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Highlights

The World's Toughest Bacterium

Histopathological Grade and Subtype

Low Molecular Weight Nucleic Acids

Blood Bank at a Tertiary Care Hospital

Discovering Thoughts, Inventing Future

VOLUME 20 ISSUE 2 VERSION 1.0

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Deinococcus Radiodurans: The World's Toughest Bacterium. A Review

By Dr. Sujan Narayan Agrawal, Satyaram Satpathy & Debashish Samal

Abstract- Deinococcus Radiodurans is the "world's toughest bacterium" as per the Guinness book of world record. It is the most radiation-resistant bacterium ever known. It can withstand severe dehydration, cold, vacuum, acid, lack of nutrition, and survive to the radiation dose, a fraction of which is sufficient to kill the human being. The meaning of its name is 'strange berry that withstands radiation.' This remarkable talent is extensively studied by the biologist and scientist to find out how it survives the extreme life-threatening conditions. This knowledge is being used to find out the means to survive in radiation exposure and also to handle toxic waste.

Keywords: *deinococcus radiodurans, extremophilic bacterium.*

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I. Introduction

The name Deinococcus is derived from Greek, the dinos, meaning strange or unusual, and coccus, meaning a "terrible grain/berry", and in the Latin radius and durare, meaning "radiation surviving"[1] It is a Gram-positive, red-pigmented, nonsporulating, non-pathogenic Bacteria occurring in diads and tetrads with an average cell diameter of 1 _m (range, 0.5 to 3.5 _m). [2] It is an Extremophilic bacterium. It is one of the most radiation-resistant organisms ever known to humanity. It can survive extreme cold, dehydration, vacuum and, acid. It is therefore known as a polyextremophilic bacterium. [3] In the Gunnies Book of World records it is listed as the toughest bacterium. It belongs to Genus Deinococcus, the type species is radiodurans; The other known members of this genus are D. proteolyticus, D. radiopugnans, D. radiophilus, D. grandis, D. indicus, D. frigens, D. saxicola, D. marmoris, D. deserti, D. Geothermalis, and D. Murrayi. [4] All Dienococcus species are distinguished by their extraordinary ability to tolerate the lethal effects of DNA-damaging agents, particularly those of ionizing radiation and UV radiation. [5].

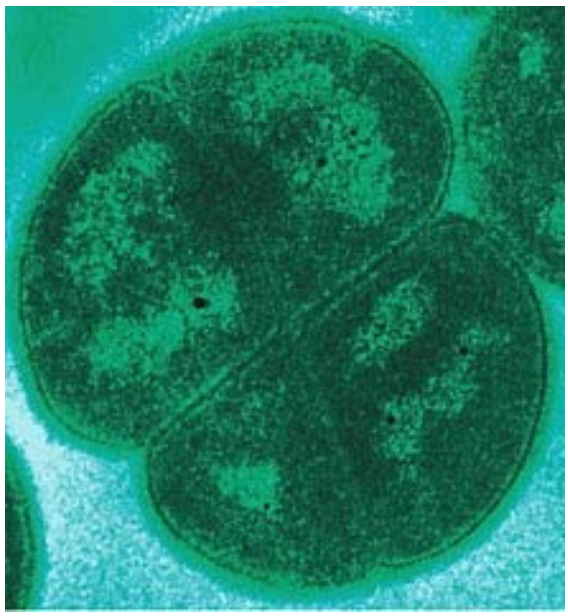

Figure 1: Deinococcus Radiodurans

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II. The Discovery

D. radiodurans was discovered in 1956 by Arthur Anderson at the Oregon Agricultural Experiment Station in Corvallis Oregon. The discovery occurred during an experiment to find out, whether, canned food can be sterilized using gamma irradiation? In the experiment, a tin of meat was exposed to high doses of radiation sufficient to kill all the known life forms, but the meat was spoiled, and D. Radiodurans survived and isolated. [6]

The cell Stains gram-positive, although its cell envelop is unusual and is reminiscent of the cell walls of Gram-negative bacteria. It is due to its multilayered structure and lipid composition.D. Radiodurans is a spherical bacterium with a diameter of 1.5 to 3.5 μm. Four cells stick together, forming a tetrad. It is non-motile and does not form endospores. It uses oxygen to derive energy from organic compounds in its environment. It is often found in habitats rich in organic materials, such as sewage, meat, feces, or soil. It is also isolated from the medical instruments, room dust, textile, and dried food. [5] It is extremely resistant to ionizing radiation, ultraviolet rays, desiccation, and electrophilic agents. [7]

III. The Genome

The genome consists of two circular strips of chromosomes. It contains about 3195 genes. In the normal stationary phase, each bacterial cell has four copies of this genome. When they are rapidly multiplying, each bacterium may have 8-10 copies of the genome. It is capable of withstanding a dose of 5000 Grays (Gy) or 500,000 rad of ionizing radiation without any loss of viability. As compare to this, the human being can be killed by a radiation dose, as low as 5 Gy. [8-9]

It is a gram-positive nonsporulating bacterium that usually grows in a tetrad form. It is can survive the extreme radiation exposure due to its ability to repair the genome, without loss of genomic integrity or mutation. This remarkable feature is due to the presence of a robust DNA repair system that can accurately restore genomic integrity following the introduction of hundreds of double-stranded genomic breaks. (DSBs). [5] The Deinococcus radiodurans isolates the damaged segments in a controlled area and repairs it. These bacteria can also repair many small fragments from an entire chromosome. Its survival property from high ionizing radiation is due to the presence of multiple copies of its genome and its rapid DNA repair mechanism. The ionizing radiation brings several breaks in its genome. These breaks in chromosomes are repaired within 12-24 hours by a two-step process. It seems that several genome maintenance proteins work together to mediate the process of DNA repair. After the double-stranded breaks the genome reconstruction occurs in two phases:

1. In the first phase within one hour, a process called "extended synthesis-dependent single-stranded DNA annealing (ESDSA) resects DSB ends to produce 3′ single-stranded DNA (ssDNA) extensions. These ends are then paired with homologous duplex DNA to create templates for DNA synthesis by DNA polymerases.
2. In the second phase, which occurred after 1-2 hours of radiation damage RecA-mediated recombination, which requires removal of SSB and resolution of interlinked chromosomes, completes the repair process. [10]

It is interesting to note that this process does not introduce any more mutation than, a normal round of replication work. It is also capable of genetic transformation. It is a process in which DNA derived from one cell can be taken up by another cell and integrates into the recipient genome by homologous recombination. [11] "The organism can put its genome back together with absolute fidelity," says Claire M. Fraser, of The Institute for Genome Research (TIGR) in Rockville, Maryland. She was the leader of the TIGR team that sequenced D. radiodurans in 1999.

Michael Daly suggested that the bacterium uses Manganese complexes as antioxidants, thereby protecting itself from oxidative damages. [12]. Michael Daly of the Uniformed Services University of the Health Sciences in Bethesda, Maryland, and his team come up with a possible explanation. It is because this bacterium store a high level of manganese and relatively low levels of iron. It seen that bacteria which shrivel up with a dose of radiation have little manganese and more of Iron. Michael further suggests that the manganese helps to clean up the free radicals that are released by the bacterium during the metabolic process. This manganese store makes the bacterium healthie, r and they are better equipped to mend the radiation damages. This theory is now tested by elevating the manganese levels of E.Coli bacteria. If the experiment and the said theory are proved then, it may help to prevent the radiation damage during chemotherapy in cancer patients. But it is too premature speculation since we still do not know that the survival of this bacterium from radiation damage is really due to high levels of manganese or otherwise. Michael has also suggested that "the protein, rather than the DNA is the principal target of the biological action of [Ionizing radiation] in the bacteria. The extreme resistance in Mn-accumulating bacteria is based on protein protection" [13]. M.Peana and C.Chasapis in 2018 proposed a model for Manganese interaction with the DR Proteome network involved in ROS response and defense. [14]

There are other possible explanations for the extreme resistance of this organism to radiation, like its

protection against prolonging desiccation, nitrous oxide, and S-layer complex. This S-layer Deinoxanthin Binding Complex (SDBC) contributes to its extreme radio resistence. This S-layer acts as a shield against electromagnetic stress, as in the case of ionizing radiation exposure. It also stabilizes the cell wall against possible consequences of high temperature and desiccation. [15-16]

IV. Applications

In Bioremediation: It refers to a process where microorganisms, fungi, plants, or enzymes are used to restore the contaminated environment to its natural state. The soil, sediments, and water may be contaminated by the nuclear waste in various situations. This contamination may be with a radionuclide, like Uranium, strontium, and cesium or heavy metals like chromium, lead, and mercury, the toxic solvents like Benzene, toluene, xylenes and chlorinated hydrocarbons, etc. The decontamination of such sites poses a real challenge and available cleanup technologies are expensive and dangerous. An alternative is the use of bioremediation with the help of specialized microorganisms that can detoxify the metallic and organic elements and are made harmless to the environment.

The common organisms cannot be used for decontamination because they perish due to high levels of radiation; here D. radiodurans may play a role, since it is known to have resistance to high doses of radiation. It can be used to treat nuclear energy waste. This bacterium (D. Radiodurans) is engineered genetically to consume and digest the solvents and heavy metals in this radioactive environment. The mercuric reductase gene has been cloned from E.Coli into Dienococcus to detoxify the ionic mercury residue. This residue is a waste generated from the nuclear weapon manufacturing process. [17] These researchers have developed a strain of Dienococcus that could detoxify both mercury and toluene in mixed radioactive waste. A gene encoding a non-specific acid phosphatize from Salmonella enteric serovar Typhi and the alkaline phosphatize gene from Sphingomonas have been introduced in the strains of D.radiodurans for the bio precipitation of uranium in acid and alkaline solutions respectively. The bioengineered D. Radiodurans has already established itself as a useful agent to decontaminate radioactive waste sites.

a) Application in Biomedical field

Aging and cancer are associated with increased DNA and protein oxidation due to ROS generation. There is also a decline in the ability of the cell to protect itself from oxidative damage and to repair the damage of DNA [18]

A focal point of aging and cancer research is to identify factors that antagonize the aging process and carcinogenesis and to design adequate therapeutic strategies. In this field, the bacterium D.radiodurans can be used to study the process of aging and cancer. It is known that the physiological changes that bring about aging and cancer are related to damage to DNA, RNA and, oxidative damage to the cell, thereby weakening its defence and repair mechanism. The D. Radiodurans is known to protect itself from oxidative damages and efficiently repairs its damage to DNA. The same property may be applied to human cells also in the future.

The free radical theory of aging and cancer postulates that the damage caused by the production of ROS is the underlying cause of aging and cancer; Alzheimer's disease and Parkinson's disease are also clearly associated with oxidative stress. Oxidative stress occurs when ROS production is accelerated or when antioxidant defense enzymes are impaired. Oxidative stress affects both DNA and proteins. The efficient repair, therefore is a critical component in the protection against aging and cancer. Since the oxidative stress plays a significant role in the aging and cancer processes, the strategies to combat this process is to reduce the oxidative damage or boost the defense mechanism. The ability of protection of D. radiodurans against oxidative damage can be harnessed to this crucial process, to delay aging and prevent cancer and other age-related diseases. The future researches are directed to employ deinococcal antioxidants to prevent or reduce age- and cancer-related protein modifications and DNA damages.

V. Discussion

The Deinococcus Radiodurans is a polyextremophilic bacterium. It can withstand any adverse environmental conditions like cold, heat, desiccation, radioactivity, etc. It is because of multiple copies of genome and exceptional ability to repair the damaged DNA. These unique properties can be used for bioremediation, and biomedical applications. In the field of bioremediation it can be used for decontamination of the toxic environment. This bacterium (D. Radiodurans) is engineered genetically to consume and digest the solvents and heavy metals in radioactive environment. It can also be used to tackle the nuclear energy waste. The D. Radiodurans is known to protect itself from oxidative damages and efficiently repairs its damage to DNA. Cancer and aging cells die due to oxidative damage in human cells. Experiments are going on to study whether the properties of this bacterium can be applied to the human cells also to prevent it from oxidative damages. The ability of protection of D. radiodurans against oxidative damage can be harnessed to this crucial process, to delay aging and prevent cancer and other age-related diseases.

Conflicts of interest: Nil

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Global Role of Low Molecular Weight Nucleic Acids in Biological Systems

By Zemskov, V.M., Neymann, V., Zemskov, A. M. & Pronko, K. N.

Abstract- Some considerations and reports are made regarding personal scientific developments carried out by author V.M. Zemskov in partnership with colleagues team and my close colleague prof. Zemskov A.M. for many years, specifically, 50 years. This is a problem, to which almost entire life has been devoted. It relates to a completely new global consistent pattern that we managed to stumble upon in those distant years, and that is implemented in any biological systems - whether it's a higher or a lower organism, a human being, or various microbial and cellular populations. Realized by low molecular weight RNA or oligonucleotides of RNA.

Keywords: low molecular weight RNA, bacterial and cellular populations, immunity, metabolism, infectious and somatic diseases.

GJMR-C Classification: NLMC Code: QW 4

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Keywords: low molecular weight RNA, bacterial and cellular populations, immunity, metabolism, infectious and somatic diseases.

I. Introduction

Somewhere in late sixties (1967-1968) I and my colleagues drew attention to several works of Dr. Werner Braun where it was demonstrated that DNA fragments (oligonucleotides, not nucleosides) addition to various microbial populations led to substantial changes within such populations that included the intensification of microorganisms reproduction and selection of virulent cell clones, even if initially their concentration was 0.001 %.

After a short time, populations turned out to be almost 100% virulent, whereas Dr. Braun even managed to find out several mechanisms of this process - predominant virulent cells selection in a mixed population, the formation of factors which suppressed bacteria avirulent clones reproduction, microbes respiration intensification, increased kinase systems activity, etc. The same phenomenon arose if along with microbes, DNA specimens were introduced into the body, which was the source of their kinase systems activation, etc. This phenomenon also emerged if, along with microbes, DNA specimens were introduced into the body, which source was not of importance. Moreover, if DNA specimens were introduced into animals before infection, they developed a strong resistance to several microbes infection, and if drugs were introduced together with various antigens, the immune response was enhanced. The same idea of immuno-enhancing (adjuvant) action of DNA specimens was confirmed by Dr. Nakano, Johnson, Schmidtke, et al.

I became very interested in this issue and started research in related spheres, but along with the application of various high or low molecular weight RNA obtained from yeast fungi, different animal organs, transfer RNA, informational RNA, or high molecular weight RNA, decomposed by RNases (ribonucleases). I tried to maximize the purification of RNA specimens by different methods and obtained extremely pure specimens, which didn't contain protein, DNA, or polysaccharides impurities. These specimens' activity even enhanced.

a) Microbial populations alterations and infection worsening

Me and my colleagues have established (Zemskov, 1969; 1970a,b; 1972; 1974b; 1975a; 1977c; Zemskov VM and Zemskov AM,1992a; Zemskov et al., 1974a; 1977a,b; 1978a,b; 1985a; 2007) that various RNAs also have potent affection microbial populations (list of key publications related to this issue is outlined). They caused the acceleration of reproduction of the following microorganisms in vitro- St. aureus, albus, and No. 209, Shigella flexneri, boydii, and sonnei, Y. pestis (vaccine strain), leptospira, causative agents of tularemia, Francisella, E. coli, salmonella, anaerobic bacteria, conditionally pathogenic enterobacteriaceae, Candida albicans, perfect fungi. If the control leptospira grew to a maximum concentration on the nutrient medium without causing turbidity in it for about a week, with the addition of RNA, the medium became cloudy after a day, and the concentration of microorganisms was maximum. The same happened with slowly growing tularemia pathogens. When cultivating bacteria in the medium with RNA, the increase of their virulence and antigenicity was observed. Moreover, virulent microorganisms turned out to have a larger response to specimen, weakly virulent and conditionally pathogenic, appeared to be less responding. In contrast, to control cultures which quickly died and lost their virulent properties, more effective bacteria survival and typical properties preservation was noted in annual storage in the RNA-containing mediums. Same processes developed in animals' bodies if they were infected with

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staphylococci, Shigella, pathogenic Escherichia coli, salmonella, and other pathogens. There was a tremendous acceleration of the lethal infection clinical course, an increase in the number of microbes in organs, and produced toxins. If mice were intradermally infected with a specifically titrated small dose of toxicogenic staphylococcus (strain 0-15), which didn't cause skin lesions, in case if staphylococcus was administered with RNA - extensive skin necrotic lesions developed. Passaging of pathogenic E.coli and Shigella at the same time with RNA via mouse organism led to the sharp increase of microbe virulence compared with passaging without RNA. Passaging of three aforementioned Shigella strains in RNA-containing medium significantly increased the microorganisms sensitivity to antibiotics such as laevomycetin (chloramphenicol), tetracycline, penicillin, streptomycin.

Such a wide list of microorganisms exposed to RNA could not be accidental and demonstrated only the fact that this phenomenon is universal and wide spread, possibly plays a significant role in the development of infections in the body and even in some biological aspects.

b) Tachyphylaxis induction and immune response enhancement

Our further works (Zemskov,1975b; Zemskov AM and Zemskov VM, 1992b; 1995b; Zemskov VM and Zemskov AM, 1992a; Zemskov et al., 1977a; 1978b; 1985a; 2007; 1978c; 1979; 1981a; 1988; 1989; 1995a; 2019; Kochergina et al., 1986) allowed to find out that RNA specimens from various sources turned out to be interferonogenes that were clearly shown, and caused a state of increased resistance to different viruses — we showed this on the mouse influenza viruses APR8, western and eastern encephalomyelitis in horses, and tick-borne encephalitis which mice were infected with. Oral and intranasal specimen administration routes turned out to be effective. RNA specimens created animals' resistance to most diverse pathogenic and highly pathogenic microorganisms – I have revealed that at following microorganisms - E.coli, pathogenic Salmonella (Typhimurium, enteritidis, typhi abdominalis), Shigella, Staphylococcus, Proteus vulgaris, Kl. Pneumoniae, B. subtilis, cholera vibrio, actinobacillus mallei, and pseudocolor, Pseudomonas aeruginosa, then it was demonstrated by my followers and students using other infection models. It is important that increased resistance to infection by pathogenic microorganisms occurred already 4 hours after drug administration and persisted for 72 hours after a single injection. Repeated administration of RNA specimens was not accompanied by the emergence of drug tolerance; their effectiveness only increased. Using very low doses of RNA, but many times, it was possible to reduce the stimulator dose by 100 times while maintaining its effectiveness. The oral route of administration has proved quite effective.

i. *Detoxification of bacterial toxins, elimination of toxicity of hormones, cytostatics, antibiotics*

It was revealed that RNA specimens suppress microbes reproduction in tissues, neutralize bacterial toxins, activate antibacterial defense factors - both cell-mediated and humoral, increase body ability to detoxify toxins. Conducting specific studies (Zemskov VM and Zemskov AM, 1992a; Zemskov et al., 1978b; 1985a; 1984a; Bogdanova, 1980), we managed to prove that RNA led to bacterial exotoxins neutralization (gas gangrene pathogen toxin, staphylococcus hemolysin, pathogenic E. coli endotoxins) in case of specimen administration before and even after already happened organism intoxication. Significantly, RNA oral administration turned out to be most effective.RNA removed the toxicity of hormones (prednisone), cytostatics (cyclophosphamide), antibiotics (penicillins), antihistamines (diphenhydramine), bacterial polysaccharides, etc. It was possible to demonstrate using not only animals but in the clinical practice as well, which I will further speak about.RNA specimens increased sensitivity to various antibiotics, and therefore their administration with RNA allowed a sharp decrease in the dose of antibiotics with the same or even greater effect. By the way, in the treatment of people with severe lung diseases or some autoimmune diseases, it was possible to completely remove the toxic effect of drugs (hormones, cytostatics) and "transform," for example, hormone-dependent bronchial asthma into hormone-independent, i.e., completely refuse from hormones use.

ii. *Immune response enhancement*

RNA (Zemskov, 1975b; Zemskov AM and Zemskov VM, 1992b; Zemskov et al., 1977a; 1978b,c; 1981a; 1985a; 1988; 1989; 1995a; 2007; 2019; Kochergina et al., 1986)enhanced formation of the immune response to the soluble (typhoid Vi antigens, tetanus toxoid) and corpuscular (sheep erythrocytes, bacterial corpuscular vaccines) antigens - antibody formation increased, they appeared earlier and lasted longer, transplantation immunity increased when donor skin was transplanted to recipients, "delayed-type hypersensitivity" (sheep erythrocytes antigens, methylated bovine serum albumin), and the manifestation of "immediate hypersensitivity" in the model of anaphylactic shock decreased, therefore, RNA in the future was useful in various manifestations of allergies. The same immune response was achieved by using a combination of RNA with a 2-3-fold lower dose of the vaccine than without RNA, and significantly restored immunity after X-rays exposure of animals and increased cellular immunity in low-response (red blood cells) BALB\c inbred line mice to level of highly responsive animals of the CBA inbred line that cannot be done without RNA. Therefore, in this case, it was

possible to carry out the phenotypic correction of a low immune genetically determined response. The mechanism of the adjuvant action of RNA consisted in the formation of a complex with antigens and their facilitated penetration into macrophages that process antigens because RNA is polyanionic and electrostatic charge substance; in enhancing the migration and cooperation of T- and B-lymphocytes and bone marrow stem cells, protein synthesis, activation of T-helpers and precursors of T- and B-cells, suppression of antigen-specific T-suppressors.

iii. *Metabolism intensification*

Strong activation of phagocytic cells was noted (Zemskov AM and VM, 1987; Zemskov VM and AM, 1992a; Zemskov et al., 1985a; 2007; 1981a,b; 1985b,c; Shcherbakova et al., 1981) macrophages and neutrophils – increase of their spontaneous migration, pathogenic microorganisms killing, pinocytosis and phagocytosis, oxygen metabolism, expression of Fcγ receptors and integrin adhesion molecules, spreading on the substrate and adhesion, activation of enzymes involved in oxidative metabolism and cell detoxification (glutathione peroxidase) and enzymes of oxidative phosphorylation, glycolysis, Krebs cycle, urea cycle, and amino acids catabolism, hexose monophosphate shunt, lysosomal hydrolases and phosphatases, NAD-dependent dehydrogenase, mitochondrial enzymes and enzymes of fatty acid metabolism, etc. Macrophages increased in size; polyribosomes, mitochondria, and lysosomes increased in number. RNA specimens caused a very rapid migration of neutrophilic phagocytes into the bloodstream from the depot of the body, the number of which could be increased in animals in as little as 90 minutes after oral administration.

c) Clinical efficiency

It is clear that having discovered such powerful "biodynamic effects" (the term was introduced by Werner Brown) of RNA, we tried to find its officinal drugs in the Russian Pharmacopoeia and apply them in the clinical practice. Such a drug was found - it turned out to be sodium nucleinate, which was a sodium salt of low molecular weight yeast (baker's yeast used in the baking industry) RNA and was used to combat agranulocytosis and leukopenia. At that time, nothing was known about the immunomodulatory properties of this drug.

We prepared new pharmacopoeial instruction for Pharmacology Russian Committee and have confirmed it. By now (Zemskov VM and Zemskov AM, 2014a; Zemskov et al., 1989; 1995a; 1982a,b; 1993; 1994a,b,c; 2000; 2013; 2014b; 2016a; Kanchurina et al., 1995;Mayorov et al., 1992;Provotorov et al., 1984; Revishvili et al., 2018b) we have conducted very extensive clinical studies of actually 30 various disease nosological entities with participation of more than 10 000 patients.Nosology is very wide - chronic and acute infectious bacterial and viral diseases (pneumonia, bronchitis, acute respiratory viral diseases, sexually transmitted infections, simple and genital herpes, cytomegalovirus infection and infection caused by Epstein-Barr viruses, hepatitis), autoimmune processes, various inflammations, immunodeficiencies, surgical complications, and mental illnesses, skin diseases, pyoderma and furunculosis, slow viral infections, delayed tissue regeneration, trophic ulcers, stomach, and intestinal ulcers, allergies (bronchial asthma, asthmatoid bronchitis), chronic fatigue syndrome, intestinal dysbiosis, cirrhosis of the liver and alcoholism, male impotence, diabetes. We apply methods of so-called alternative therapy that consist of simultaneous application of immunosuppressive drugs and RNA specimens that allow reducing doses of antibiotics, hormones, cytostatics, toxic medicinal drugs, and decrease or completely reduce toxic impact of all drugs above without general treatment efficiency deterioration. This approach has proven itself in the treatment of severe autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, glomerulonephritis, bronchial asthma, multiple sclerosis). Of course, we have published a large number of reports, about 25 scientific monographs. This specimen is commonly used in Russia.

We quite succeeded in the prevention of acute respiratory viral diseases in military contingents, in hazardous industries - organic synthesis enterprises, “hot” shops, chemical plants, electrolysis production, child care facilities, etc. A huge advantage of RNA specimens is the practical absence of contraindications and side effects; the fact that they are natural components of our body and the foods we take daily, all without exception contain RNA; RNA specimens are also administered orally. These specimens are small RNA fragments that do not carry genetic information and, in this respect, are completely safe.

d) Non-genetic heuristic role of low molecular weight nucleic acids. New conception

It seems that nature “invented” a compound that is not by chance present in all cells and organs of living creatures, in soil, food, water and air, microbial communities - and performs an important regulatory and creative role in biological systems. It is the ubiquity of these substances, their extensive and universal properties that make us assume this most important key function (not counting the determining genetic information !!) that is not yet fully understood and known by us, but which most likely participates in maintaining homeostasis, evolutionary processes, development, aging, etc. The content of nucleic acids (Zemskov AM and Zemskov VM, 1995b; Zemskov VM and Zemskov AM, 1992a; Zemskov et al., 1985a; 1995a) in food products is quite high, especially in animal products - in fish - 1.6%, beef liver - 24 %, pig kidney - 2.7%, etc. A

person with a balanced diet receives about 1 g of nucleic acids per day. Nucleic acids in the soil are in a free state, unlike the cells - this means that the information fund of the biosphere is not inactive but performs an important function. There is an opinion that there is a complete exchange of information between all living things without their taxonomic restrictions (Zemskov et al., 1995a). It is very important that RNA molecules "combine" genetic, protein-synthetic, and enzymatic functions, and this is the deepest meaning of their participation in the exchange of information, processes of evolution, differentiation, and reproduction of cells, and other key processes.

It would seem that in microbial populations and the animal organism the effects of RNA are "opposite" - however, this assumption is erroneous and confirms only one thing - the mechanism of action of RNA is universal, and uniform at all levels — microbial populations change because their reproduction period is on average about 20 minutes, and somatic cells of the body - 24 hours. That is why, if microbes enter the body along with RNA, they multiply rapidly, causing infection, while somatic cells do not have time to strengthen their antimicrobial and immune power that requires a genetically programmed time. If the drug is administered before infection in a few hours, the cells manage to migrate, multiply, increase their functional activity, and then the microbe enters the prepared body and is not able to break through the immune defense.

Years of experience in this direction led me and my employees to a certain universal concept (Zemskov, 1970b; ZemskovAM and Zemskov VM, 1992b; 2016b; Zemskov VM and Zemskov AM, 2014a; Zemskov et al., 1984a; 1985a; 2007; 2019; 1994b; 2014b; Revishvili et al., 2018a,b), built based on non-genetic and non-informational properties of RNA and DNA that, it seems to me, may lead to completely unexpected and fundamental knowledge in the field of biology and medicine and new ideas about the development of infections, immune response, tissue homeostasis, etc. This approach may be marked by the development of completely new methods of treating infectious diseases that are not associated with either an effect on microorganisms or the body's immune system. It can also lead to the creation of fundamentally new therapeutic approaches that may be based on directed transport of activated body cells to foci of infection, pathology, or cancer targets. In this regard, I have already carried out preliminary experiments that confirm the correctness of the idea. Although, of course, there is still much work to do.

Unfortunately, due to objective circumstances, I have not yet managed to complete these final works.

However, there is no doubt that this problem will still arise, and it will be resolved in the future.

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An Analytical Study of Discarded Units of Whole Blood and its Components in a Blood Bank at a Tertiary Care Hospital in Vadodara

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Abstract- *Background*: Blood is precious and there is no alternative for human blood. Proper utilization as well as rationale use of blood is necessary with minimal discarding of blood units and implementing various interventions that can be used to optimize blood and its components use by training and education.

Aim: An analytical study of discarded units of whole blood and its components in a blood bank at a Tertiary care hospital in vadodara.

Study designs and methods: Data on the number of discarded whole blood units and its components, reasons for discard, number of blood components processed as well as the number of collected blood units were obtained from blood bank records and registers. The data obtained was analyzed.

Results: The total number of blood units collected from Jan 2016 to Dec 2018 was 13249 from which 36447 units of components were prepared. The total number of discarded whole blood units and its components was 5097.

GJMR-C Classification: *NLMC Code: WF 330*

Strictly as per the compliance and regulations of:

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Ashu Dogra [α] & Devanshi Gosai [σ]

Abstract- *Background:* Blood is precious and there is no alternative for human blood. Proper utilization as well as rationale use of blood is necessary with minimal discarding of blood units and implementing various interventions that can be used to optimize blood and its components use by training and education.

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Results: The total number of blood units collected from Jan 2016 to Dec 2018 was 13249 from which 36447 units of components were prepared. The total number of discarded whole blood units and its components was 5097. Platelets recorded the highest discard rate of 35.11% (3629/5097 units). Non utilization was the major cause of discard at 69.06% (3520/5097 units). Other causes of discard included TTI positivity 13.06% (666/5097 units), leakage 11.69% (596/5097 units), lipemic 2.29% (117/5097 units), underweight 0.58% (30/5097 units), clotted 0.54% (28/5097 units) and haemolysis 0.51% (26/5097 units).

Conclusion: Properly implemented blood transfusion policies, training of staff notification of permanently deferred donors will help in discarding less number of blood bags from collected units. These discarded bags, because they are unutilized are both financially as well as socially harmful to blood bank.

I. Introduction

Blood Transfusion services play a significant role in Patient management. Therefore a well organized and efficient Blood transfusion services is a prerequisite for better patient care, which could contribute towards the development of health care in the country.(1)

In resource constraint settings like ours, there is a requirement of blood after every 2 second, and therefore policies should be made about more judicious use of blood. Both medical and surgical specialists require a steady supply of blood from healthy voluntary blood donors. Rational use of blood and its components is the need of hour, since each unit is precious. Discard rate of Blood is also one of ten quality indicators defined by National Accreditation board of standards and Health care and reflects quality assurance of system (2), (3).

The blood bank needs to put enormous efforts to collect a sufficient amount of safe blood from voluntary non remunerated, healthy, and low- risk donors. Since blood can't be manufactured artificially therefore, efficient use of resources is required to collect human blood and preparation of its components. (4)The aims of present study is to analyze the discard rate of blood and its components and thereafter educate, train the staff, and introduce new measures to minimize the discard rate of blood to a reasonable value.

II. Material and Methods

Study design: A Retrospective study was carried out in the blood bank of Tertiary care hospital involving analysis of discard rate of whole blood and its prepared components for a period of three years, i.e., from Jan 2016 to Dec. 2018.

Inclusion criteria: After complete Medical history and brief clinical examination by medical officer, Blood donors fulfilling WHO criteria for donor selection are included in present study. The donors included in the study are replacement and voluntary donors.

Data collection: Data required for study retrieved from Blood Bank Registers. Information collected for the study involved mainly

Daily total number of blood collections.

Daily total number of blood components prepared.

A Number of units of various components discarded and the reason for discard.

III. Data Analysis

Screening of Blood bags are done for TTI Infections. Seroreactive blood bags are discarded. Expired blood bags due to non utilization, failed tap or quantity not sufficient collected from donors, because of any reasons, including donor reactions are discarded. Other reasons included, signs of hemolysis, leakage or tear during centrifugation, clotted blood, lipemia and greenish colored plasma.

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Statistical Analysis: Descriptive statistical methods were used to analyze the data.

IV. Results

The total numbers of blood units collected from Jan 2016 to Dec 2018 were 13,249. (Table no. 1) All the collected blood units are screened and processed for the preparation of blood components. The percentage of blood kept as whole blood was 0.77%.The total number of blood components prepared was 36,477.

Rates of discarded blood

In present study the overall discard rate observed was 13.87%. Amongst it the highest discard is observed for platelets 35.11%, for whole blood is 26.5%, PCV 2.57%, FFP and Frozen plasma 8.18%. The lowest rate of discard observed for cryoprecipitate and SDPs (Table no.1)

Table 1: Distribution numbers of prepared and discarded blood and its components.

Blood and blood components	Number of Blood & its components prepared	Number of blood discarded	Discard Rate (%)
Whole Blood	279	74	26.5
PCV	12,970	333	2.57
FFP and Frozen plasma	12,970	1061	8.18
Platelets	10,335	3629	35.11
Cryoprecipitate	198	Nil	0
SDP	4	Nil	0

Definition of Discard rate:

Number of (whole Blood, RBC, Platelet, FFP, cryoprecipitate) discarded

---------- x 100

Number of (whole blood, RBC, Platelet, FFP, cryoprecipitate) Prepared

Reasons for discarded blood components:

The Blood Bank followed WHO guidelines as standards for discard of blood and its components as shown in *Table 2*. (1)

Table 2: Explanations of the reasons for discarding

Reasons of discard blood and blood components	Explanation
Red cell contamination	Occurs during production and results from ineffective separation of red cells and platelets or plasma
Leakage in bag	That is already opened or broken
Underweight bag	Less than 10% of blood bag standard volume respectively
Lipemia	Excessive amount of fatty substances (lipids) in the blood including cholesterol and triglycerides.
Haemolysis	Break down of red cell membranes and the subsequent release of free haemoglobin
Icterus	Yellow discoloration due to high bilirubin content in blood.
Clots	Clots are formed in blood due to activation of clotting processes and can be a mixture of clotting proteins and platelets.

Distribution of discarded blood with reasons is as shown in *Table no.3.*

Table 3: Summarizes the Reasons of discarded blood and blood components

Blood and its component	RBC Contami-nation (%)	Leakage (%)	Lipemic (%)	Under weight (%)	Clotted (%)	Haemolysis (%)	TTI (%)	Expired (%)	Total
Whole Blood	-	12	8	30	10	14	-	-	74
PCV	-	06	-	-	18	12	285	12	333
FFP	56	329	69	-	-	-	285	-	1061
Frozen plasma	33	249	40	-	-	-		-	
Platelets	25	-	-	-	-	-	96	3508	3629
Cryoprecipitae	-	-	-	-	-	-	-	-	-
Total	114 (2.23%)	596 (11.69%)	117 (2.29%)	30 (0.58%)	28 (0.54%)	26 (0.51%)	666(13. 06%)	3520 (69.06%)	5097

No blood unit discarded because of overweight, Greenish appearance or Icterus

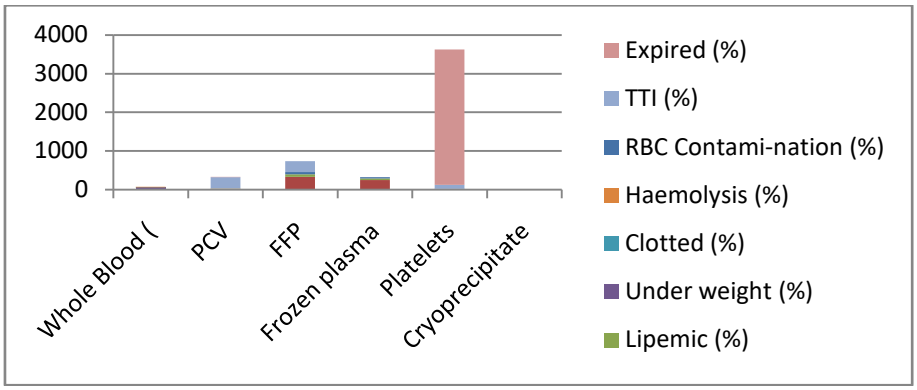

Figure 1: Summarizes the reasons for discard of whole blood and its components

The main reason for discard of blood and Blood component at our centre was expired units, which accounted for 69.1%, TTI reactive units accounted for 13.1% and the third reason is leakage at 11.7%. Other reasons for discard are less than 5%.

The significant reason for discarding whole blood is underweight which accounted for 0.59%. The major reason for discarding packed cells is TTI positivity which accounts for 5.6%.

Most of platelets discarded at our centre due to expiry. FFP are discarded due to leakage and TTI.

V. Discussion

From January 2016 to December 2018, a total of 279 whole blood and 36,447 blood components prepared. Of these, 5097 (13.86%)(%) units were discarded. There are many reasons for discard like expiry due to non utilization, seropositivity to TTIs, leakage observed as the most common causes of blood and components. *Table 4* shows a comparison of reasons for discarding whole blood and components in various published studies with the present study.

Table 4: Shows comparison of reasons for discarding whole blood and components in various published studies with present study

Study	Number of units collected	Number of units discarded%	TTI Positive %	Expired %	Less quantity %	Leakage %	Others %
Deb et.al				242 (14.61%)			
Morish et.al	390634	8968(2.3%)			353 (3.9%)	2306 (25.7%)	6309 (70.4%)
Kumar et.al	10582	888(8.4%)	300 (33.8%)	513 (57.8%)	18 (2.0%)	27 (3.0)	20 (3.4%)
Patil et.al	14,026	2888(20.6%)	953 (33.0%)	1531 (53%)	48 (1.7%)	97 (3.4%)	186 (6.4%)
Present study	13249	5097	666 (13.06%)	3520 (69.06%)	30 (0.58%)	596 (11.69%)	285 (5.59%)

In a study done by Deb etal., (5) an average of 292(14.61%) bags from the total collection were discarded, and out of this 292 units, non utilization contributed to 242 units. Various protocols that can reduce the rate of expiry of blood units are:-1) Proper management of Rh-negative units since there requirement is less ,2) To arrange blood units of near expiry, and maintenance of proper inventory management in blood bank.(6) The Second most common cause of discard, was seropositivity to TTI, which accounted for 13.06%. complete screening of donor is key factor to avoid wastage.

Platelets concentrate scored the highest at 3629/ 5097 (71.1%) when compared with other blood components. The reason behind discard being short shelf life of 5 days and red cell contamination.(7) In the present study 25/114 (21.9%) platelets and 89/114 (78%) of plasma was wasted due to red cell contamination. In similar study, by Morish et al., RBC Contamination of platelet concentrate was the main reason behind discard. (8)

Another main cause of discarded blood and blood components was leakage 596 (11.69%) seen in mainly FFP and Plasma units. In a similar study by Kumar et al. discard due to leakage was 26%. (9).The main reasons for leakage noticed were due to the mishandling of blood bags during storage or manufacturing errors. Another reason for leakage was

seen during the centrifugation process, as it happens because the blood bag is forced to sharp interior bottom/wall junction or corner, resulting in bag material being stretched too far, causing a tear. Always visually check the blood bags for any defect/leakage during processing, before freezing, and after thawing. It is recommended to store plasma and FFP in polystyrene protective bags to minimize the risk of breakage of FFP during storage, handling and transportation.

Another next reason for discard of blood and its components observed was gross lipemia 117 (2.29 %). Lipemic blood units interfere with the ability to perform viral marker tests, and hence the units are discarded. (10) Doctors and nurses during predonation should interview carefully, the history of donors for intake of fatty meal before coming to donate blood.

0.58% (30 Bags) were discarded due to underweight. Various reasons responsible for low volume collected can be due to discontinuation of blood donation as donors suffered adverse donor reactions, small vein selected for phlebotomy, and duration exceeded by 15 minutes. The discard rate due to underweight bags can be reduced by careful selection of donor, training and monitoring, the staff involved in donation procedures.

VI. Conclusion

TTI and expired blood units are mostly responsible for high discard rate. Platelets are the highest amongst discarded components. Discard due to nonutilization of blood components can be financially as well as socially harmful to blood bank.

We conclude our study with the following recommendations:

1. Donor history questionnaire should be conducted properly
2. TTI Positive donors should be notified for there permanent deferral
3. Hospital transfusion committee meetings and transfusion policies should be made from time to time to promote rational use of Blood and components.
4. Whole blood collected should be kept to minimum to prevent expiry and non utilization.
5. Networking and interlinking with other blood banks to outsource excess blood n components can prevent wastage.

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Her2/Neu Overexpression in Gastric Cancer and its Correlation with Histopathological Grade and Subtype

By Dr. Kuldeep Kaur, Dr. Molly Joseph, Dr. Jagriti Yadav,
Dr. Hema Goyal & Dr. Richa Jindal

Abstract- Gastric cancer is one of the leading causes of cancer mortality in the world. At advanced stage majority of cases are diagnosed. The survival rate of patients with advanced unresectable gastric cancers remains poor despite new treatment strategies, such as perioperative chemotherapy or adjuvant chemoradiation [1]. In certain gastric tumors added therapy gives superior survival benefits. One such targeted protein of interest is HER2 /neu. We have undertaken this study to evaluate the overexpression of HER-2/Neu gene in gastric cancer and its correlation with several pathological features.

Keywords: gastric adenocarcinoma, grade and subtype, her2/neu overexpression, immunohistochemistry, her 2 scoring in gastric cancer, trastuzumab.

GJMR-C Classification: NLMC Code: QW 4

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Her2/Neu Overexpression in Gastric Cancer and its Correlation with Histopathological Grade and Subtype

Dr. Kuldeep Kaur [α], Dr. Molly Joseph [σ], Dr. Jagriti Yadav [ρ], Dr. Hema Goyal [ω] & Dr. Richa Jindal [¥]

Abstract- **Gastric cancer is one of the leading causes of cancer mortality in the world. At advanced stage majority of cases are diagnosed. The survival rate of patients with advanced unresectable gastric cancers remains poor despite new treatment strategies, such as perioperative chemotherapy or adjuvant chemoradiation [1]. In certain gastric tumors added therapy gives superior survival benefits. One such targeted protein of interest is HER2 /neu. We have undertaken this study to evaluate the overexpression of HER-2/Neu gene in gastric cancer and its correlation with several pathological features.**

Keywords: gastric adenocarcinoma, grade and subtype, her2/neu overexpression, immunohistochemistry, her 2 scoring in gastric cancer, trastuzumab.

I. Introduction

Gastric cancer is one of the leading causes of cancer mortality in the world, with the majority of cases presenting at an advanced stage. Gastric cancer is the fifth most common cancer overall and it is the third most common cause tumor-related deaths globally [1].The incidence of gastric cancer in India is 10.6 per 100000 population [2].

The mainstay of treatment is surgical resection and can cure patients with early-stage cancer. The survival rate of patients with advanced resectable gastric or gastroesophageal junction (GEJ) tumors, however, remains poor despite new treatment strategies, such as perioperative chemotherapy or adjuvant chemoradiation [3]. Improvements in the treatment modality of gastric cancer, including combination chemotherapy, have resulted in improved overall survival. In certain gastric tumors added therapy gives superior survival benefits.

Human epidermal growth factor receptor 2 (HER2/neu) protein is a cellular target for the added therapy. It is a growth factor of EGFR family with intrinsic protein tyrosine kinase activity and is associated with tumor proliferation, migration and differentiation. The production of HER2/neu protein, is regulated by the HER2/neu gene. Amplification of HER2/neu gene is seen at different sites like breast, stomach, colon, etc. and its overexpression is associated with poor prognosis.

Recently published data, from the randomised, prospective phase III clinical trial TOGA provided first documentation of the clinical benefit of Trastuzumab, anti-HER2/neu an antibody, when used in combination with chemotherapy in the setting of advanced gastric carcinoma [4]. The Stage is the most important prognostic factor for gastric carcinoma followed by the histological subtype and since there is limited data available on HER2/neu overexpression in gastric cancer and its correlation to histopathological stage, grade and subtype, we propose to conduct this study to evaluate the same since an accurate assessment of HER2/neu overexpression in gastric cancer patients is of great utility in the optimal selection of patients for Trastuzumab therapy.

II. Material and Methods

A total of 49 patients, with gastric carcinoma, were included in this study period of seven years (Jan 2011 to May 2018) in the Department of Pathology, St. Stephen's Hospital, New Delhi, India. The detailed clinical history and results of relevant investigations were obtained from the patient's case files. The method of study was immunohistochemistry, using the HER-2/Neu antibody.

III. Statistical Analysis

Qualitative variables are expressed as frequencies/percentages and compared between groups using Chi-square Test. Quantitative variables are expressed as mean±sd and compared across groups using ANOVA and unpaired t-test. A p-value < 0.05 is considered statistically significant. The data is analysed using Statistical Package for Social Sciences (SPSS) version 16.0 software.

Study Design: Cross-sectional study

Sample size determination:

The formula used for sample size estimation is:

$$n = z2\ P(1 - P)/d2$$

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Author σ: Head of department (St. Stephen's Hospital, Delhi).
Author ρ: Resident (St. Stephen's Hospital, Delhi).
Author ω: Senior Resident (St. Stephen's Hospital, Delhi).
Author ¥: Senior Specialist (St. Stephen's Hospital, Delhi).

IV. Result and discussion

During January 2011 to May 2018, a total of 50 samples (from 49 patients) reported as gastric adenocarcinoma on histopathological examination at St.Stephen's hospital, Delhi were included in the study.

Among 49 patients, gastric carcinoma had a peak incidence in the age group of 50 to 60 years. The oldest age of presentation was 85 years and the youngest was 24 years.

a) Demographic data in our study

Our study included 50 cases. The age of the patients varied from 24 years to 85 years, with a mean age of 57.69 years. In our study, the incidence of gastric carcinoma in males and females were 77.1% and 22.9% respectively (male: female ratio =3:1)

b) Clinical manifestations

In our study, chief complaints of patients were dysphagia (43.7%) followed by loss of appetite (35.4%), pain abdomen (33.3%), vomiting (29.2%), weight loss (22.9%), hematemesis (6.2%) and melena (4.2%). Gastric carcinoma often produces no specific symptoms when it is superficial and can be removed surgically, although up to 50% of patients may have nonspecific gastrointestinal complaints such as dysphagia, anorexia, nausea, vomiting, weight loss as well as abdominal pain that is vague and insidious.

Site

The most common site of gastric carcinoma in our study was the antral region.

Table 1: Comparison of Location of Gastric Carcinoma:

Location	H R Raziee et al. [5]	C Fondevile et al. [6]	Czyzwski J et al. [7]	Our study
Cardia	37%	7%	15.6%	6%
Body	33%	40%	20%	22%
Antrum	30%	51%	60%	52%

c) Histopathological subtype

In our study, poorly cohesive carcinoma (66%) was the most common subtype followed by tubular carcinoma (26%). However, intestinal-type was the most common subtype (Lauren's classification) according to studies done by Raziee et al.(5) and ToGA trial (4). This difference could be explained by the low sample size in our study and heterogeneity of pathological classifications. The increase in the proportion of poorly cohesive carcinoma can be explained by changes in the pathological classification systems used to characterise these cancers. Since the publication of the WHO classification of gastric cancers in 1990, signet ring cell adenocarcinoma constitutes one specific histotype and therefore can be better identified among gastric cancers. WHO 2010 further classified Signet ring cell and diffuse variety into a single group of poorly cohesive carcinoma. Previously, signet-ring cell adenocarcinoma was classified as "diffuse-type" according to Lauren's classification[8] and "infiltrative type" by Ming[9].

d) Histopathological grade

Table 2: Comparison of Histopathological Grades of Gastric Carcinoma

Grade	H R Raziee et al. [5]	Lazar et al. [10]	Fondevila et al. [6]	Our study
Well	54	3.2	4	0
Moderately	17	32.8	47	46
Poorly	29	64	49	54

In our study, poorly differentiated grade tumors were more common than other grades accounting for 54% of cases, which is similar to observations made by Lazar et al.(64%) and Fondevila et al. (49%) in their studies.

e) *Depth of Infiltration*

In our study, a higher proportion of tumours belonged to T4 subtype 63.6% which is similar to the observation made by Lazar et al [8] (approximately 50%).This is explained by later presentation of gastric carcinoma due to nonspecific symptoms and hence delayed diagnosis.

HER2 Overexpression

In our study, HER2 overexpression is noted in 20% of cases, which is similar to observations made worldwide by Marx et al.(19%), Xie et al.(18.8%), Lee et al.(17.4%), and Yoshida et al.(17%) in their studies.

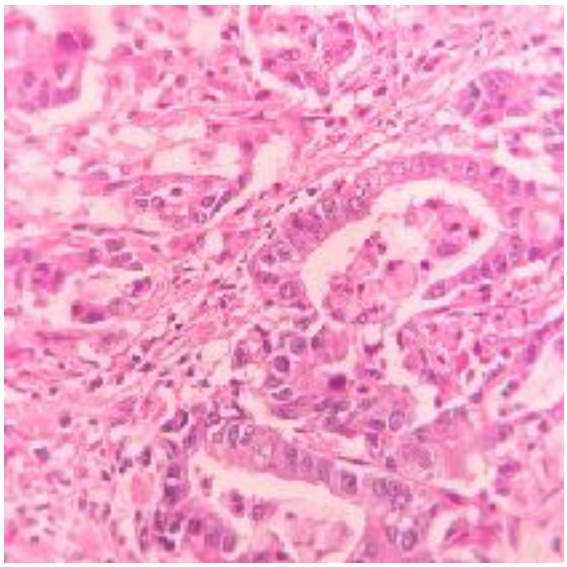
Table 3: Comparison of the rate of HER2/neu positivity in various studies

Authors	Year	Population studied	No of patients	HER2 positivity
Hofmann et al. [11]	2007	Germans	178	10.7 %
Raziee et al. [5]	2007	Iranians	100	26 %
Marx et al. [12]	2009	Germans	166	19 %
Xie et al. [13]	2009	Chinese	218	18.8 %
Lee et al. [14]	2010	Australians	178	17.4 %
Sekaran et al. [2]	2011	Indians	52	44.2 %
Lakshmi V et al. [15]	2014	Indians	78	35.9 %
Yoshida et al. [16]	2014	Japanese	207	17 %
Our study	2018	Indians	48	20%

Correlation of HER-2/Neu OverExpression with Various clinico-pathological factors.

In our study, there is no correlation between HER-2/neu overexpression and various clinicopathological factors such as age, gender, complaints, site or gross appearance in gastrectomy specimens. Increased frequency of HER-2/neu overexpression was associated with elderly age, male gender, poorly cohesive carcinoma (according to WHO subtype), moderately differentiated grade and T4 level of infiltration, but statistically insignificant.

IMAGES



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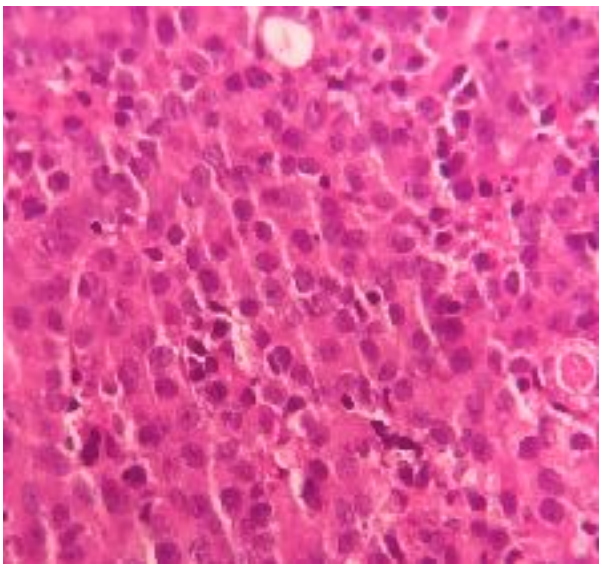

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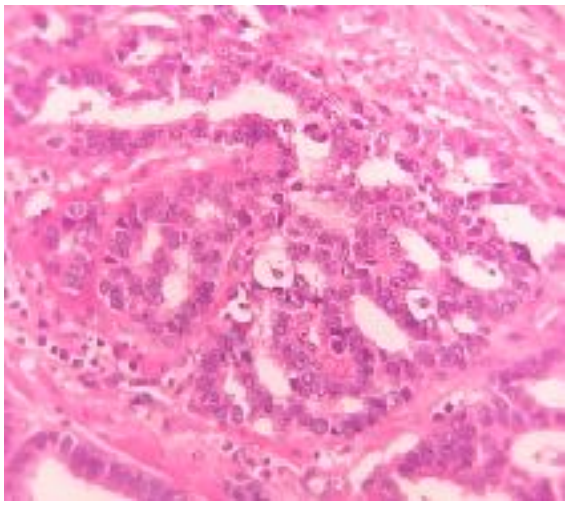

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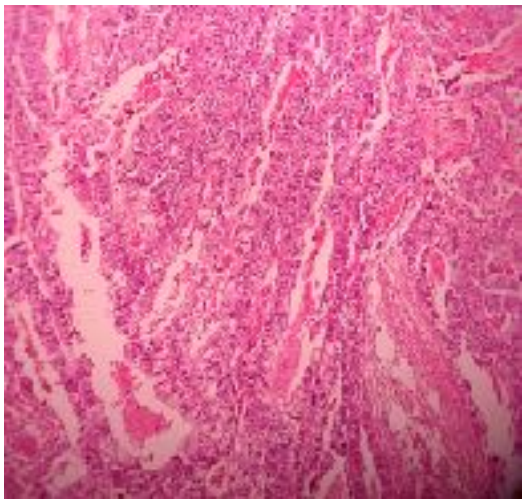

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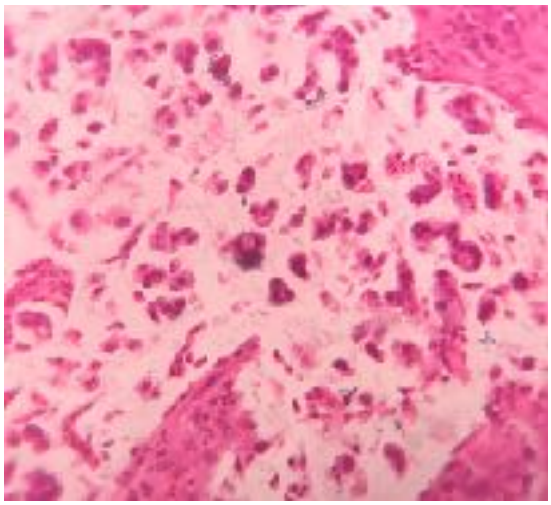

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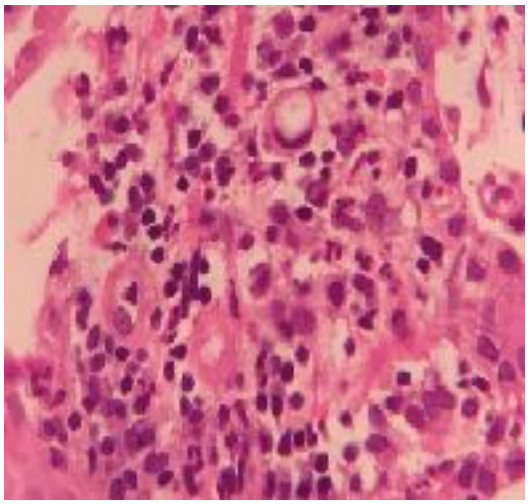
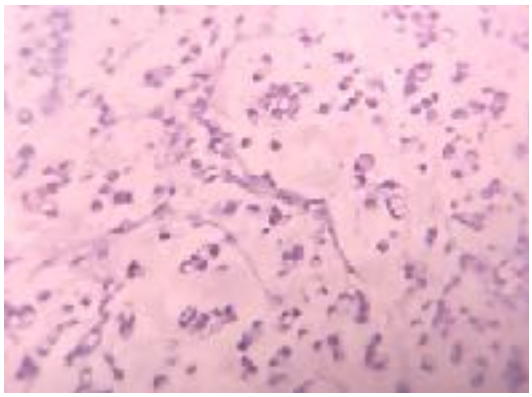


[ADENOCARCINOMA WITH SIGNET RING]



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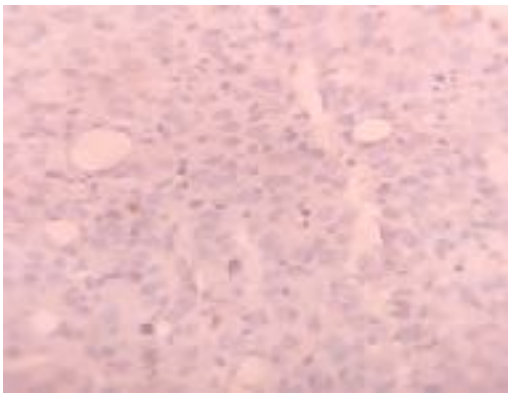
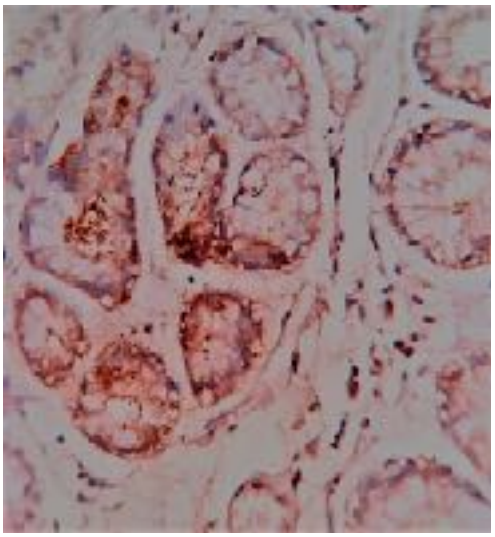
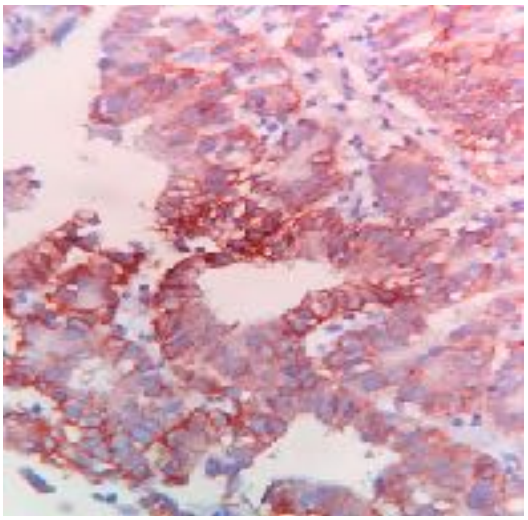


[HER2 SCORE 1 +]



[HER2 SCORE 2 +]



[HER2 SCORE 3+]

V. Conclusion

1. The present work reported that advanced age, especially in male patients is a risk factor for gastric carcinoma.
2. The percentage of HER2/neu overexpression in gastric adenocarcinoma is correlating with other studies.
3. Correlation between HER2/neu overexpression and clinico-pathological variables like age, gender, site, gross, subtype, grade and depth of tumor infiltration is statistically insignificant.
4. Majority of cases overexpressing HER 2/neu were of poorly cohesive subtype (according to WHO classification, 2010), but results were statistically insignificant.

VI. Recommendation

1. Larger sample size and follow up might shed more light on the role of HER 2/neu in gastric carcinoma. Increasing the sample size in future studies, and designing prospective studies with close observation of survival, the utility of HER2/neu overexpression as an important prognostic marker can be enhanced.
2. Geographical differences, tumor heterogeneity, differences in scoring systems, and pathologist expertise may have caused the variations in HER-2/neu positivity rates between the studies.
3. The precise role of Her2/neu in cancer development and progression need to be detected to modulate the current therapeutic approaches targeting those proteins. It is mandatory to standardize Her2/neu staining and scoring methods for accurate assessment of its role in gastric carcinogenesis and tumor progression besides avoiding the failure of molecular target therapy.

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Financial

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Associates are authorized to organize symposium/seminar/conference on behalf of Global Journal Incorporation (USA). They can also participate in the same organized by another institution as representative of Global Journal. In both the cases, it is mandatory for him to discuss with us and obtain our consent. Additionally, they get free research conferences (and others) alerts.

Career | Credibility | Financial

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We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

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3. Ensure corresponding author's email address and postal address are accurate and reachable.
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Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

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It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

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Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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