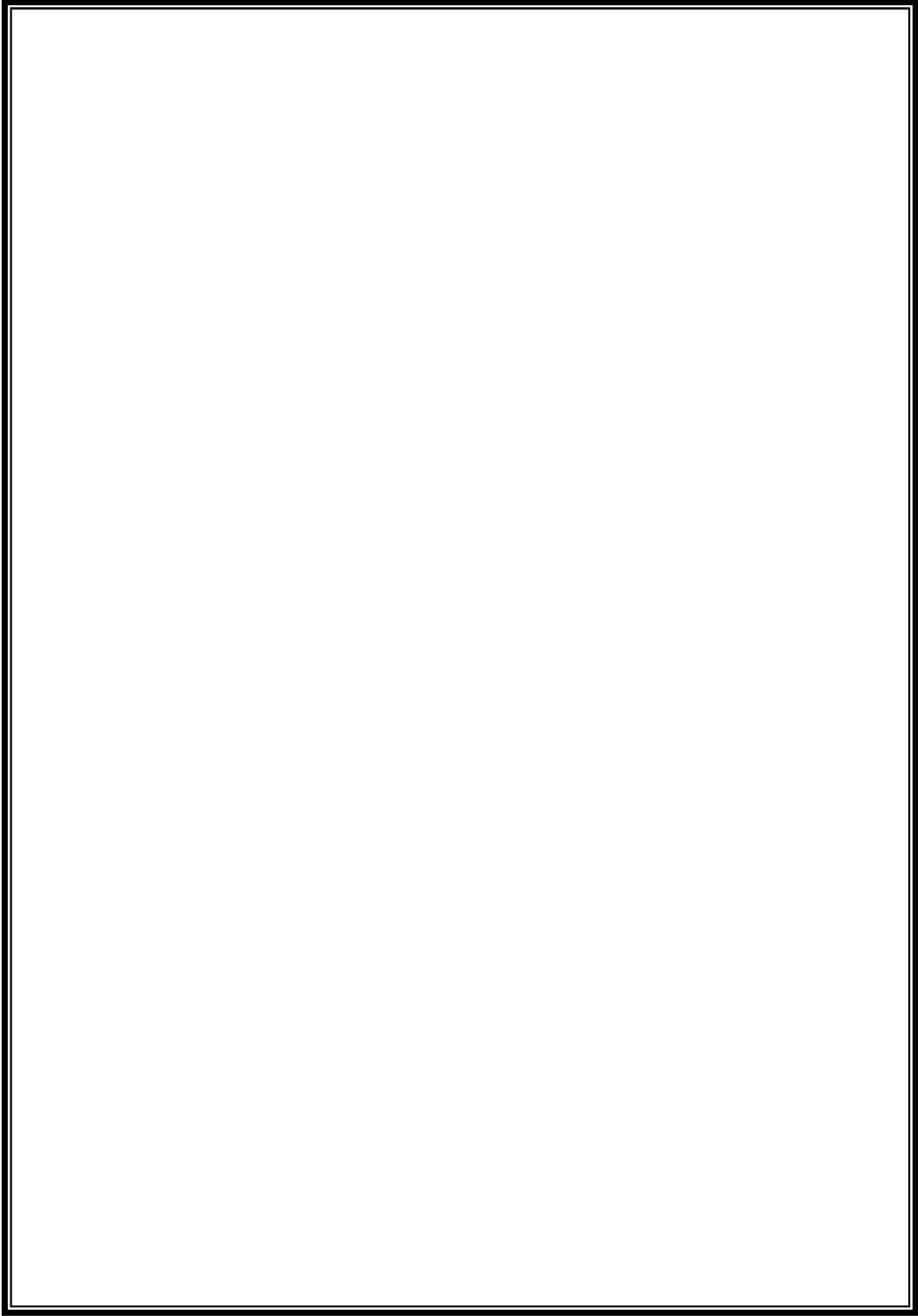


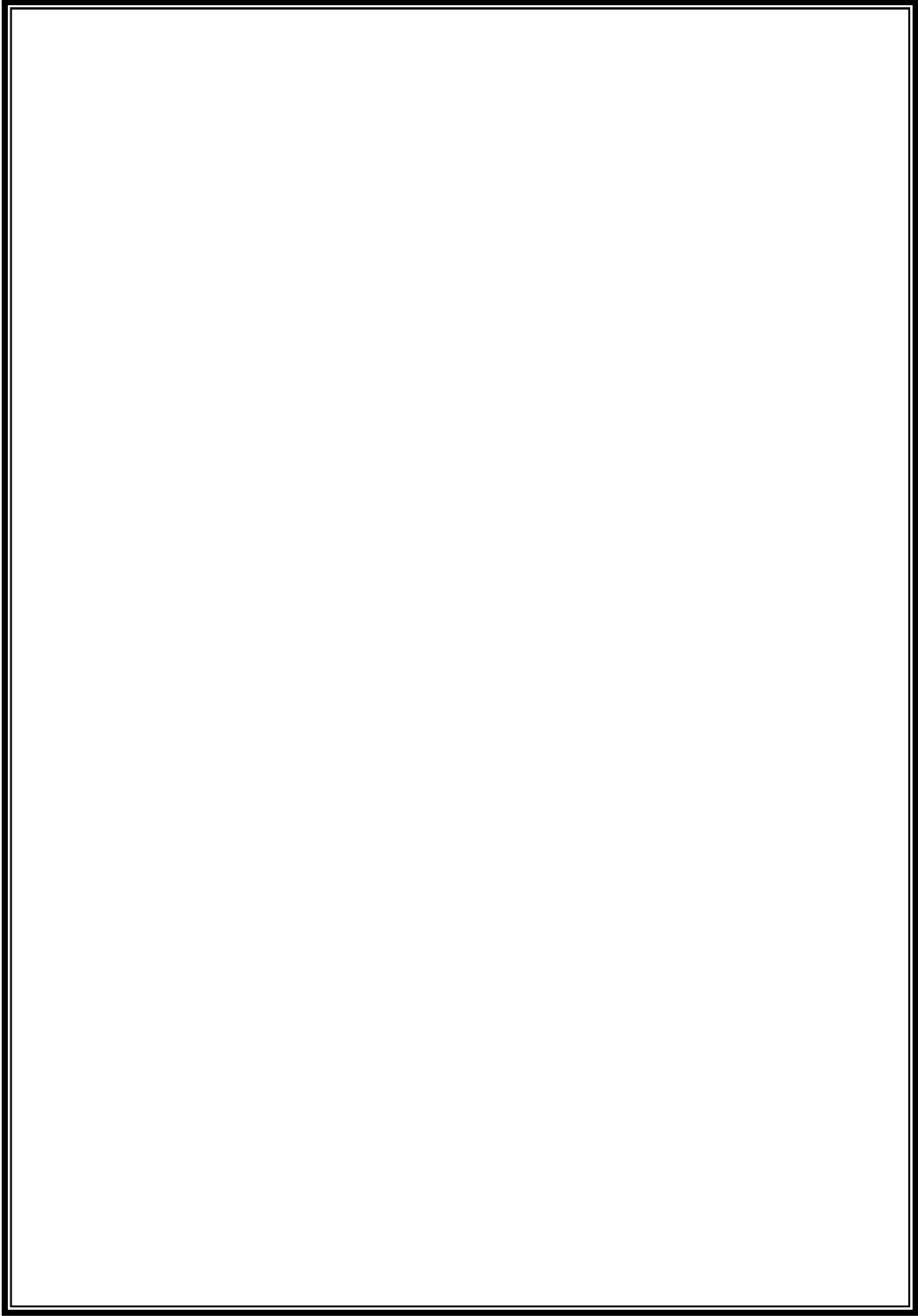


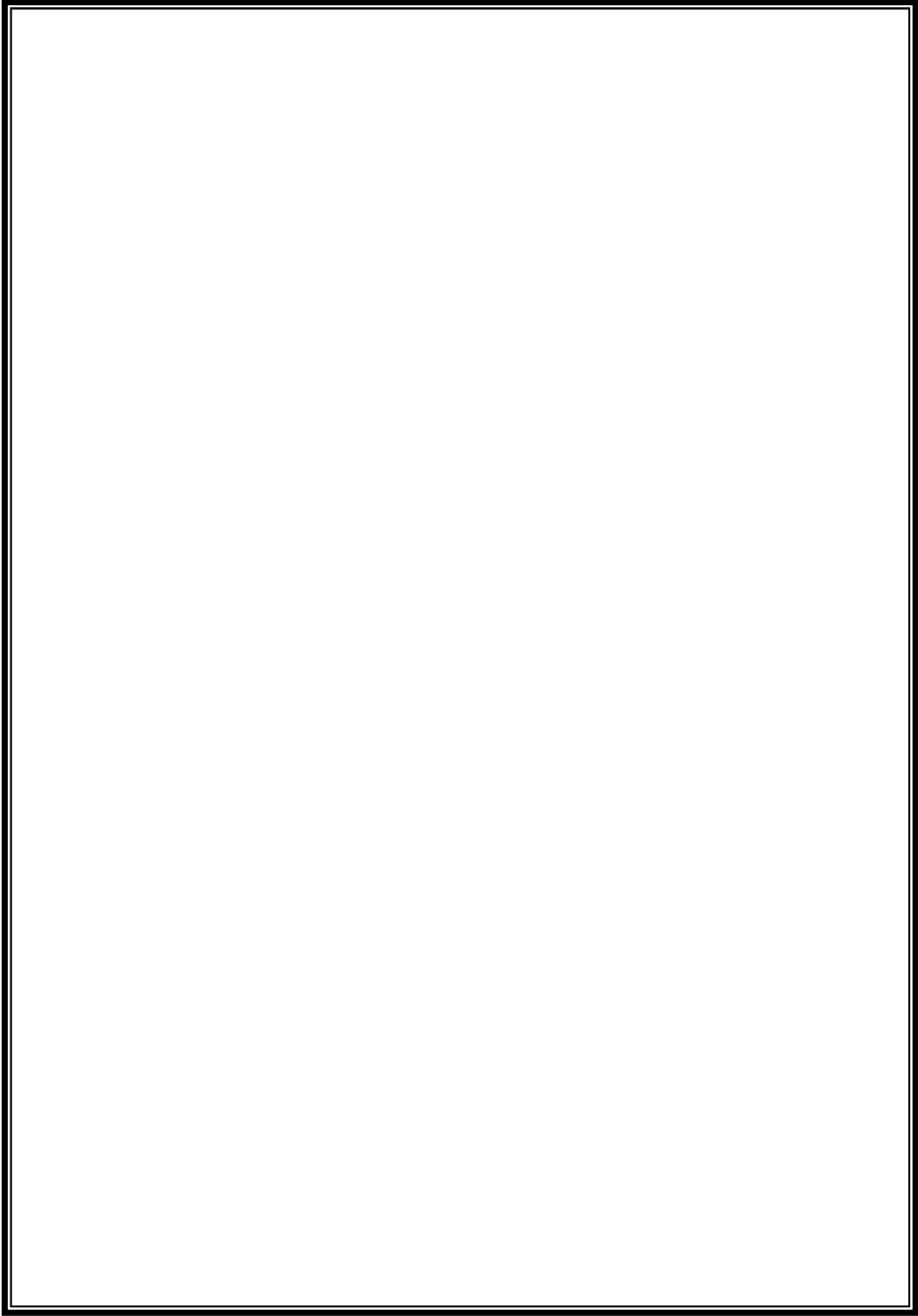


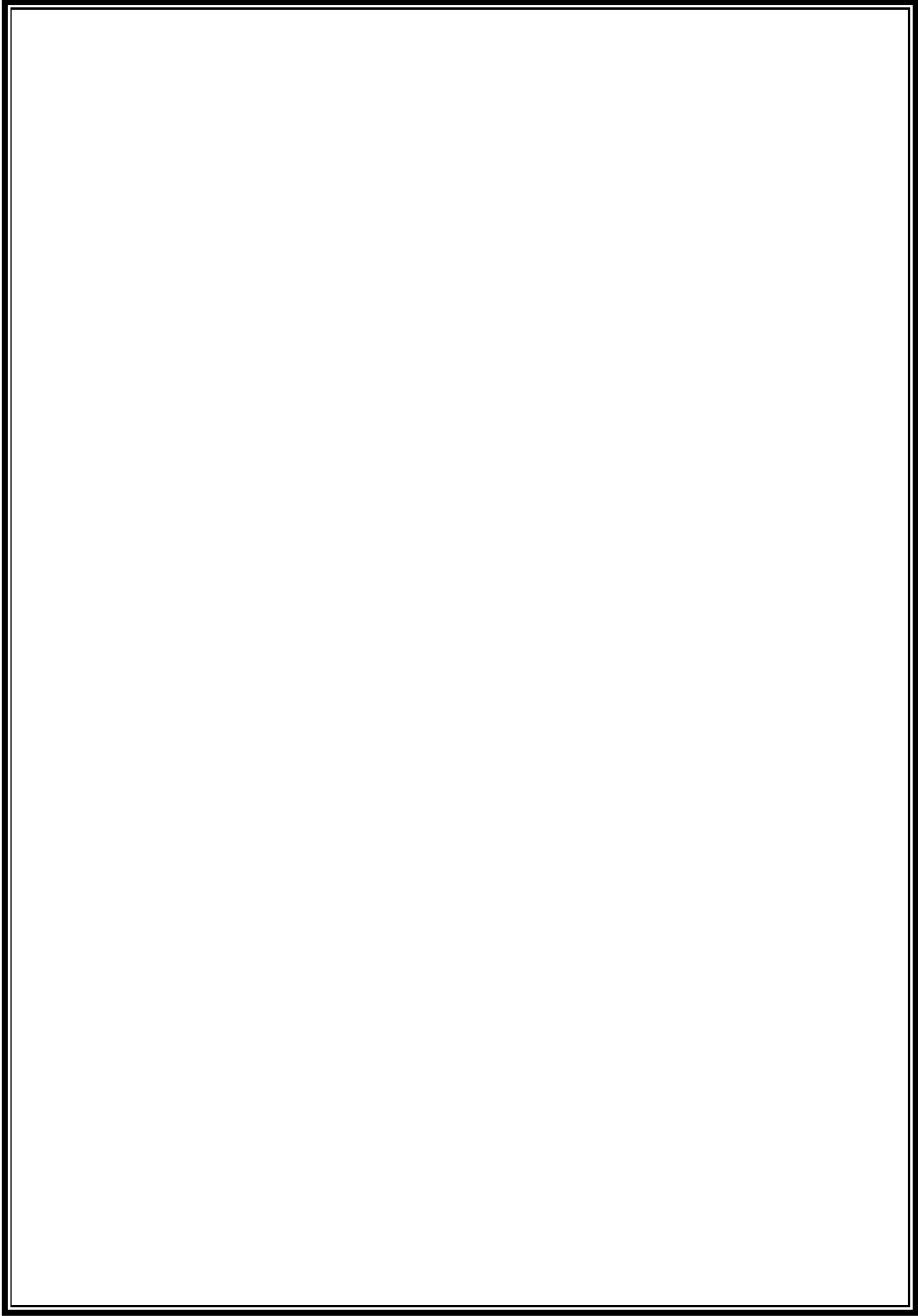


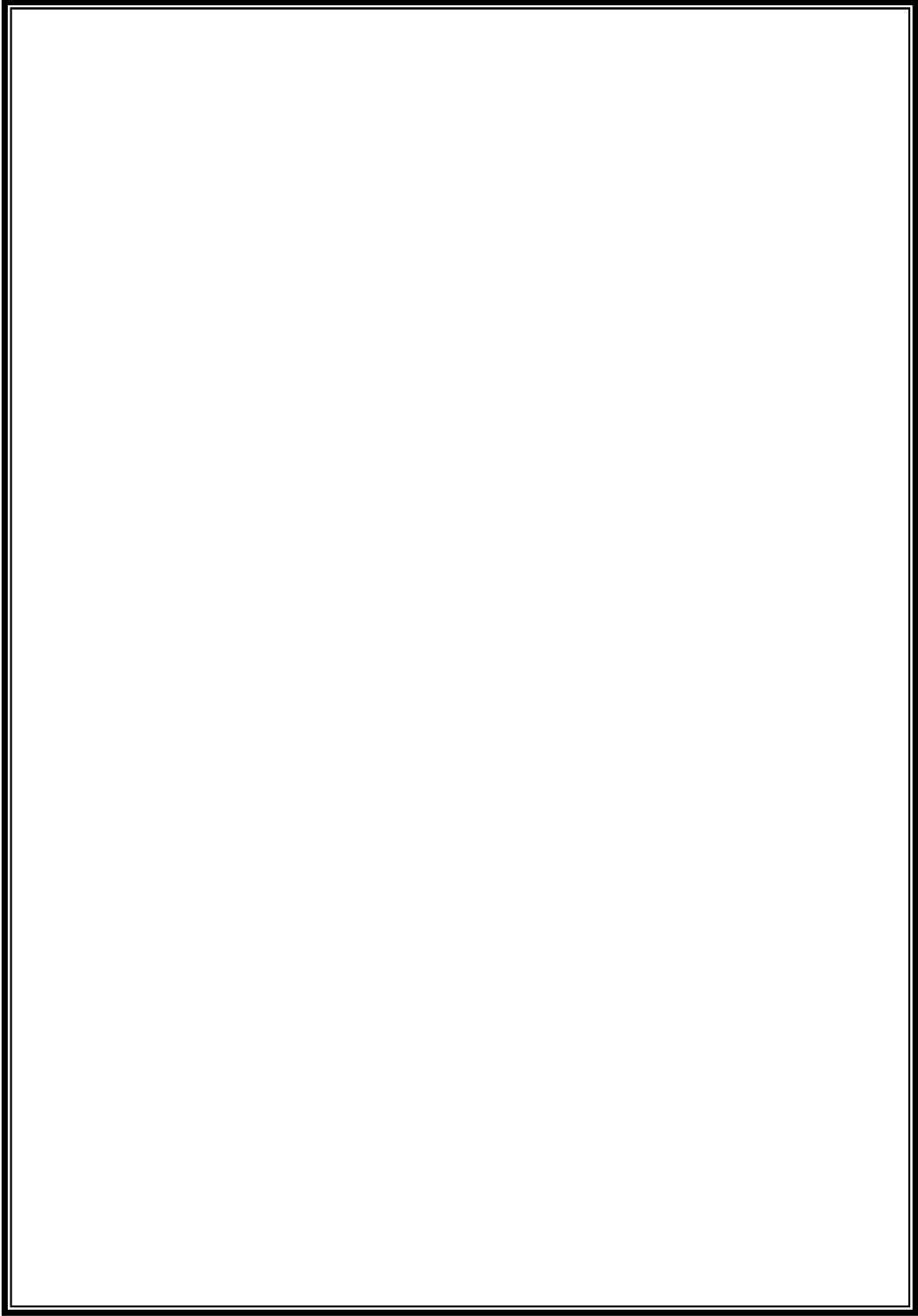


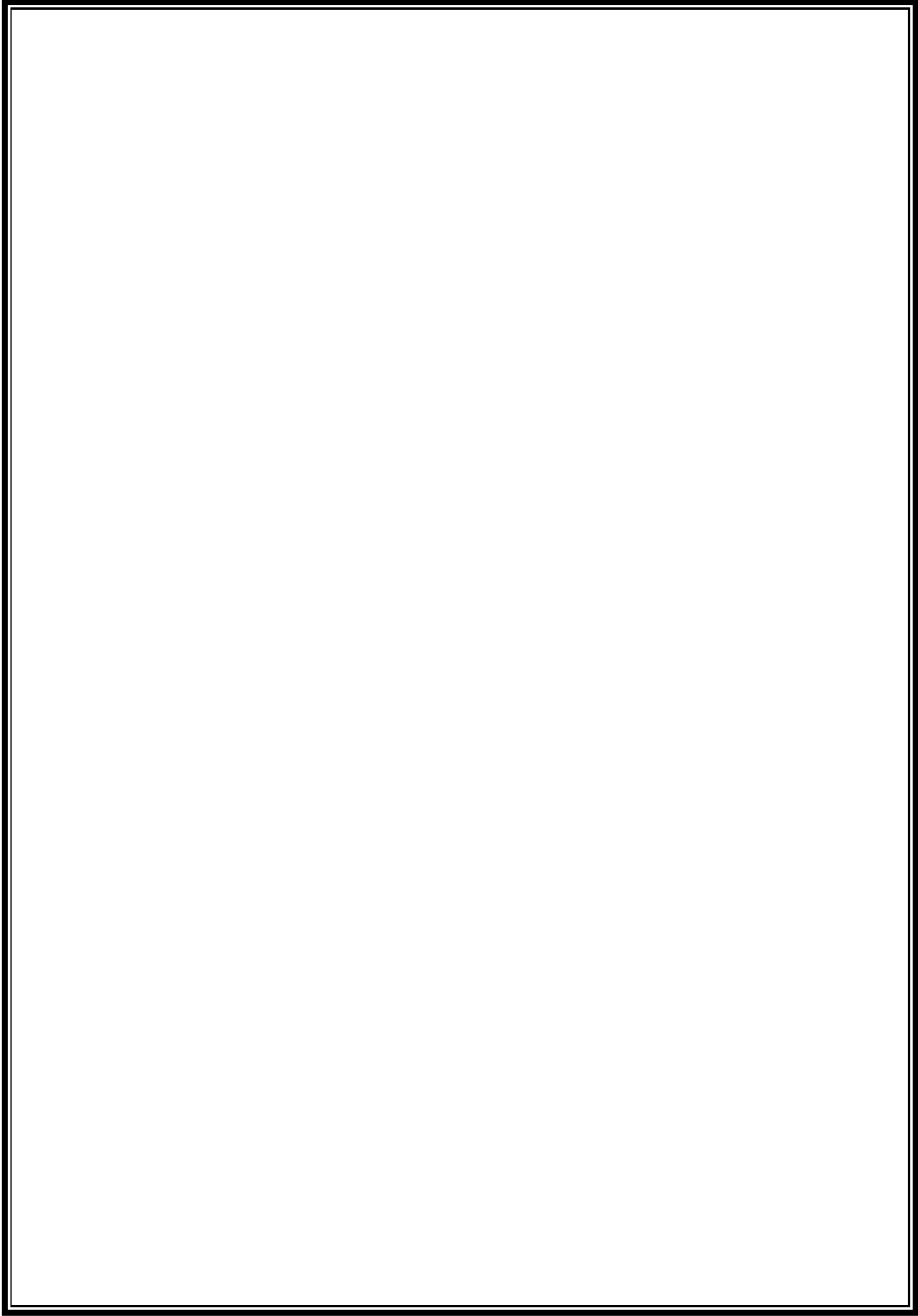


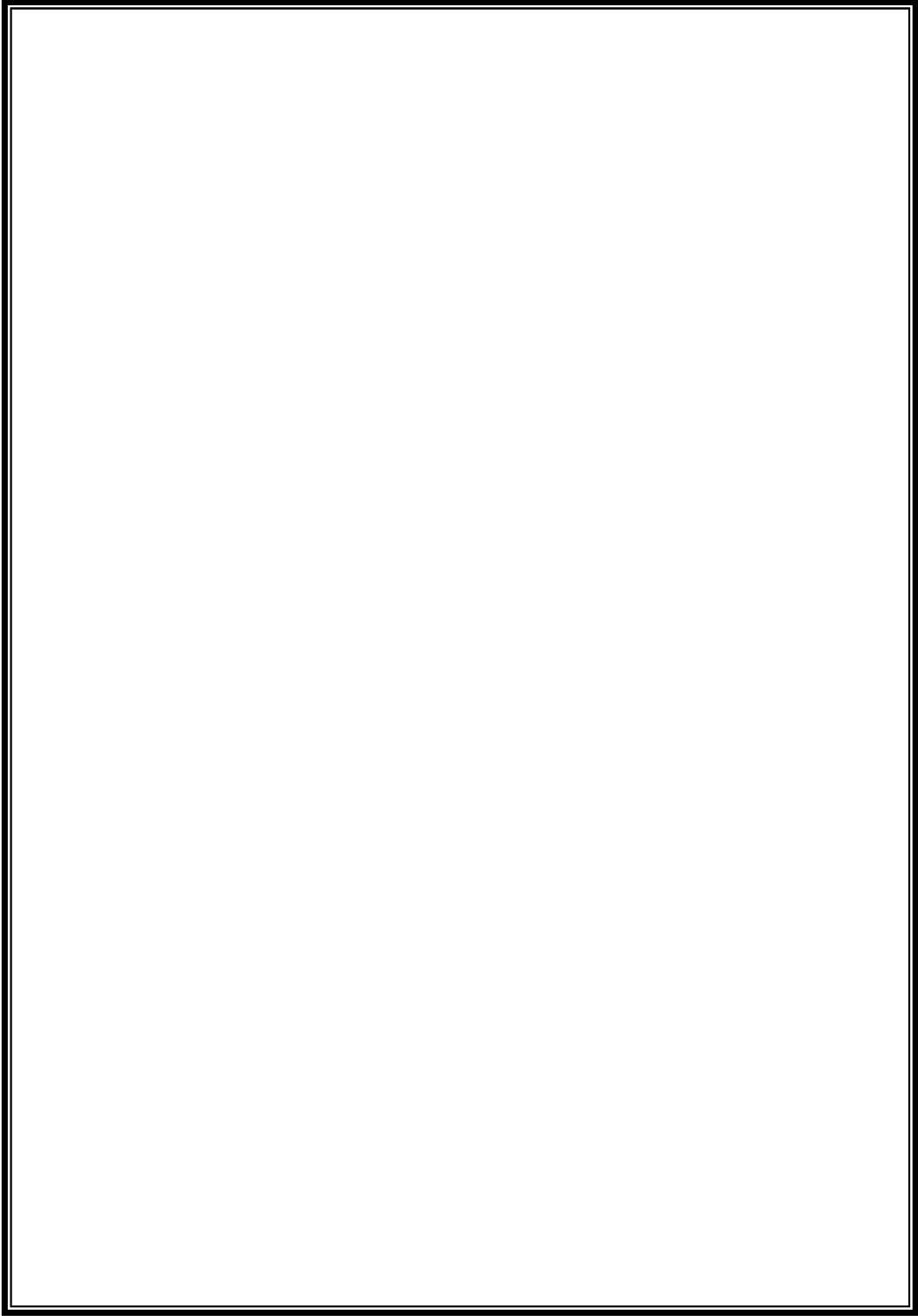


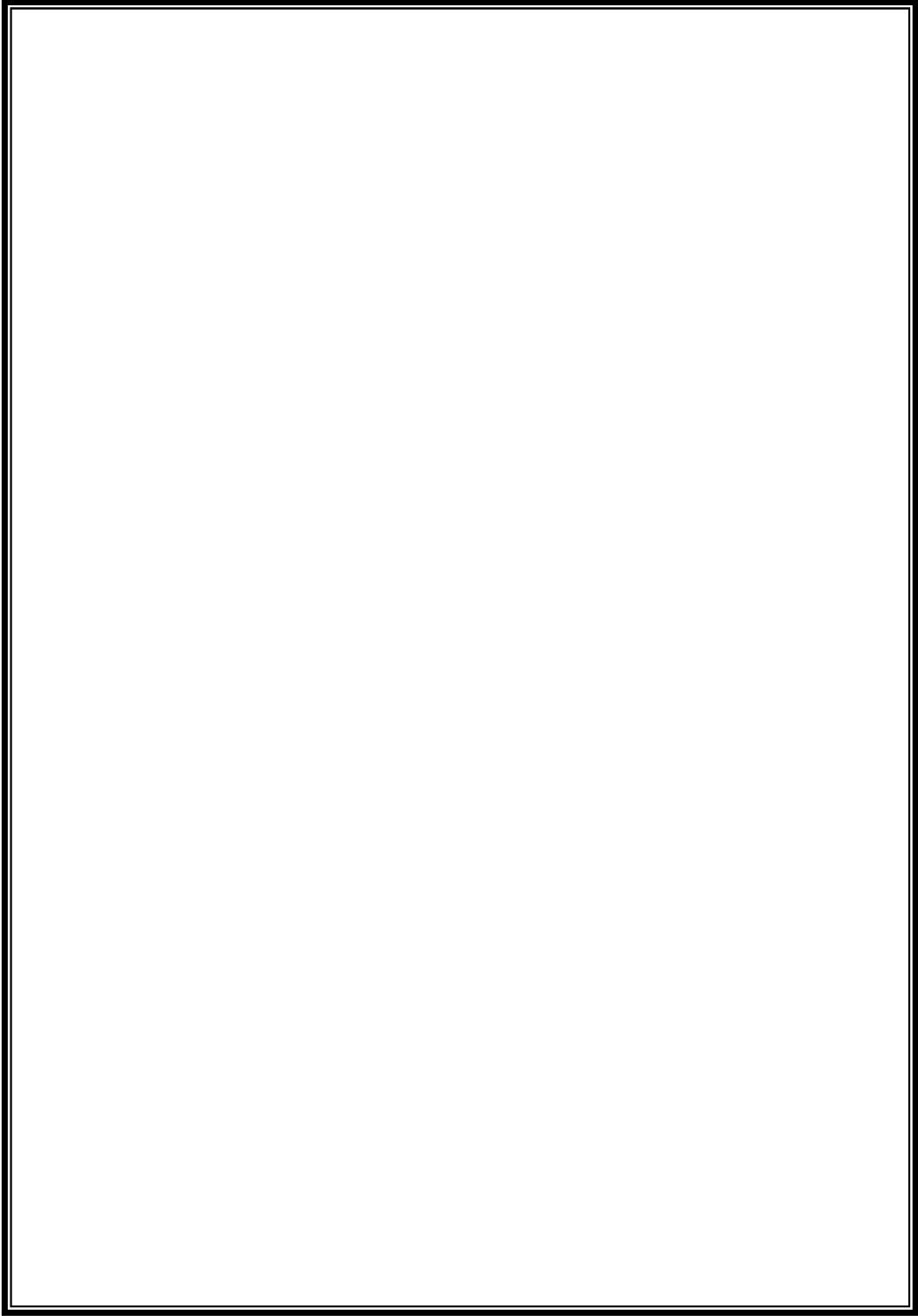


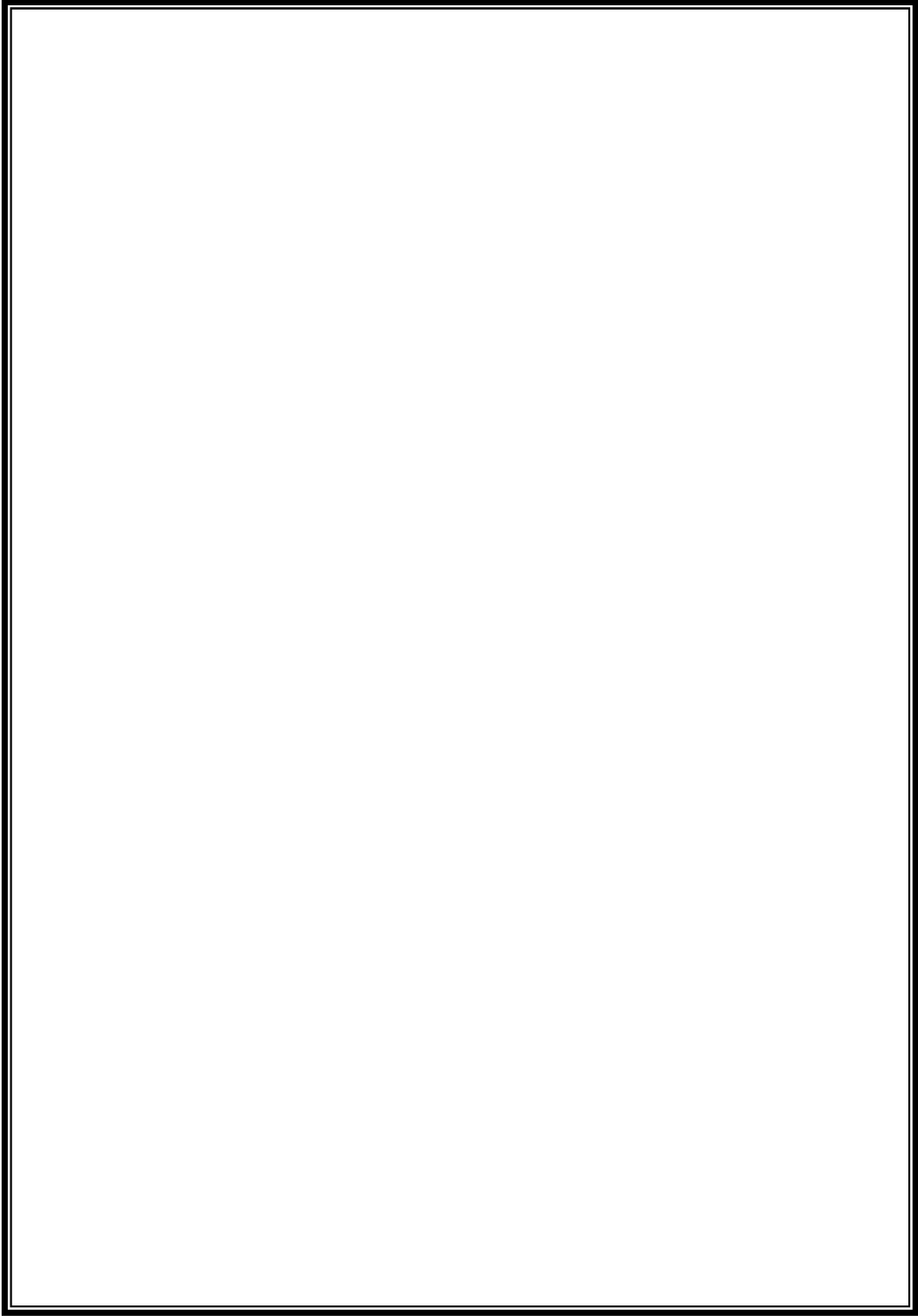


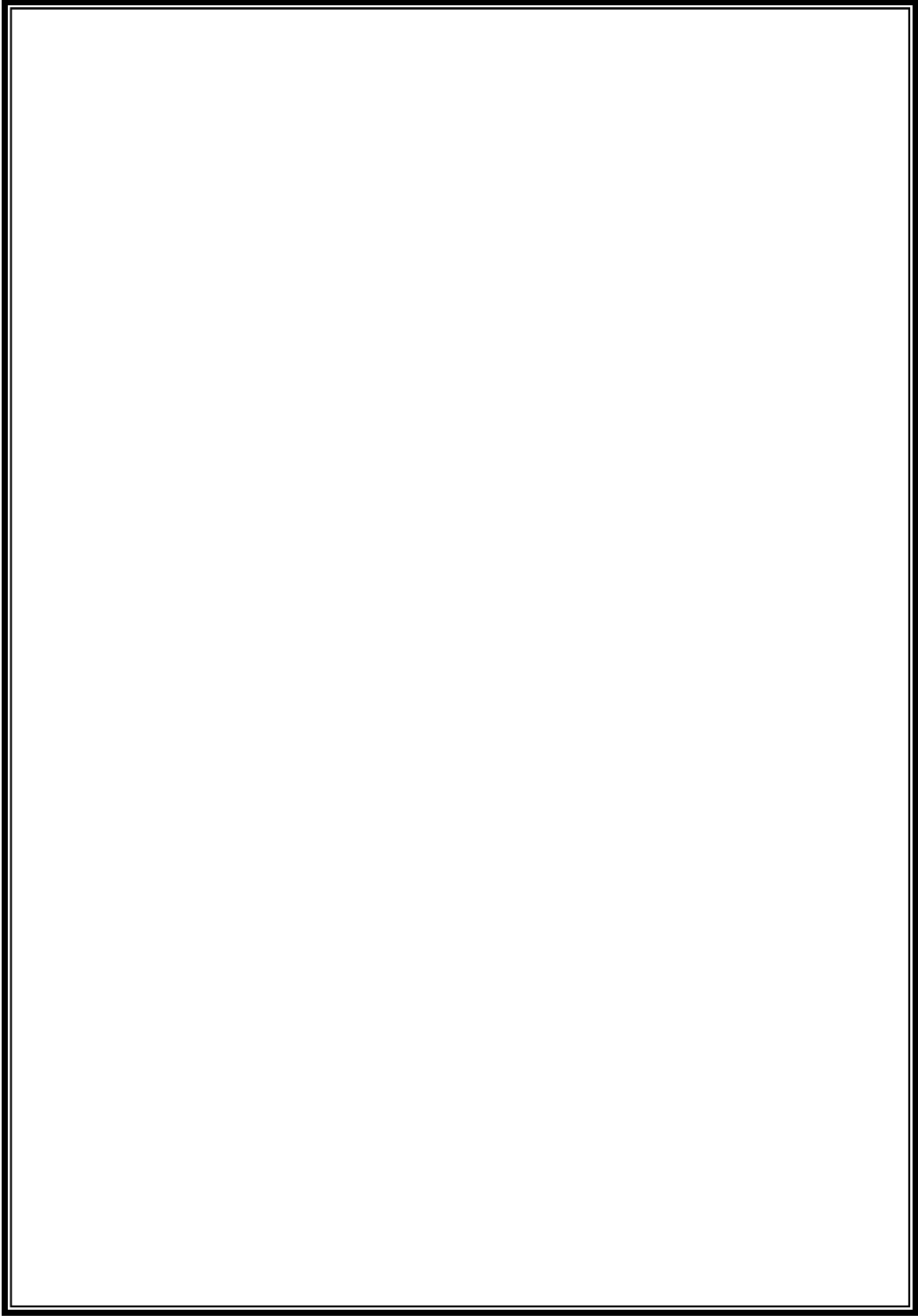


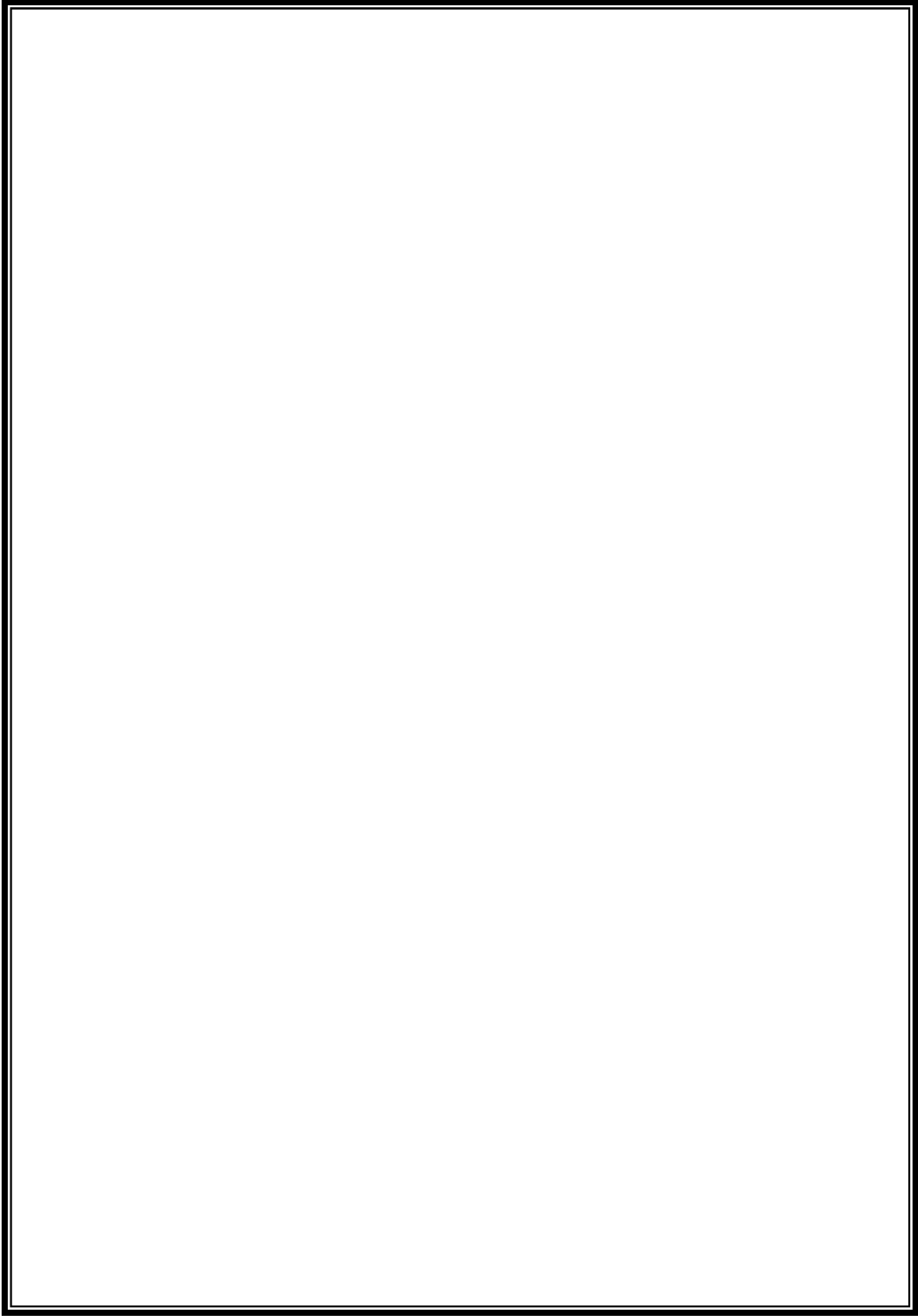


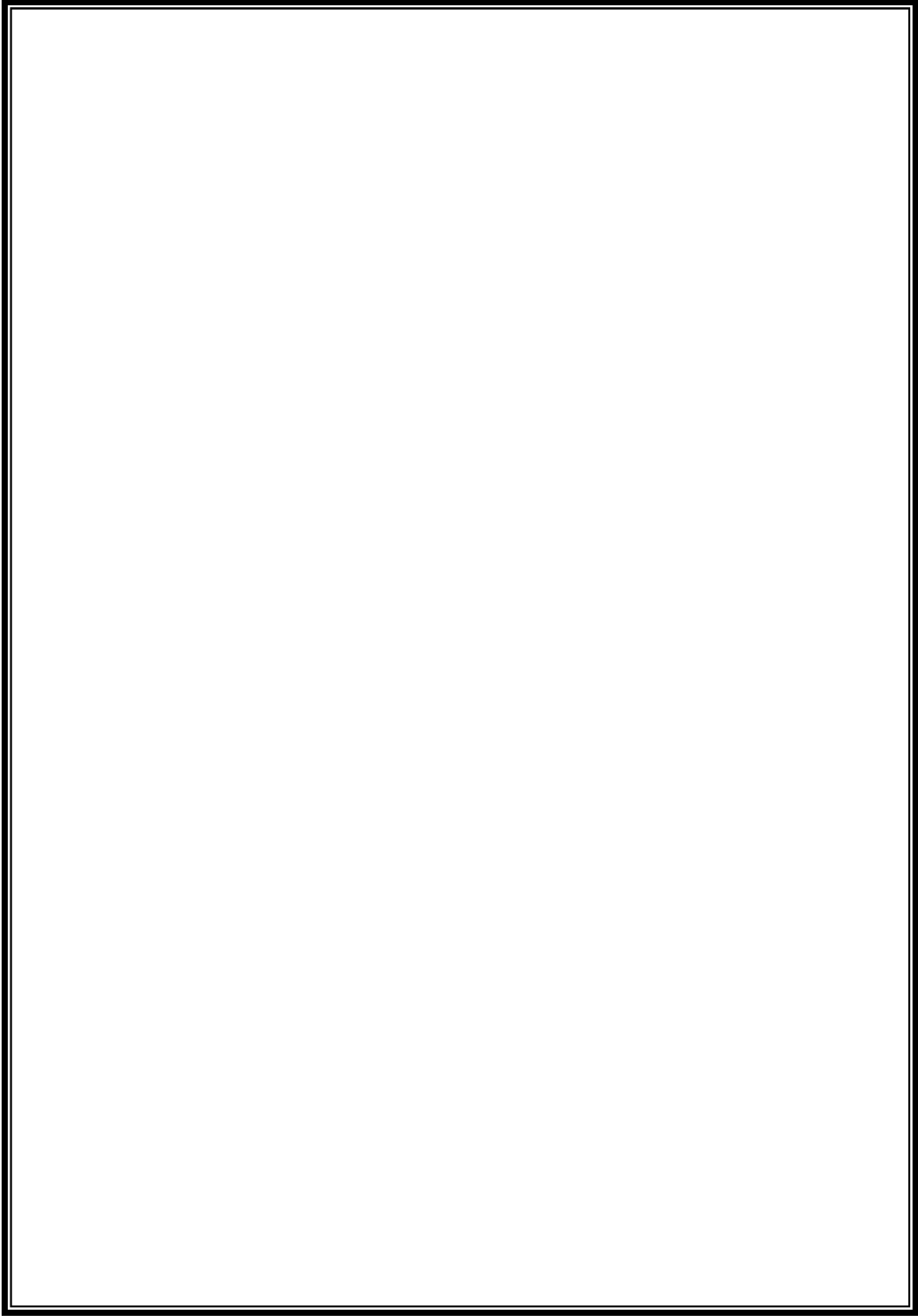


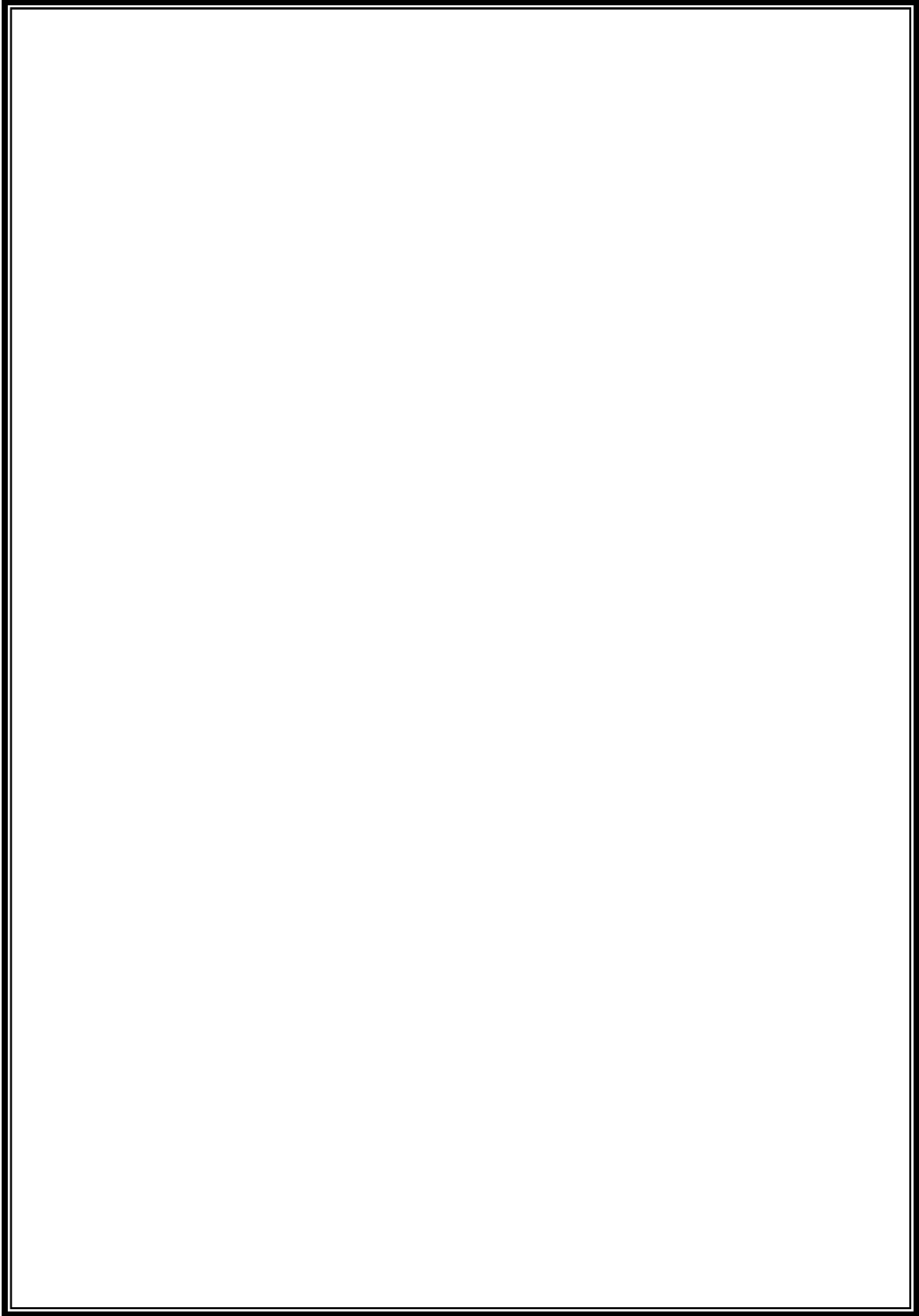


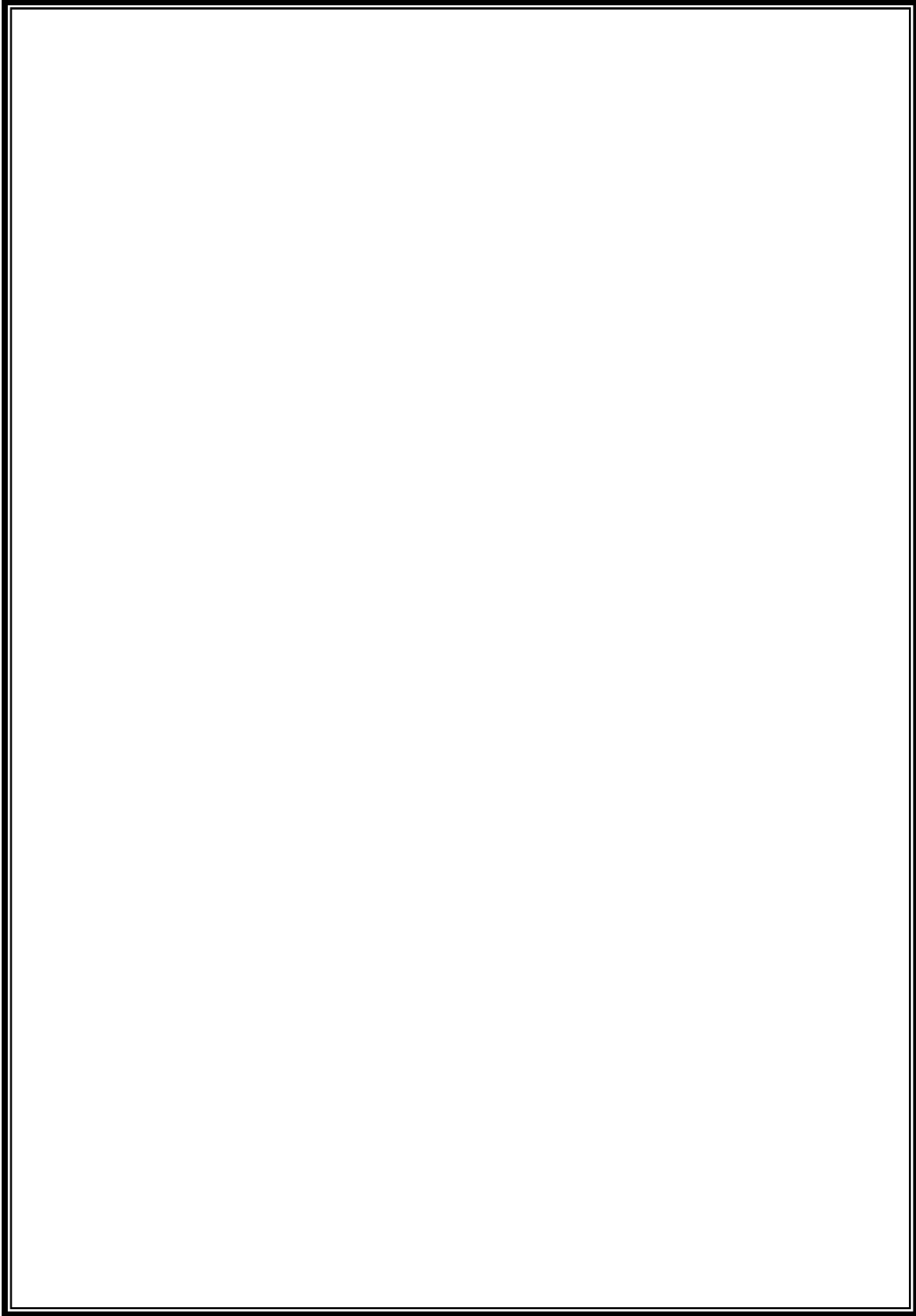


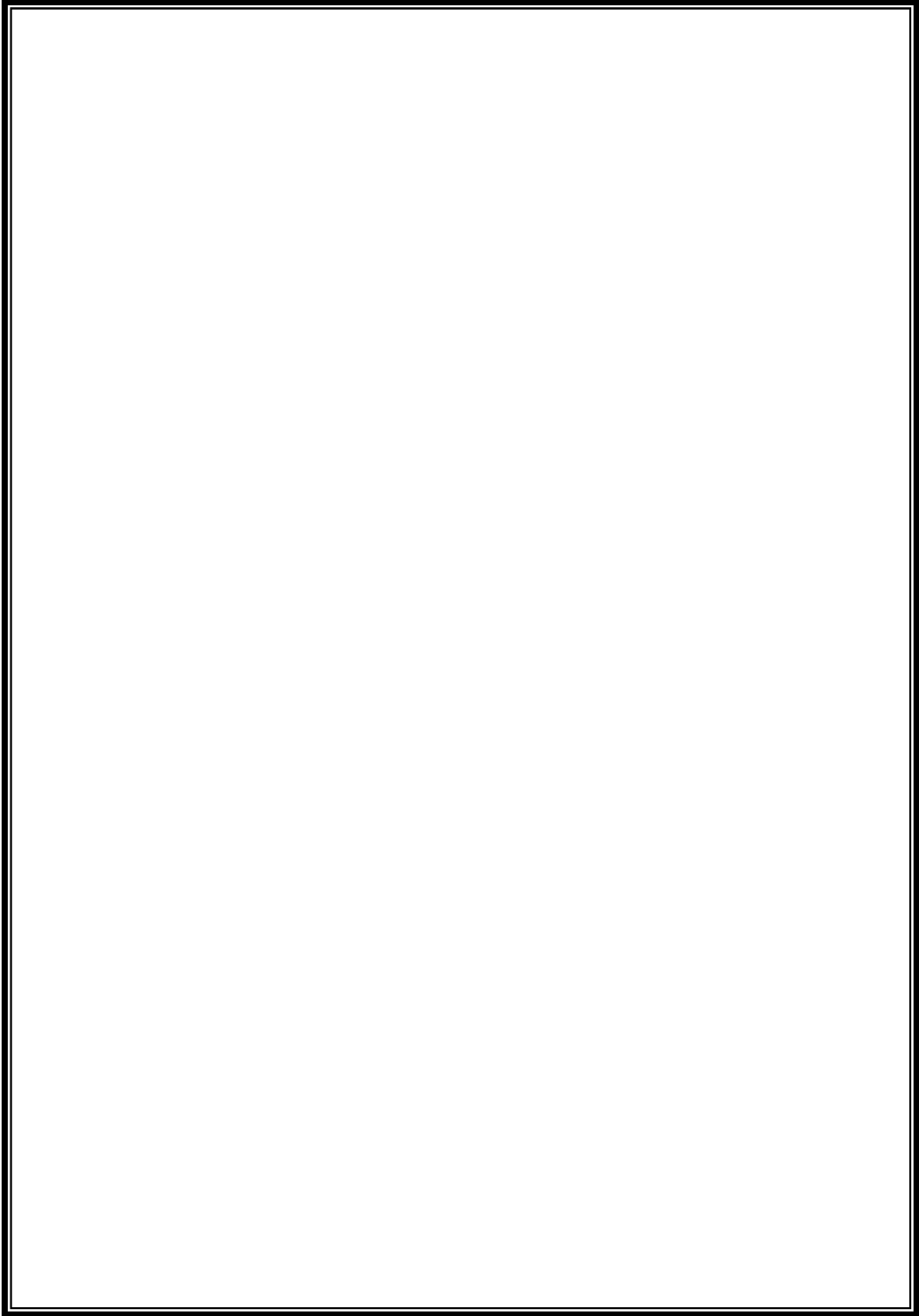


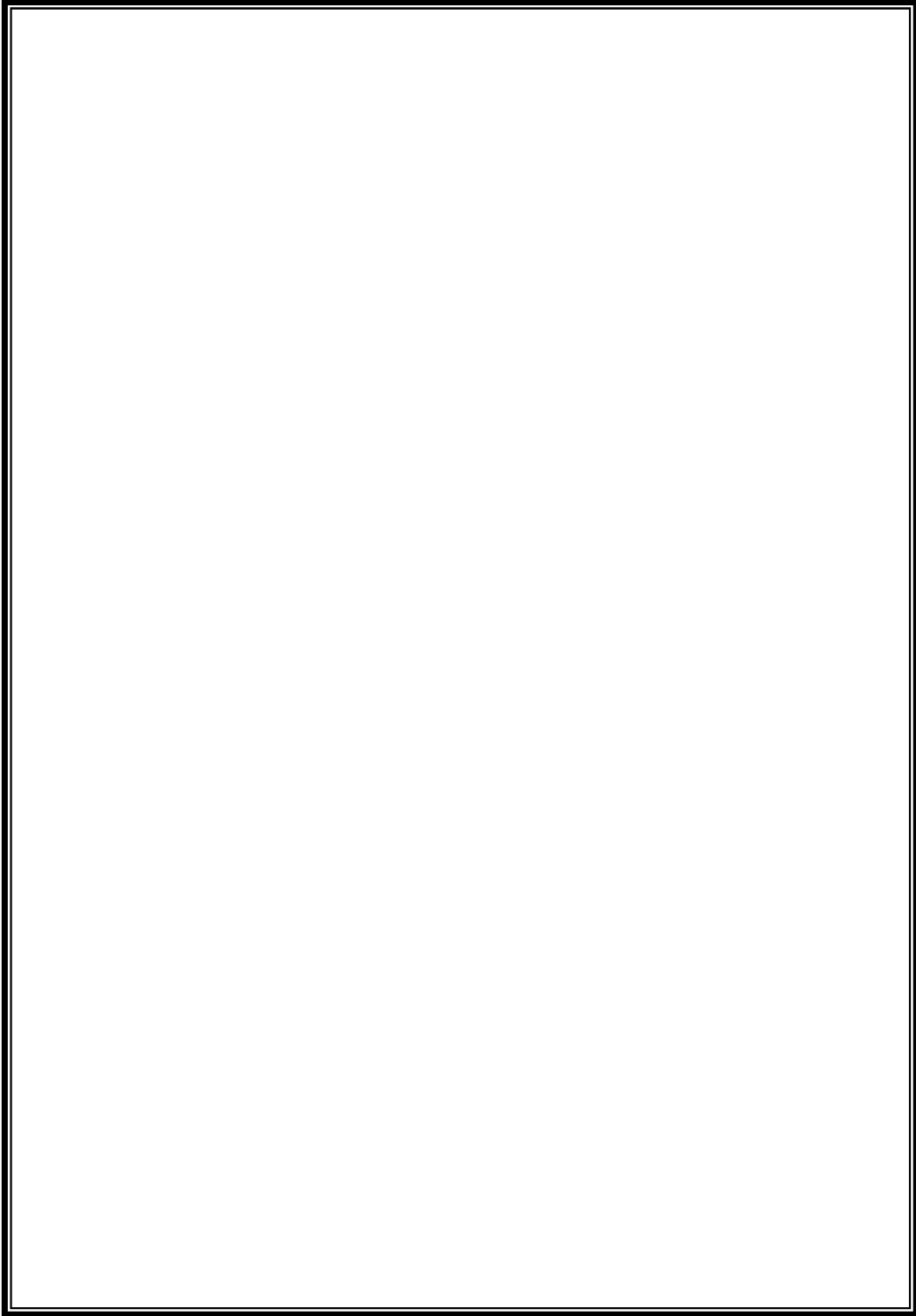


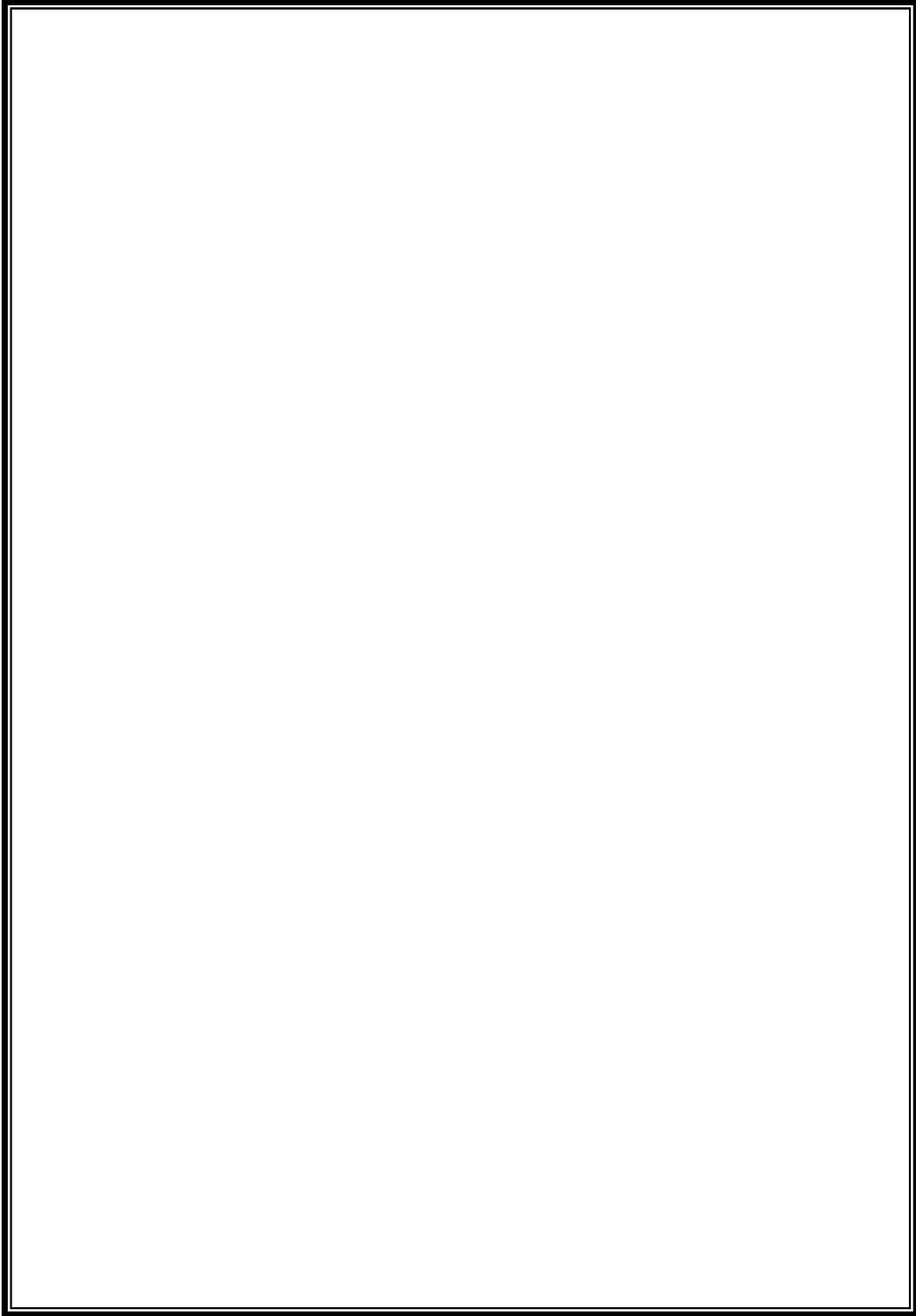


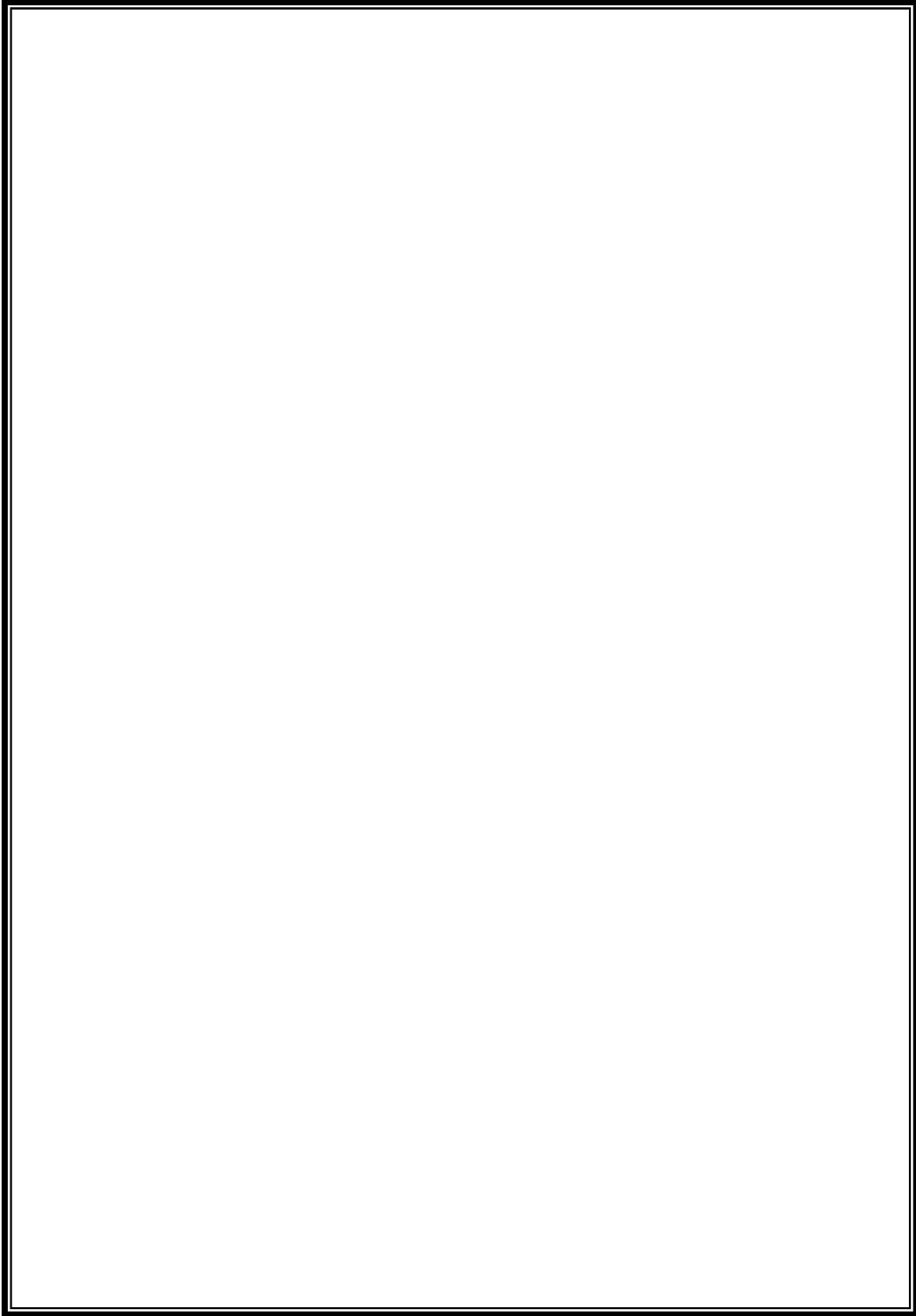


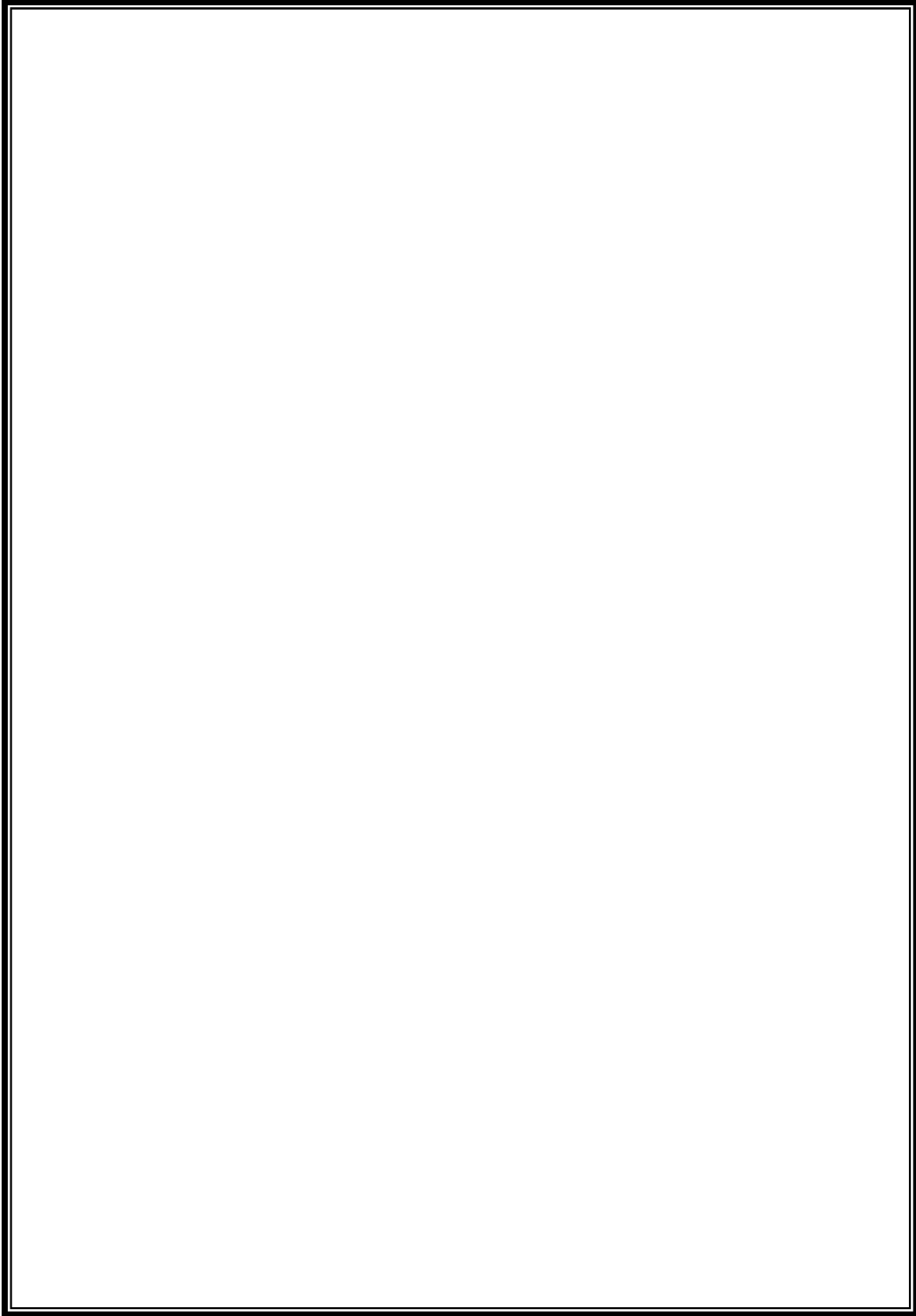


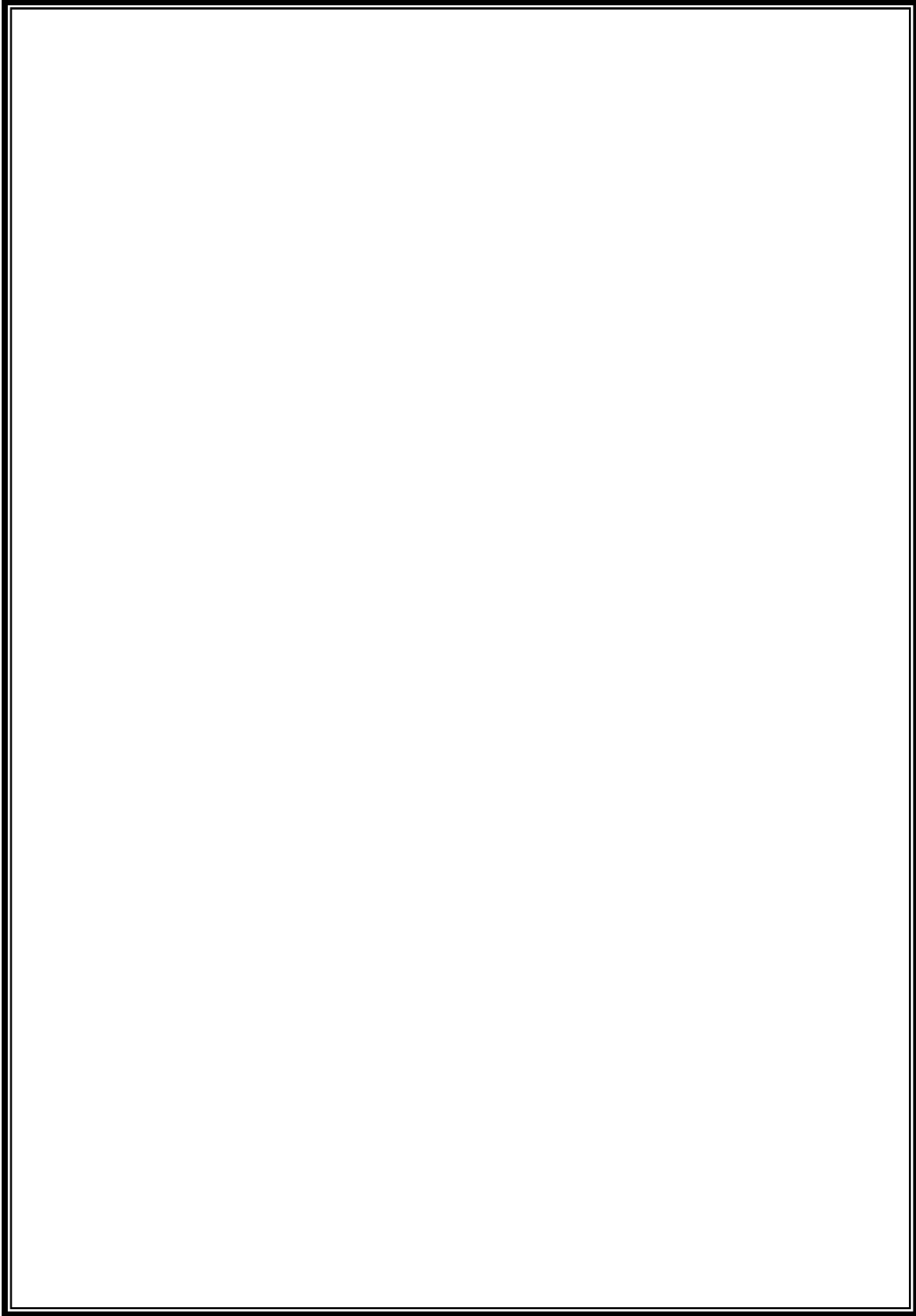


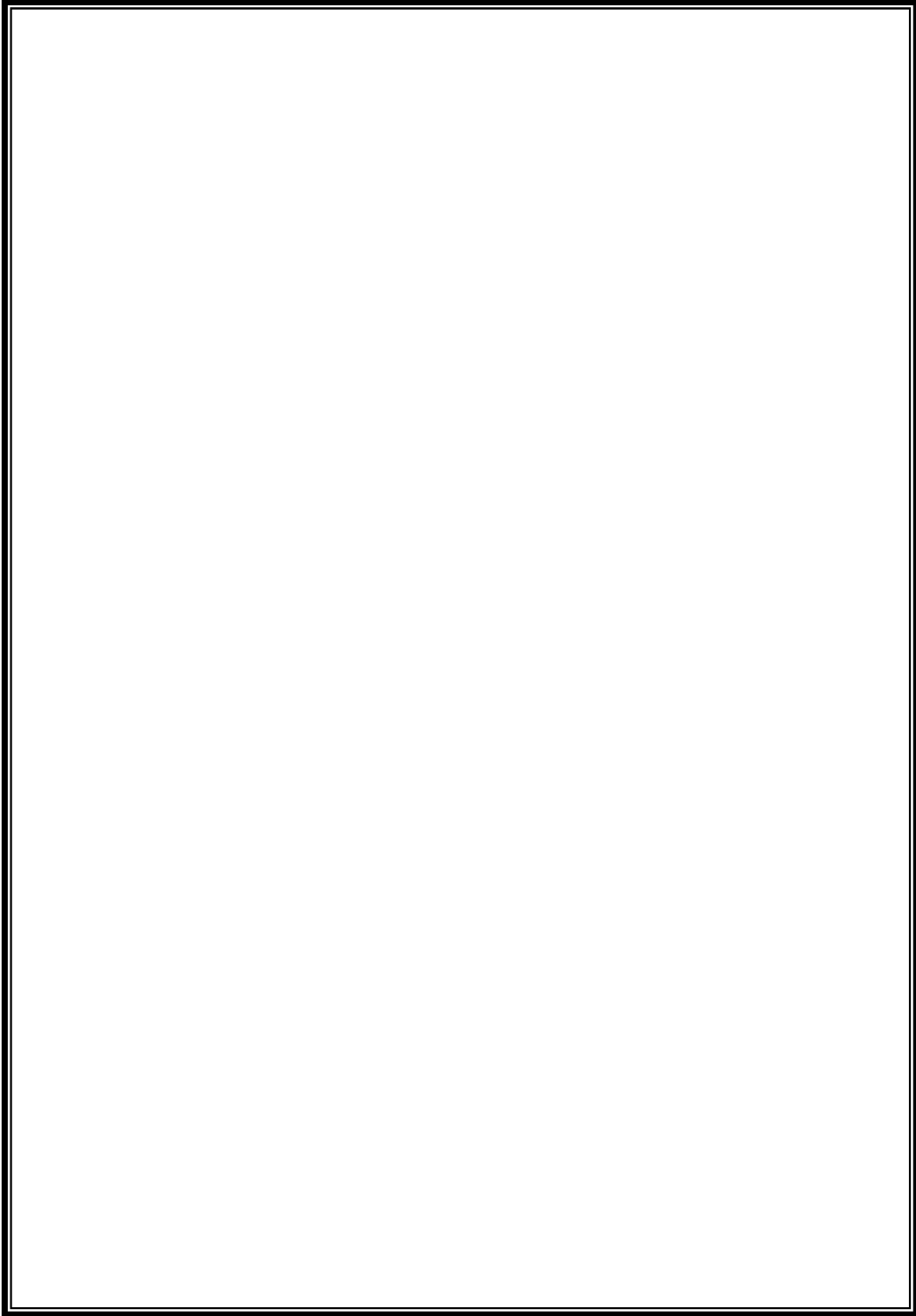


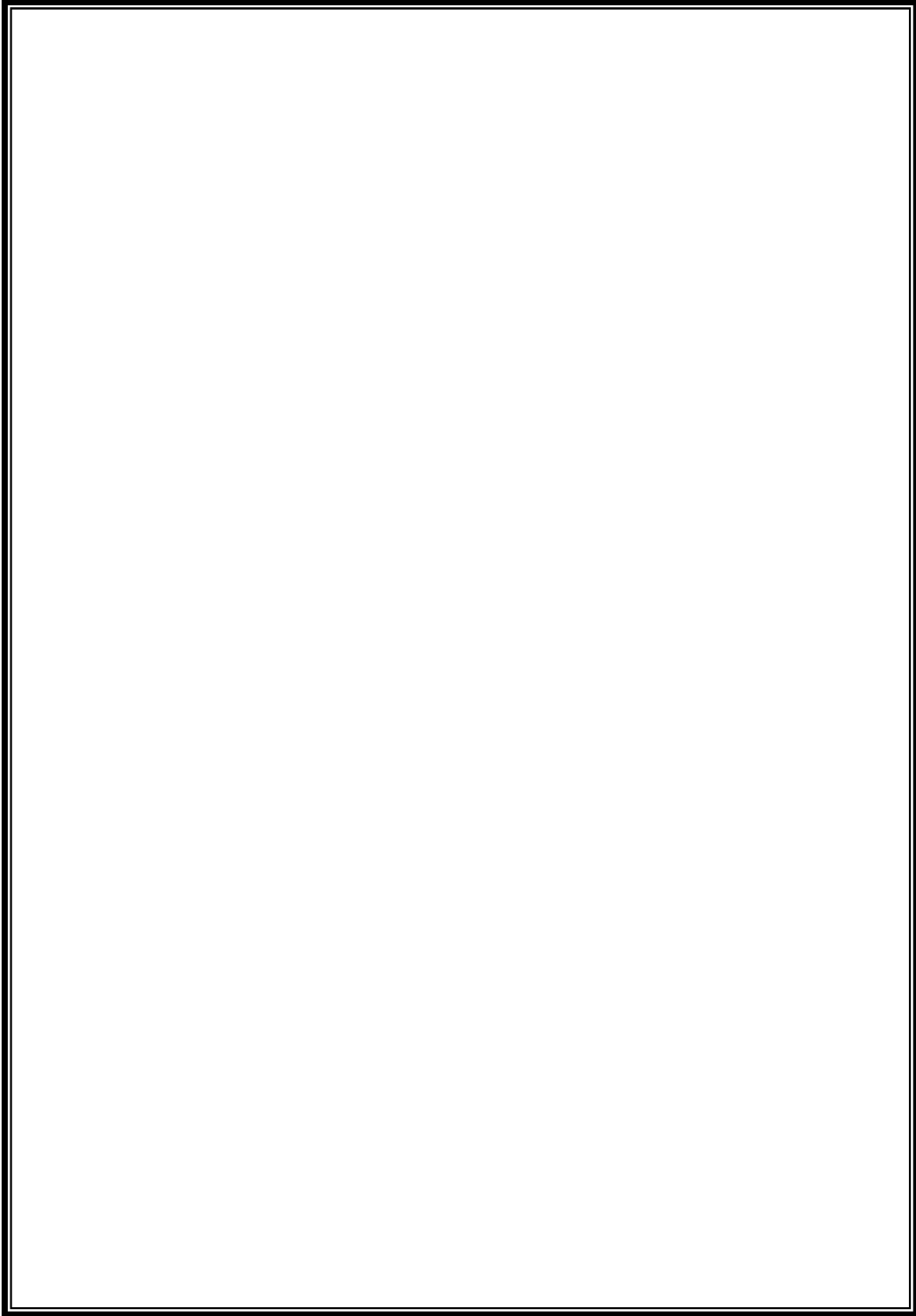


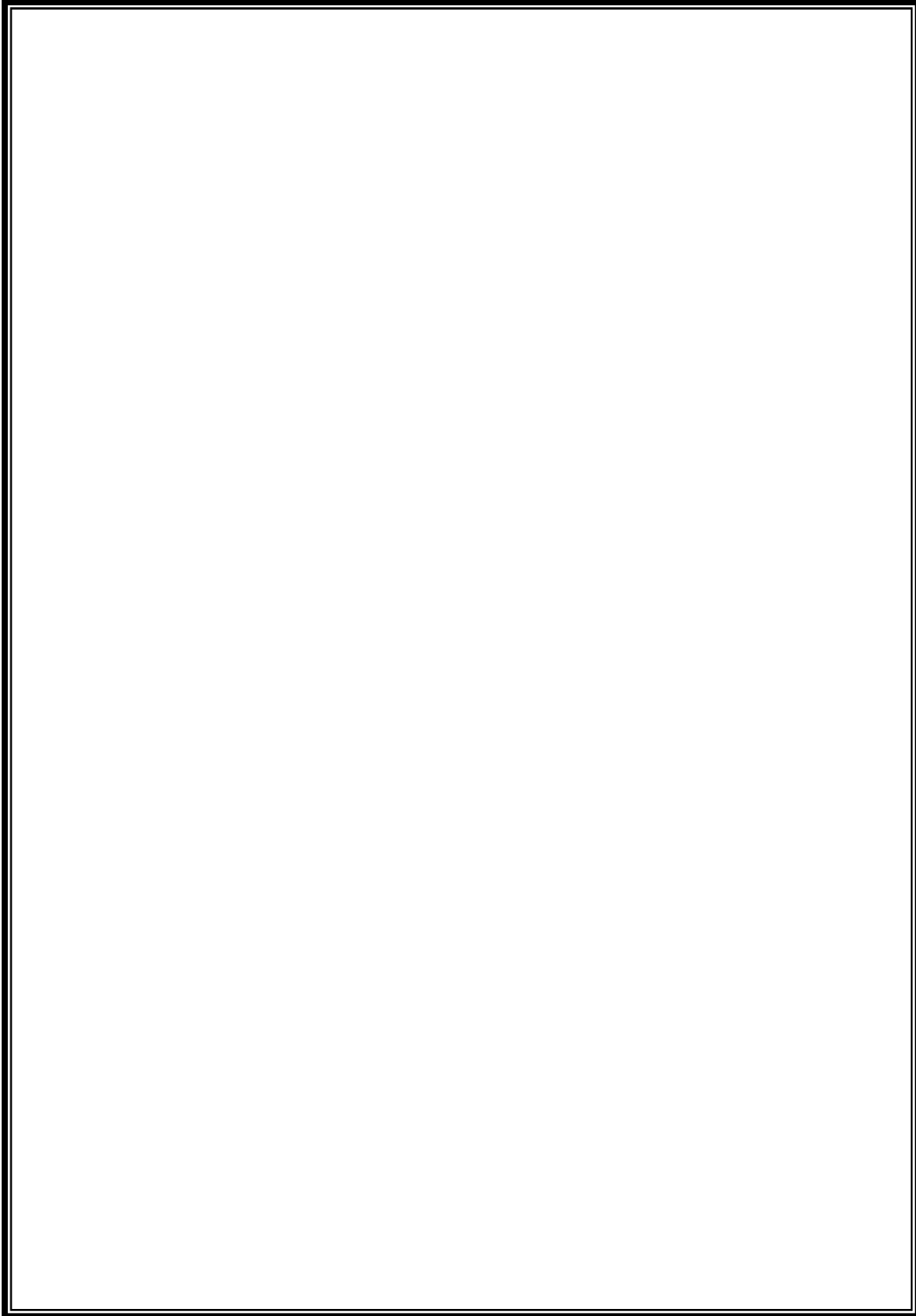


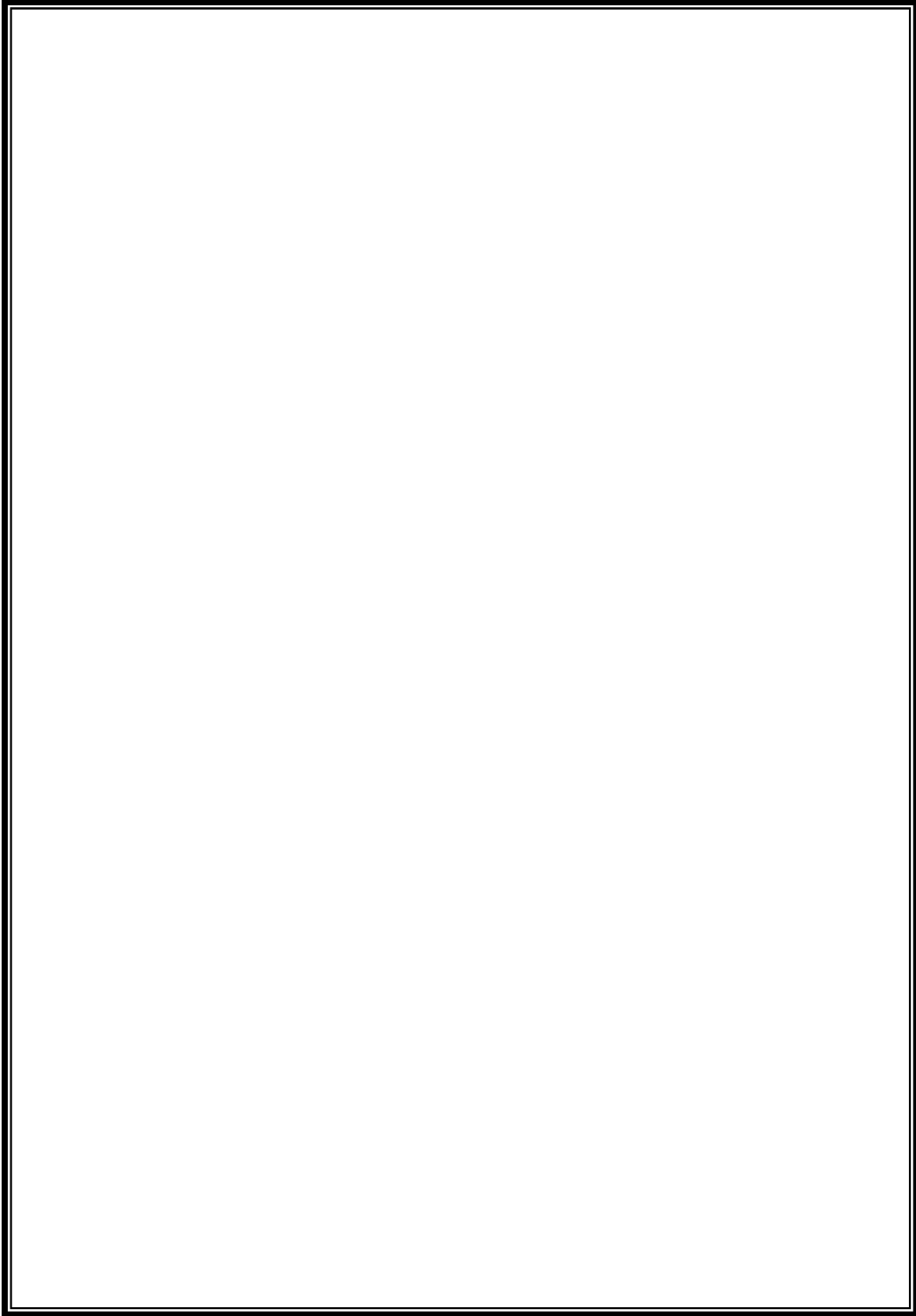












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CONTENTS

	<i>Page</i>
EXECUTIVE SUMMARY	1
1. INTRODUCTION	3
2. OBJECTIVES OF THE MEETING.....	4
3. GLOBAL AND REGIONAL SITUATION	4
4. COUNTRY REPORTS	6
4.1 Bhutan	6
4.2 Bangladesh	6
4.3 India.....	6
5. KALA-AZAR SURVEILLANCE	8
6. DIAGNOSIS AND CASE MANAGEMENT.....	9
7. NEW DRUGS IN THE TREATMENT OF KALA-AZAR	11
8. VECTOR ECOLOGY AND CONTROL	12
9. FIELD VISIT TO KALA-AZAR ENDEMIC VILLAGE PANDIT KA PURVA AND INSTITUTE OF MEDICAL SCIENCES, VARANASI	15
10. REGIONAL STRATEGIC PLAN FOR ELIMINATION OF KALA-AZAR	16
11. GROUP WORK.....	19
12. RECOMMENDATIONS.....	20

Annexes

1. Sensitivity, Specificity and Limitations in the Diagnosis of Kala-Azar	22
2. Treatment of Kala-Azar	24
3. Programme.....	26
4. List of Participants.....	27

EXECUTIVE SUMMARY

A WHO informal intercountry consultative meeting on elimination of visceral leishmaniasis was held at Varanasi, Uttar Pradesh, India, from 10 to 14 November 2003. The participants in the meeting comprised national programme managers, researchers from endemic countries and WHO staff from HQ, Regional Office and country offices. In the meeting the progress in visceral leishmaniasis control programme was presented, and evidence-based diagnosis and treatment as well as integrated vector management were discussed. The draft strategic plan for elimination of the disease, prepared by the WHO Regional Office was reviewed and action points and recommendations identified for progress towards elimination of the disease.

Anthroponotic visceral leishmaniasis is primarily restricted to East Africa and the Indian subcontinent (Bangladesh, India and Nepal). Those three countries of the SEA Region account for 20% of the global disease burden. The estimated annual cases of kala-azar in the Region is about 100 000. A kala-azar control programme is in place in all the three countries. Control strategy comprises early diagnosis and complete treatment, epidemiological and entomological surveillance, vector control through indoor residual spray/insecticide treated nets (IRS/ITN), IEC promotional activities, and annual active search during the kala-azar fortnight (India only). India initiated the kala-azar Control Programme in 1990 with an immediate objective of control and ultimate goal of elimination. India's National Health Policy 2002 has targeted kala-azar elimination by 2010, while Bangladesh and Nepal agreed to develop country plans to eliminate the disease.

Laboratory diagnosis and treatment for kala-azar was reviewed. Currently - used diagnostic methods included bone marrow and splenic puncture, DAT, rk 39 dipstick and polymerase chain reaction (PCR). The merits and demerits of these tests were discussed. Standard therapeutic options for the treatment of kala-azar include Sodium Stibogluconate, which is the most affordable drug except in North Bihar which has recorded unresponsiveness in up to 60% in a few areas, followed by second-line drugs, Pentamidine, which is expensive and causes high toxicity-insulin dependent diabetes mellitus (IDDM), should be abandoned. Amphotericin B and Lipid

Amphotericin B are the available second line treatment. Miltefosine, the first oral drug, with about 98% cure rate with least side-effects was considered to be the drug of choice.

The role of NGOs and the private sector in the diagnosis and treatment of visceral leishmaniases was discussed. Major constraints in this sector included treatment without appropriate diagnosis, and inadequate doses and duration. The need for good clinical practices (GCP), good laboratory practices (GLP) and standard operating procedures (SOP) were recommended for enforcement in private and NGOs' clinics.

Bio-ecology of *Phlebotomus argentipes*, the vector species, was discussed in relation to epidemiology and control of the disease. Factors favouring ecological stability of disease foci and social determinants were highlighted. Control of kala-azar in India by DDT spray under National Malaria Eradication Programme before resurgence was reviewed and the factors which helped in the elimination of kala-azar in Tamil Nadu foci were identified. The use of Remote Sensing / Geographical Information System technologies for the mapping of disease foci and for building up cost-effective and sustainable control strategies in an integrated vector management (IVM) approach were considered.

The draft Regional Strategic Plan for kala-azar elimination was presented and the Member countries were urged to prepare a work plan considering their resources and infrastructural facilities and set their goals of elimination. The feasibility of elimination of kala-azar was discussed. This enabled the participants to identify areas which would require strengthening for achieving the goal of elimination.

1. INTRODUCTION

An Informal Intercountry Consultative Meeting on Elimination of Visceral Leishmaniasis was held at Varanasi, Uttar Pradesh, India, from 10 to 14 November 2003. The meeting was attended by senior programme officers responsible for Leishmaniasis control and research from the endemic countries of the Region viz. Bangladesh, Bhutan and India. Representatives from Nepal could not attend. Representatives from WHO headquarters, South-East Asia Regional Office, country offices and Temporary Advisers attended the meeting (see Annexes 1 and 2 for the List of participants and Programme respectively.)

At the inaugural session, Dr Chusak Prasittisuk, Regional Adviser, Malaria, read out the message of Dr Uton Muchtar Rafei, Regional Director, WHO, South-East Asia Region, New Delhi who could not attend due to his preoccupations. In his message, Dr Uton said that the global burden of Leishmaniasis was 2.4 million DALYs lost each year of which about 0.50 million was in SEA Region. The disease predominantly affected the poor and adversely affected socioeconomic development in the endemic countries. In the SEA Region, kala-azar was reported from Bangladesh, India and Nepal which accounted for about 20% of the global burden of the disease. The estimated annual incidence of kala-azar in the Region was about 100 000 cases.

Since the early 1990s, national governments had renewed their commitment for the control/elimination of kala-azar. The affected countries had developed plans for the same. However, due to resource constraints and lack of agreement on strategies for disease control/elimination, these were not fully implemented. Since the mid-1990s, ministers of health from the affected countries had endorsed their commitment to eliminate kala-azar through cross-border collaboration in the control of priority communicable diseases (HIV/AIDS, TB, malaria, kala-azar and Japanese encephalitis).

The main strategies for the elimination of kala-azar included early diagnosis and complete treatment, integrated vector management (IVM),

disease surveillance and community participation. There had been a major breakthrough in treatment. Research supported by Tropical Diseases Research (TDR) and carried out by the Indian Council of Medical Research (ICMR) had shown that Miltefosine was effective in up to 98% of cases. The drug given orally, had few minor side-effects, and was cheaper than other drugs and could be easily stored.

Dr Uton said that advantage should be taken of the strategy of IVM, recommended by WHO. Indoor residual spraying (IRS) was very effective in the control of kala-azar, but it was important to do it selectively through micro stratification. Community participation and intersectoral collaboration were indispensable. Networking of institutions to ensure quality control in diagnosis and treatment was important. This would help contain and control the emergence of drug resistance. A draft strategic plan for elimination of kala-azar had been developed by The WHO Regional Office. This would help Member countries to develop their work plans.

Dr N B L Saxena (India) was elected Chairperson of the meeting and Dr M Rahman (Bangladesh) as the rapporteur.

2. OBJECTIVES OF THE MEETING

The objectives of the meeting were:

- (1) To review the progress made in visceral leishmaniasis control programme in South Asia countries
- (2) To review the regional strategic plan for elimination of visceral leishmaniasis in 3 countries of South East Asia
- (3) To establish technical support networks for elimination of visceral leishmaniasis

3. GLOBAL AND REGIONAL SITUATION

Dr P Desjeux, WHO/HQ, summarized the global situation of kala-azar. Leishmaniasis includes four major eco-epidemiological entities, zoonotic and anthroponotic visceral leishmaniasis, and zoonotic and anthroponotic cutaneous leishmaniasis. In anthroponotic forms, humans are considered to

be the sole source of infection for sandfly vectors. In zoonotic transmission cycles, animals are reservoirs which maintain and disseminate the leishmania parasites. Leishmaniases is endemic in 88 countries with an estimated yearly incidence of 1–1.5 million cases of cutaneous leishmaniases (CL) and 500 000 cases of visceral leishmaniases (VL). The population 'at risk' is estimated at 350 million (with an overall prevalence of about 12 million). Anthroponotic visceral leishmaniasis (AVL) is primarily restricted to East Africa and the Indian sub-continent (Bangladesh, India and Nepal). The parasite is *leishmania donovani* and several sandfly species act as vectors. Human cases, both untreated and post-treated, (with post kala-azar dermal Leishmaniases – PKDL) disseminate the parasite. Anthroponotic visceral leishmaniasis epidemics are frequent with high death rates. For control of VL, research has brought new and more cost-effective tools. These include new diagnostic tests-rk39, new oral drug miltefosine and a personal protection method – long-lasting insecticide treated nets. The new oral drug should be used judiciously. In order to prevent resistance, possible combination therapies are under evaluation. Other studies aim at determining the efficacy of Miltefosine in the treatment of PKDL, in HIV-positive patients and in children.

Dr Chusak Prasittisuk, WHO-SEARO elaborated on the scenario in Bangladesh, India and Nepal, the three countries in the Region affected by kala-azar. About 147 million population of the Region are at risk of kala-azar. During 2000-2002, the reported cases were 24 287, 18 472 and 22 030 respectively. Estimates indicate about 100 000 cases per year in the Region. In Bangladesh, 34 districts are affected. In India, 35 districts in Bihar, 10 in West Bengal, 3 in Jharkhand and 2 in Eastern Uttar Pradesh report the disease. In Nepal, 12 districts are affected. The border districts in Bhutan are at risk. In the SEA Region, socio economic and cultural factors contribute to the maintenance of the disease. In Bihar (India), 75% of the VL patients have a daily income of less than US\$ 1. Consequently, compliance for treatment is low, treatment interruptions are frequent. The lack of response to first line drug, pentavalent antimonials have been increasing sharply in some parts of India (in > 60% of the patients in some areas). Cross-border collaboration has been initiated in four districts of India and Nepal and India and Bangladesh. All the affected countries have agreed to develop plans to eliminate kala-azar.

4. COUNTRY REPORTS

4.1 Bhutan

Mr Wangchuk Dukpa provided an update on the situation in Bhutan. Kala-azar is not a public health problem in Bhutan and no indigenous cases have been reported from the country so far. A few kala-azar cases reported in the past were found to be imported on verification. However, high receptivity of alluvial plains within Bhutan and proximity to endemic areas of West Bengal (India) makes it a 'high-risk' country for the introduction of the kala-azar.

4.2 Bangladesh

Dr A T M Mustafa Kamal, presented the kala-azar control programme in Bangladesh. Kala-azar is reported in 34 districts of which three are highly endemic contributing about 50% of the total cases of the country. An estimated 10 000 cases occur annually. The kala-azar Control Programme was introduced in 1995 with a focus on early diagnosis and prompt treatment (EDPT), Epidemiological and entomological surveillance, vector control measures with IRS and ITN, IEC promotional activities and operational research. DDT in the country has been exhausted and therefore a new insecticide has to be chosen. There is a shortage of drugs, trained manpower, direct agglutination tests (DAT) kits for rapid diagnosis, and laboratory infrastructure.

4.3 India

Dr N B L Saxena presented the salient features of the kala-azar elimination programme in India and its implementation status. Kala-azar has been endemic in 50 districts in Bihar, Jharkhand, West Bengal and Uttar Pradesh, besides sporadic incidence in a few districts in eastern Uttar Pradesh. An organized, centrally sponsored Kala-azar Control Programme (KACP) was launched in 1990 on a cost-sharing basis between the centre and the states. NAMP is the national nodal agency for KACP. The state government implements the programme which comprises early diagnosis and complete treatment and vector control through IRS with DDT up to six feet height from the ground, IEC, capacity building and monitoring and close supervision with periodic review/evaluation strategies. Surveillance system is based on passive surveillance supplemented with annual/periodic active case searches as 'kala-azar fortnight'. Within three years of intensification (1992-1995) there was a

70.66% decline in annual incidence and 80.48% decline in deaths. By 2002, as compared to 1992, the decline was 85% in incidence and 88% decline in deaths. In the initial three years after introduction of the intensified control programme, reduction in both morbidity and mortality was very remarkable, i.e. > 70 and 80% respectively. However, in the next seven years, improvement was slow. Under-reporting, particularly of PKDL cases, inadequate support to the programme by the states, indiscriminate use of drugs by private practitioners, drug unresponsiveness to SSG (the first line drug) in some areas of Bihar and inadequate vector surveillance are the major constraints in the programme.

The national health policy (2002) in India envisages KA elimination by 2010. Strategic plan that articulates mid-term targets was developed. The plan targets zero deaths by 2004, zero incidence of KA by 2007, no PKDL by 2010, provides for post elimination surveillance, decentralized surveillance, and diagnostic and treatment policies, networking and community education. The plan takes into consideration inadequacies in the states and provides 100% central support.

Discussion

Kala-azar has shown geographic spread all over the Region. In India, foci, which were restricted to north Bihar, have now spread south of the Ganges. Disease burden is persisting despite intensified efforts. In India, an intensified campaign initiated in 1992 yielded dramatic results in the first three years but in the next seven years improvements were slow. Corrective action is required to arrest the slow down, through appropriate programme strengthening. DDT is the cheapest insecticide for vector control, but is only available in India. Pyrethroids are an alternate but are costly. Long-lasting nets have not yet been evaluated adequately and its supply would require external funds. To attract external funding, adverse economic impact needs to be worked out and used for advocacy. Kala-azar foci in all the three countries are in contiguous areas where there is high a level of cross-border migration. Therefore this should be coordinated by WHO as a sub-regional initiative.

Action points

- Kala-azar should be treated as a regional problem affecting three endemic countries. Although each country will manage its own KA elimination programme, there is a need to develop a uniform strategy

for operation in the same time-frame to achieve elimination. WHO should facilitate coordination of the activities through inter-country meetings and periodic evaluation and by forming of a Regional Task Force to support and monitor elimination initiative.

- Persistent disease burden may be due to technical, managerial, financial, operational and political constraints. These constraints should be identified and addressed to achieve the goals of KA elimination.
- DDT is still the insecticide of choice because of continued susceptibility of *Phlebotomus argentipes* to the vector. However, in countries where DDT has been banned, pyrethroids are the alternate to DDT. A situational analysis should be carried out to develop the strategy for IVM including IRS and ITN.
- In depth eco-epidemiological studies should be carried out to: identify distribution of the disease in new areas (sporadic or contiguous), identify risk factors related to epidemiological, entomological, meteorological, socio-cultural, socioeconomic and developmental activities and to develop area-specific IVM control strategies to achieve interruption of transmission.

5. KALA-AZAR SURVEILLANCE

In all the three affected countries of the Region, kala-azar surveillance is carried out by active case detection (ACD) and passive case detection (PCD). In Bihar, India, kala-azar is a notifiable disease, but this has not proven to be successful. Health workers during their routine visits detect and refer suspected cases (based on agreed case definition - fever of more than 2 weeks not responding to antibiotics and antimalarials) to the hospitals. In India, a special fortnight drive is undertaken to list all suspects based on above case definition of kala-azar which are then diagnosed by a doctor before initiating treatment. Passive case detection is done in hospitals and health centres.

Discussion

The gap between reported and estimated cases is very wide. A small-scale study carried out in north Bihar by the National Institute of Communicable Diseases (NICD) found four-fold under-reporting. Active case detection is

poor either due to lack of infrastructure or inadequate surveillance. In the private sector, treatment cost is very high because of which many poor people do not persist with it. Similarly, deaths occur most of the time at homes and remain unregistered. It is important to narrow down the gap between reported and real incidence by estimating the disease burden. This will help to set targets for the elimination strategy.

Action points

Periodic special house-to-house searches should be undertaken to elicit the real disease burden. Initially, these house-to-house searches can be carried out once a year in all the three endemic countries. With declining trends, searches may be intensified. Both public and private sector health care units should be encouraged to report the cases to the public health authorities.

6. DIAGNOSIS AND CASE MANAGEMENT

Dr S K Bhattacharya reviewed the laboratory diagnosis of kala-azar. At the peripheral level, these include formal gel test (Aldehyde test), rk 39 dipstick test, indirect fluorescence antibody test (IFAT) and enzyme linked immunoabsorbant assay (ELISA). At the secondary and tertiary levels, bone marrow aspirations and splenic puncture, polymerase chain reaction (PCR) and PCR-ELISA are done. Many of these tests are difficult to carry out at the peripheral level. The Sensitivities and specificities, along with the limitation of the presently used methods are included in Annex 1.

Case management of kala-azar in public sector was summarized by Dr Shyam Sunder. The situation remains highly unsatisfactory. Until recently, anti-leishmanial drugs, sodium stibogluconate (Sb), pentamidine and amphotericin B, had to be administered parenterally for long periods and all the three are toxic. The first line drug Sb, being used at 20 mg/kg without ceiling for 30 days, has developed specific resistance in up to 62% cases in some studies conducted in North Bihar. However, there is little evidence of drug resistance in areas south of the Ganges, West Bengal and Uttar Pradesh. Delayed response or no cure builds up the reservoir and spread of the disease. Pentamidine, the second line drug, besides being expensive, is toxic and causes insulin dependent diabetes mellitus (IDDM) with occasional deaths. Efficacy has also declined from 100% to 70% in the 1990s. Amphotericin B, a polyene antibiotic, is an alternate to pentamidine and

carries a cure rate of >96% including Sb resistance cases. Drug is toxic, thrombophlebitis is common, but myocarditis, although serious, is uncommon. Occasionally, it leads to death. Besides being expensive, use of this drug is restricted to large hospitals. Miltefosine is the first non-toxic oral drug with nearly 100% cure rate. This drug is already licensed in India. However, wider induction is possible after the conclusion of phase IV trials.

For treatment of PKDL, sodium stibogluconate at 20 mg/kg for 60 to 120 days and Amphotericin B at 1 mg/kg infusions/day upto 90 days, are recommended. The existing regimen is difficult to deliver because of non-compliance. Details of therapeutic options are summarized in Annex 2.

Dr S K Bhattacharya reviewed case management practices in the private sector in India. Patients of VL often seek treatment from quacks, private practitioners and NGOs. Specific treatment starts on clinical grounds, sometimes based on aldehyde test. The dose and duration are often inadequate. Generally stibogluconate is used. Amphotericin B is also used in some areas. The information on treatment practices in the private sector is unsatisfactory.

Prof Abul Faiz (Bangladesh) presented the prevalent practices of KA diagnosis and treatment in Bangladesh. At the PHC level, the diagnosis is based on clinical signs and aldehyde test. Rapid tests (rk39) are a recent introduction. A tertiary level parasitological confirmation is carried out by splenic puncture and bone marrow aspirations. Sodium antimony gluconate is the drug of choice. No evidence of Sb resistance has been recorded so far.

Discussion points

Early and rapid diagnosis of kala-azar for early initiation of treatment at the peripheral level is important. This has gained urgency in view of the increasing unresponsiveness of sodium stibogluconate, the first line drug. Achievement of the goal of early diagnosis in inaccessible and remote rural areas is a challenge for the programme. Serological tests, particularly aldehyde test, in spite of its limitation of becoming positive after 2-3 months of illness and being relatively non-specific, is being practised in rural areas. Similarly, DAT requires cold chain facility, which is non-existent in most rural health care facilities in KA endemic areas on a continuing basis. This logistic issue needs to be addressed.

The problem in treatment with the first line drug of stibogluconate includes primary unresponsiveness (8%) slow responders, relapses, secondary

unresponsiveness and resistance. There are many factors which influence the outcome of the treatment, viz. delayed diagnosis, late presentation of patients and secondary infection with various bacteria due to suppression of immunological defences due to kala-azar, malnutrition, diarrhoea and use of substandard and poor quality drugs. These practices get amplified in the private sector where treatment starts without confirmation of diagnosis, with inadequate doses/duration and without monitoring of the progress of recovery.

Action points

- Aldehyde test in the absence of DAT and dipstick test in spite of its limitation in remote/inaccessible areas, coupled with clinical diagnosis, remains an affordable test for initiation of the treatment until other tests are introduced. Although DAT test gives 100% specificity, shaking during transportation hampers the antigen. Therefore, cold chain becomes essential. Batch-to-batch variations in the sensitivity of antigens poses problems. Availability of freeze-dried antigen is likely to obviate these needs. Standardization and operational feasibility of DAT should be assessed. Dipstick test ('rk 39') is very sensitive but requires quality assurance. Affordable price factor will help in improving treatment in the private and public sector.
- Treatment should start as early as possible after diagnosis. Patients should be observed for clinical and parasitological recovery and in cases of slow responders and primary unresponsiveness, drug doses and duration should be adjusted. Quality control (QC) quality assurance (QA) and good manufacturing practices (GMP) for diagnostic test kits and drug manufacturing should be in place. Training of private practitioners and laboratory personnel in GCP and GLP should be optimized. Patients showing concurrent presence of tuberculosis/other infections should be treated for both the ailments. Suitable corrective measures should be undertaken in malnourished children and in the presence of diarrhoea.

7. NEW DRUGS IN THE TREATMENT OF KALA-AZAR

Dr Juntra Karbwang (WHO/HQ) and Dr S K Bhattacharya presented initiatives in product development through private/public partnerships coordinated by

TDR. After a successful evaluation of Miltefosine through collaboration of ICMR/Zentaris and TDR, two more drugs under similar arrangement are in the pipeline. The study on Paromomycin: started in March 2003 with 350 patients. A dose of 15 mg/kg IM for 21 days versus amphoterecin B (3:1) is being evaluated for efficacy and safety. Results are expected by June 2004. The study on PKDL: (ICMR-TDR-Zentaris collaboration) is in progress. Dose ranging study for oral Miltefosine was initiated in two groups. Efficacy, safety and dose range are being studied at 8 and 12 weeks.

8. VECTOR ECOLOGY AND CONTROL

Mr N L Kalra described vector ecology and analysed the data on control of kala-azar in endemic areas of India during DDT spray under NMEP before resurgence of the disease (see Table below). *P. argentipes*, the vector of kala-azar requires capillary bound moisture in soil with organic matter for breeding. These conditions vary with soil conditions. The Indo-gangetic plains, adjoining Nepal, Bihar and West Bengal in India, Brahmaputra and Padma flood plains across Assam (in India) and Bangladesh (all rich in alluvial soils) provide favourable conditions for the prevalence of vector species. Variable incidence of the disease in endemic areas is related to water and food cycle of the species. North Bihar and West Bengal have glacier fed river system that maintains the requisite moisture and humidity for greater part of the year and extended transmission with ecologically stable disease foci. In South Bihar (South of the Ganges), the rivers are monsoon fed and dry up. This restricts transmission to shorter periods. Consequently, these disease foci are sporadic and unstable. Socio-cultural and economic factors determine the distribution of the disease. Poor people raise poultry which provides organic matter for sandfly breeding but do not provide blood meal. Hence, sandflies seek human blood resulting in higher incidence of the disease. People in the higher economic strata rear cows; provide both organic material as well as blood for feeding of sandflies. This may be an explanation for lower incidence of the disease in the rural areas since they commonly own cattle. Indoor resting and feeding, low fecundity (30-40 eggs per gonotrophic cycle) and extended life-cycle (40-45 days) give biological advantage for the control of kala-azar, through IRS. Once decimated, the sandfly population, rebuild takes several months. Microstatification using new tools of RS and GIS can further help in the identification of disease foci for building up cost-effective and sustainable control strategies through integrated vector management (IVM).

Table: Kala-azar control by DDT spray under NMEP before resurgence

	Disease foci	Disease incidence before DDT spray	DDT spray year / round	Spray withdrawal year	Disease incidence (impact)	Resurgence year
A. Stable						
i	North Bihar	1933-37 Highly endemic >50 000 annual cases.	1953 Two rounds of DDT spray	1966	Reported incidence rare, but large hospitals continued to record over 50 cases annually. Infection dormant	Reported in 1971 peaked in 1977 >100 000 case 4 500 deaths. 21 districts out of 39 affected
ii	West Bengal*	Epidemic 1922 >15 000 cases 35 147 – 1949	Same as above	1966	Sharp declining trend 9 to 43 cases respectively.	In 1980 Indigenous case reported
iii	Assam	Highly endemic earned the name of 'Sarkari Bimari' (Govt Disease)	Same as above	No DDT withdrawal (over 50 year, now)	No epidemic	Special hospital based survey 1974-79 - 27 cases. Epidemic potential high
B. Unstable						
i	Madras (Urban)	>2 500 cases annually	1954 peripheral areas 1 round/ 1 gm/m ²	1961 1round/ 1gm/m ² 1962-75 focal spray	1975 only 6 cases. 11 cases in the last decade (1975-85)	
ii	Ramanathapuram (Rural)	>4 000 annually	1954 1 round 1gm/m ²	1962 coastal dist 2 round/ 1 gm/ m ²	5 cases	
iii	Tiruvelli (Rural)	>2 000 annually	1959-60 1 round	1960-64 focal spray	No case	

*There were no cases reported in 1970s and resurgence occurred in 1980 with indigenous case report

In stable foci of North Bihar and West Bengal resurgence occurred within 5-10 years of withdrawal of DDT. Factors responsible for the elimination of kala-azar in Tamil Nadu (unstable foci) included a strong political commitment, DDT spray oriented to vector ecology of sandflies, increased access to medical care, higher socioeconomic status, anti kala-azar unit with strong infrastructure (1-2 trained entomologists for each district), active search every four months and well supervised implementation of the programme.

Prof Ashford stressed on the need for more information on the bio-ecology of *P. argentipes* to elicit information for understanding better the complexities of epidemiology and for developing control strategies under the IVM strategy. He identified entomology, vector control, mathematical ecology, epidemiology and landscape ecology as thrust areas. He also suggested an evaluation of alternate sandfly control measures, including use of larvicides, improvement of housing, long-lasting nets, cowtraps and application of insecticides (sponging) on animals.

Discussion points

The distribution of *P. argentipes* is focal because of its specialized requirements for capillary bound moisture and organic material. The species also does not take direct flight but takes short hops to enter houses for selecting resting sites. The species has to make several movements for feeding (indoor) and breeding (cattle sheds - outdoors) during each gonotrophic cycle. A control strategy, based on spraying of portal of entry (doors/windows) needs to be evaluated. Kala-azar endemic areas have been under DDT spray during the National Malaria Eradication Programme (NMEP) and later under an intensified campaign for control of kala-azar in Bihar. Recent susceptibility studies carried out in Bihar have detected evidence of declining susceptibility in pockets in the districts of Dharbanga and Vaishali. In Bangladesh and Nepal, where the use of DDT is either banned or stocks have exhausted, the option is to use other insecticides. These are costly. A second round of spray in Bihar is done in May-June. No spray is done during the monsoon due to logistic problems. In the absence of any feasibility studies in KA endemic areas, the role of long-lasting nets should be evaluated prior to scaling up.

Action points

- The quality of data on ecology of the vector species should be improved and mapping of vector distribution and disease foci done

by using RS/GIS technology. Similarly, data on the bionomics of larval and adult population should determine the feasibility of alternative methods of control through IVM. A study in kala-azar endemic areas with two rounds of DDT spray @ 1 gm/ m² and single round with 2 gm/m² to assess the duration of protection is recommended.

- There is a need for coordinated epidemiological and entomological studies to better understand the disease. This may help in achieving elimination status.
- In Bangladesh and Nepal, where the use of DDT has been banned, national governments should be urged to either lift the ban on the use of DDT through WHO or cost-effective control strategies through IVM should be urgently implemented.

9. FIELD VISIT TO KALA-AZAR ENDEMIC VILLAGE PANDIT KA PURVA AND INSTITUTE OF MEDICAL SCIENCES, VARANASI

Prof Shyam Sundar and his colleagues at the Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, arranged a visit to a kala-azar endemic village – Pandit ka Purva, which experienced an outbreak in November-December 1995. The visit was organized for familiarization of participants on epidemiological and entomological features that are conducive to the spread of the disease. The kala-azar affected village, 'Pandit ka Purva' (population 518), is situated about 10 kms from the venue of the meeting on the eastern bank of the river Ganges. Agriculture is the main occupation of the inhabitants. However, there are also weavers and small businessmen in the village. A survey carried out by Prof Shyam in November-December 1995 during an outbreak of kala-azar revealed a prevalence of 13% and case fatality of 10%. Many cases of PKDL were also seen. Participants observed that paddy was extensively grown around the village in close vicinity to the households. The soil was alluvial with high water table. Efforts were made to locate sandflies in some of the houses; however, none could be found as the village was under IRS. Soil samples were examined for the presence of immature stages of sandflies but could not be detected. Even though sandflies were not seen at the time of field visit, the potential of kala-azar transmission does exist in the area due to favourable ecological conditions.

The group also visited the Department of Medicine, Institute of Medical Sciences, Varanasi. The group was shown a case of PKDL, who had received Miltefosine treatment. Dr Shyam Sundar demonstrated a rapid diagnostic test (rk-39) on the PKDL patient. The test gave a positive result in about 3-4 minutes. In the laboratory the group was shown, under microscope, live culture of *L. donovani* being maintained.

10. REGIONAL STRATEGIC PLAN FOR ELIMINATION OF KALA-AZAR

Mr N L Kalra presented the draft Regional Strategic Plan for kala-azar elimination. Visceral Leishmaniasis in the SEA Region is anthroponotic. Consequently, deadly and sudden epidemics occur periodically. Poverty is a major determinant of VL. The disease adversely affects the socio-economic condition of the people. It is an expensive disease to treat. Malnutrition impairs immunity to VL and increases vulnerability to infection. The breeding places for the human and cattle feeding sandfly vector are located in the peridomestic animal shelters that in turn cause poor sanitation. The houses, made of local materials, such as mud and grass, provide favourable crevice habitats for the sandflies. As HIV/AIDS is increasing and spreading to rural areas, the risk of Leishmania/HIV co-infection may also increase. This can have a devastating effect. High VL endemicity and migration from rural to urban areas enhances the risk of occurrence of the two diseases. According to WHO (2003), the calculated DALYs (disability-adjusted life years) lost due to kala-azar works out to 2.4 millions (about 0.4 million for the SEA Region).

(1) Vision

To contribute to improving the health status of the vulnerable groups (poorest of the poor, marginalized people) living in kala-azar endemic areas of Bangladesh, India and Nepal by the elimination of kala-azar.

(2) Goal

Elimination of kala-azar in the SEA Region by 2015.

(3) Objectives

By the end of 2012 the annual incidence of kala-azar at the village level will be zero by reducing kala-azar morbidity rate among the vulnerable groups,

reducing the risk of kala-azar transmission among 'unreached communities', a decline in the case-fatality rate of kala-azar and preventing the emergence of kala-azar/HIV coinfection in the community.

(4) Regional Strategy

- Improving the effectiveness of programme management with a focus on the improvement of policy, regulation and planning process.
- Establishing effective disease and vector surveillance system for planning and response based on reliable laboratory support and health information system.
- Ensuring early diagnosis and complete case management of kala-azar prevention, control and management through IEC.
- Undertaking disease prevention and control through selective, stratified and integrated vector management with community participation.
- Increasing emergency preparedness capacity to prevent and control outbreaks with appropriate contingency plans.
- Improving the management and technical support system and strengthening health facilities for health sector development.

Undertake advocacy with policy-makers to renew commitment and to improve legislation, planning process and effectiveness of the kala-azar programme management. Effort should be made to mobilize additional resources to eliminate kala-azar. For the success of the programme, both international and national level partnerships amongst MoH, WHO, UNICEF and other sectors are important. Affected countries should strengthen cross-border collaboration in the elimination of kala-azar. The existing malaria control programmes should also focus on actions that meet the needs of kala-azar control in an appropriate manner. The health system, including existing disease and vector surveillance and laboratory facilities, needs to be strengthened. Kala-azar control programme should seek synergies with other ongoing programme viz. malaria, and Filariasis. Integrated vector management (IVM) approaches should be employed to obtain multiple impacts to achieve interruption of transmission. Cooperation of local NGOs for operational

support and resource mobilization is necessary. "Miltefosine", the first oral drug, is safe with minimal side-effects and should be promoted as the drug of choice for the management of VL cases. Research to improve diagnosis, treatment, entomology and epidemiology of the disease should be continued. In monitoring and evaluation, routine reporting should be strengthened and the data available converted to easy visual formats. Deficiencies should be identified and corrected. For elimination of the disease it is important to measure progress against set targets.

(5) Role of WHO

In partnerships with the countries efforts should be made to mobilize additional resources for the elimination of kala-azar. WHO should help the endemic countries to prepare a coordinated and harmonized strategic plan for elimination of the disease. It should provide technical assistance and support. A regional advisory group is recommended. Networks should be established.

Dr Vijay Kumar and Mr NL Kalra,, moderated the debate on elimination of kala-azar. It was agreed that international commitment is required to mobilize additional resources for elimination of the disease. Sustained political and financial commitment is necessary to expand the elimination programme and to sustain its implementation. Distribution of kala-azar in the three endemic countries is contiguous and represents single major foci. There is a need to implement the 'Regional Strategy' in the same time-frame to achieve a uniform rate of decline in the affected countries. To achieve this there is a need for a regional technical expert committee to oversee and support implementation of the programme. Cross border collaboration needs to be strengthened for elimination. Poverty is a major determinant and elimination needs to be linked to the anti-poverty programme. The technical difficulties include the ecological stability of the disease foci, and persistence of the reservoir of infection. Microstratification using new tools of RS and GIS can help in the identification of disease foci for building up cost-effective and sustainable control strategies, through the IVM approach. Risk factors in each foci should be determined and a control strategy formulated to address these risks to interrupt transmission. Case finding through ACD and PCD and periodic, special house-to-house search, and medical camps should be scaled

up for the detection of cases, particularly, PKDL, for initiation of early and complete treatment and to address the real disease burden for setting the targets for different phases. Sensitive and specific diagnostic test (like 'rk 39') with quality assurance should be made available at the peripheral level for initiation of treatment, at the earliest. Miltefosine should be available in sufficient quantities at an affordable price to ensure complete treatment of patients. Availability of DDT or alternate insecticide (pyrethroids) should be ensured. IEC activities, building partnerships with public/private/NGOs are essential to achieve the goal of elimination.

11. GROUP WORK

Issues and concerns in kala-azar

The participants divided themselves into two groups and discussed the issues and constraints. They were given core issues to be addressed during the discussion. The groups elected a Chairperson and Rapporteur. The action points that emerged were presented at a plenary session. These action points, along with the discussion and action points after each session, helped in preparing the recommendations of the consultation.

Action points

- Disease burden estimation (morbidity and mortality) through validation studies on sample basis is needed to determine the programme needs and economic projections. This exercise is necessary for building public-private partnership for VL elimination programme.
- Field applicable diagnostic tests are essential to improve surveillance and for early diagnosis. Currently, DAT test with freeze-dried antigen is a method of choice at the peripheral level, rk39 is promising.
- Miltefosine is the drug of choice, but operationalization issues viz., ensuring use of contraceptives to avoid teratogenic risk, non-use in early pregnancy and drug compliance need to be addressed. There is likelihood of development of resistance to Miltefosine. The induction of this drug should be carefully done by undertaking measures that

would help to contain drug resistance. Combination therapy is an alternative. This is being evaluated with assistance from TDR.

- Studies on cost-effective drug delivery strategies to secure access to the most affected populations to Miltefosine are required.

12. RECOMMENDATIONS

For Member countries

- (1) Member Countries should pursue the goal of elimination of VL by 2015 and develop national action plans with targets at different levels of programme implementation. Member countries should define specific timeline to measure progress towards the elimination of VL.
- (2) National policies and strategies are to be prepared for advocacy, consensus, resource mobilization and sustained political commitment.
- (3) To strengthen evidence base for elimination, it is important to collate and validate information on the burden of disease, socioeconomic implications, current practices for VL control at different levels of health care in public health care system, private and NGO sectors.
- (4) Countries should develop and apply innovative patient compliance strategies to strengthen current treatment practices. For preserving the efficacy of new oral drug Miltefosine, every effort should be made to avoid the use of this drug in early pregnancy and ensure that women avoid pregnancy during and two months after completion of treatment.
- (5) Surveillance for therapeutic response and drug resistance should be pursued and quality control for drugs and diagnostics ensured. This should be achieved through networking.
- (6) Indoor residual spray, which is very effective, should be continued and strengthened further by addressing important operational issues like planning, implementation, monitoring and evaluation.

- (7) Countries should intensify community mobilization and consider development of communication for behaviour impact (COMBI) for community mobilization.
- (8) To support elimination efforts, operational research on important issues like development and use of newer tools and technologies for diagnosis, treatment with proper consideration of ethics, patient compliance, vector ecology, etc. must be pursued through a collaborative approach.
- (9) There is a need for resource mobilization at regional and national levels through advocacy. A comprehensive document on action plans for VL elimination by the Member countries should be prepared for advocacy, resource mobilization from international, bilateral and local levels to support, strengthen and sustain the elimination programme.

For WHO

- (1) Undertake advocacy for a global commitment towards elimination of kala-azar and mobilize additional resources to help the endemic countries achieve the goal of elimination.
- (2) Develop standardized tools and guidelines for diagnosis and case management at the regional level. These may be suitably adapted at national and sub-national levels.
- (3) In-country and Intercountry networking and cross-border collaboration should be done for exchanging of information, improving communication with the programme and to support delivery of health care at different levels for elimination of VL.
- (4) Periodic country programme reviews are recommended to monitor progress, identify constraints and lessons learnt to strengthen, the programme during expansion, applying mid-course correction, if required.
- (5) A regional task force/expert committee should be established to support countries' efforts, networking advocacy and resource mobilization for a regional initiative on kala-azar elimination.

Annex 1

SENSITIVITY, SPECIFICITY AND LIMITATIONS IN THE DIAGNOSIS OF KALA-AZAR

1. Parasitological

Bone marrow aspiration and splenic puncture aspiration

- Invasive technique, sensitivity bone marrow (~75%), splenic aspiration >95%.
- Can be conducted under strict aseptic conditions only in hospitals.
- Requires technical skills and specialized equipment.
- Chances of complications are high. These include bleeding from splenic puncture. The procedure is not recommended if platelets are < 40 000/ μ l. or prothrombin time is more than 5 seconds as compared to controls.

2. Serological

2.1 Direct Agglutin Test (DAT)

- Sensitivity and specificity is high (100%).
- Freeze-dried antigen does not require cold storage.
- Test can be performed with blood specimens.
- Incubation is 18 hours. It requires blood/serum serial dilutions.

2.2 'rk 39' Dipstick test

- Sensitivity 86%, specificity 82%.
- Ideal for field conditions, rapid and simple. It does not need extensive training.
- Requires cold storage of running buffer.
- Test strips cannot be stored in high ambient temperature.
- Outcome of rk-39/DAT should always be interpreted together with clinical, epidemiological and other relevant test data.

3. **Molecular tests**

3.1 **Polymerase Chain Reaction (PCR)**

- Sensitivity: Blood - 70 to 96%, Tissue - 93%

3.2 **PCR ELISA – Peripheral blood**

- Sensitivity higher than IFAT, culture, direct microscopy
- Sensitivity higher with buffy coat preparation than whole blood.

Considering the limitations of each test, there is a need to use of rapid tests, that are non-invasive, have high sensitivity and specificity in field conditions, are cost-effective and can be performed at facilities without cold storage facility.

Annex 2

TREATMENT OF KALA-AZAR

The standard therapeutic options for treatment of kala-azar under PHC system are summarized below:

1. **Visceral Leishmaniases**

Sodium Stibogluconate

Meglumine antimoniate

- Dose: 20 mg/kg, 30 days, Mode IM/IV;
- Resistance: Area specific – North Bihar only > 60% in some areas
- Toxicity: Cardiotoxicity, renal failure, inferior quality lots can cause epidemics of cardiotoxicity and death
- Affordable (Rs. 1000 (US\$ 25) for 50 body weight for Indian product)

Pentamidine: second line of drug

- Dose: 4 mg/kg, 5-25 weeks, Mode IM/IV
- Sensitivity came down from 100% to 70% in the 1990s
- Toxicity: Insulin dependent diabetes mellitus (IDDM), occasional death
- Affordability: Expensive, use need to be abandoned

Amphotericin B: (second line of drug in preference to Pentamidine)

- Dose: 1 mg/kg, 20 days, Mode IV infusion
- Toxicity: Serious cardiac arrhythmias, death
- Affordability: Expensive - Rs 5000 (US\$ 110), requires hospitalization for 4 to 6 weeks

Lipid Amphotericin B

- Dose: 15 mg/kg, 100% cure rate, Mode: IV infusion 7.5 to 10 mg/kg, 90% cure rate
- Toxicity: shivering, cardiac toxicity
- Affordability: Expensive, Rs. 5000 to 7000 for 50 kg body weight

Miltefosine

- Dose: 100 mg (> 25 kg) 50 mg (< 25 kg) and children 2.5 mg/kg, Mode: Oral administration
- Toxicity: vomiting (40%), diarrhoea (20%)
- Duration: 4 weeks
- Caution: Cannot be used in pregnant females and those refusing contraception (for the treatment period and another two months after completion of treatment)
- Affordability: Expensive, Rs 6000 (US\$ 130) for 50 kg body weight

2. Treatment of PKDL

Sodium stibogluconate

- Dose: 20 mg/kg, Mode: IV/IM, 60-120 days

Amphotericin B

- Dose: 1 mg/kg infusion daily or alternate days – up to 90 infusion
- Existing treatment regimen difficult to deliver to patients. Non-compliance is very common. PKDL therefore persists.

Studies to determine the efficacy of miltefosine in the treatment of PKDL, co-infection with HIV positive cases and as combination therapies to prevent resistance are in progress.

Annex 3

PROGRAMME

Monday, 10 November 2003

- | | |
|---------------|---|
| 0800-0830 hrs | Registration |
| 0830-0900 hrs | Inaugural session |
| 0930-1000 hrs | Global situation of visceral leishmaniasis - Dr Philippe Desjeux |
| 1000-1030 hrs | Laboratory diagnosis of visceral leishmaniasis -Dr S.K. Battacharya |
| 1030-1100 hrs | Case management of visceral leishmaniasis including PKDL - Prof Shyam Sundar |
| 1100-1130 hrs | Vector control strategy for elimination of visceral leishmaniasis Dr Chusak Prasittisuk |
| 1130-1230 hrs | Issues and constraints in visceral leishmaniasis control in South-Asia - Dr Vijay Kumar |
| 1230-1300 hrs | Elimination of visceral leishmaniasis in South-Asia - Dr C.P. Thakur |

Country reports: Review of progress of visceral leishmaniasis control (situation analysis) and perspective for elimination of visceral leishmaniasis

- | | |
|---------------|------------|
| 1400-1430 hrs | Bangladesh |
| 1430-1500 hrs | India |
| 1500-1530 hrs | Nepal |
| 1600-1630 hrs | Discussion |

Tuesday, 11 November 2003

- | | |
|---------------|---|
| 0900-1200 hrs | Group discussion on tools and reporting including diagnosis, treatment, casereport form, vector control, IEC, capacity building, and technical support networks |
| 1200-1300 hrs | Presentation and discussion |
| 1400-1600 hrs | Group discussion on common policy for elimination and framework for intercountry collaborative programme, expansion of coverage, PCD, ACD |
| 1600-1700 hrs | Presentation and discussion |

Wednesday, 12 November 2003

Field visit

Thursday, 13 November 2003

- | | |
|---------------|--|
| 0900-1100 hrs | Preparation of country strategic plan (Bangladesh, India, Nepal) |
| 1100-1145 hrs | Presentation by countries |
| 1145-1230 hrs | Recommendations |
| 1230-1300 hrs | Closing |

Annex 4

LIST OF PARTICIPANTS

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