

THE BEGINNING OF BUSINESS

On May 31, 1921, the Ford Motor Company turned out Car No. 5,000,000. It is out in my museum along with the gasoline buggy that I began work on thirty years before and which first ran satisfactorily along in the spring of 1893. I was running it when the bobolinks came to Dearborn and they always come on April 2nd. There is all the difference in the world in the appearance of the two vehicles and almost as much difference in construction and materials, but in fundamentals the two are curiously alike - except that the old buggy has on it a few wrinkles that we have not yet quite adopted in our modern car. For that first car or buggy, even though it had but two cylinders, would make twenty miles an hour and run sixty miles on the three gallons of gas the little tank held and is as good to-day as the day it was built. The development in methods of manufacture and in materials has been greater than the development in basic design. The whole design has been refined; the present Ford car, which is the "Model T," has four cylinders and a self starter - it is in every way a more convenient and an easier riding car. It is simpler than the first car. But almost every point in it may be found also in the first car. The changes have been brought about through experience in the making and not through any change in the basic principle - which I take to be an important fact demonstrating that, given a good idea to start with, it is better to concentrate on perfecting it than to hunt around for a new idea. One idea at a time is about as much as any one can handle. It was life on the farm that drove me into devising ways and means to better transportation. I was born on July 30, 1863, on a farm at Dearborn, Michigan, and my earliest recollection is that, considering the results, there was too much work on the place. That is the way I still feel about farming. There is a legend that my parents were very poor and that the early days were hard ones. Certainly they were not rich, but neither were they poor.

. As Michigan farmers went, we were prosperous. The house in which I was born is still standing, and it and the farm are part of my present holding. There was too much hard hand labour on our own and all other farms of the time. Even when very young I suspected that much might somehow be done in a better way. That is what took me into mechanics - although my mother always said that I was born a mechanic. I had a kind of workshop with odds and ends of metal for tools before I had anything else. In those days we did not have the toys of to-day; what we had were home made. My toys were all tools - they still are! And every fragment of machinery was a treasure. The biggest event of those early years was meeting with a road engine about eight miles out of Detroit one day when we were driving to town. I was then twelve years old. The second biggest event was getting a watch - which happened in the same year. I remember that engine as though I had seen it only yesterday, for it was the first vehicle other than horse-drawn that I had ever seen. It was intended primarily for driving threshing machines and sawmills and was simply a portable engine and boiler mounted on wheels with a water tank and coal cart trailing behind. I had seen plenty of these engines hauled around by horses, but this one had a chain that made a connection between the engine and the rear wheels of the wagon-like frame on which the boiler was mounted. The engine was placed over the boiler and one man standing on the platform behind the boiler shoveled coal, managed the throttle, and did the steering. It had been made by Nichols, Shepard & Company of Battle Creek. I found that out at once. The engine had stopped to let us pass with our horses and I was off the wagon and talking to the engineer before my father, who was driving, knew what I was up to. The engineer was very glad to explain the whole affair. He was proud of it.

He showed me how the chain was disconnected from the propelling wheel and a belt put on to drive other machinery. He told me that the engine made two hundred revolutions a minute and that the chain pinion could be shifted to let the wagon stop while the engine was still running. This last is a feature which, although in different fashion, is incorporated into modern automobiles. It was not important with steam engines, which are easily stopped and started, but it became very important with the gasoline engine. It was that engine which took me into automotive transportation. I tried to make models of it, and some years later I did make one that ran very well, but from the time I saw that road engine as a boy of twelve right forward to to-day, my great interest has been in making a machine that would travel the roads. Driving to town I always had a pocket full of trinkets - nuts, washers, and odds ends finery.to broken watch and tried to put it together. When I was thirteen I managed for the first time to put a watch together so that it would keep time. By the time I was fifteen I could do almost anything in watch repairing - although my tools were of the crudest. There is an immense amount to be learned simply by tinkering with things. It is not possible to learn from books how everything is made - and a real mechanic ought to know how nearly everything is made. Machines are to a mechanic what books are to a writer. He gets ideas from them, and if he has any brains he will apply those ideas. From the beginning I never could work up much interest in the labour of farming. I wanted to have something to do with machinery. My father was not entirely in sympathy with my bent toward mechanics. He thought that I ought to be a farmer. When I left school at seventeen and became an apprentice in the machine shop of the Drydock Engine Works I was all but given up for lost. I passed my apprenticeship without trouble - that is, I was qualified to be a machinist long before my three-year

term had expired - and having a liking for fine work and a leaning toward watches I worked nights at repairing in a jewelry shop. At one period of those early days I think that I must have had fully three hundred watches. I thought that I could build a serviceable watch for around thirty cents and nearly started in the business. But I did not because I figured out that watches were not universal necessities, and therefore people generally would not buy them. Just how I reached that surprising conclusion I am unable to state. I did not like the ordinary jewelry and watch making work excepting where the job was hard to do. Even then I wanted to make something in quantity. It was just about the time when the standard railroad time was being arranged. We had formerly been on sun time and for quite a while, just as in our present daylight-saving days, the railroad time differed from the local time. That me a goof s ea an so I succeeded in making a watch that kept both times. It had two dials and it was quite a curiosity in the neighbourhood. In 1879 - that is, about four years after I first saw that Nichols-Shepard machine - I managed to get a chance to run one and when my apprenticeship was over I worked with a local representative of the Westinghouse Company of Schenectady as an expert in the setting up and repair of their road engines. The engine they put out was much the same as the Nichols-Shepard engine excepting that the engine was up in front, the boiler in the rear, and the power was applied to the back wheels by a belt. They could make twelve miles an hour on the road even though the self-propelling feature was only an incident of the construction. They were sometimes used as tractors to pull heavy loads and, if the owner also happened to be in the threshing-machine business, he hitched his threshing

machine and other paraphernalia to the engine in moving from farm to farm. What bothered me was the weight and the cost. They weighed a couple of tons and were far too expensive to be owned by other than a farmer with a great deal of land. They were mostly employed by people who went into threshing as a business or who had sawmills or some other line that required portable power. Even before that time I had the idea of making some kind of a light steam car that would take the place of horses - more especially, however, as a tractor to attend to the excessively hard labour of ploughing. It occurred to me, as I remember somewhat vaguely, that precisely the same idea might be applied to a carriage or a wagon on the road. A horseless carriage was a common idea. People had been talking about carriages without horses for many years back - in fact, ever since the steam engine was invented - but the idea of the carriage at first did not seem so practical to me as the idea of an engine to do the harder farm work, and of all the work on the farm ploughing was the hardest. Our roads were poor and we had not the habit of getting around. One of the most remarkable features of the automobile on the farm is the way that it has broadened the farmer's life. We simply took for granted that unless the errand were urgent we would not go to town, and I think we rarely made more than a trip a week. In bad weather we did not go even that often. Being a full-fledged machinist and with a very fair workshop on the farm it was not difficult for me to build a steam wagon or tractor. In the building of it came the idea that perhaps it might be made for road use. I felt perfectly certain that horses, considering all the bother of attending them and the expense of feeding, did not earn their keep. The obvious thing to do was to design and build a steam engine that would be light enough to run an ordinary wagon or to pull a

plough. I thought it more important first to develop the tractor. To lift farm drudgery off flesh and blood and lay it on steel and motors has been my most constant ambition. It was circumstances that took me first into the actual manufacture of road cars. I found eventually that people were more interested in something that would travel on the road than in something that would do the work on the farms. In fact, I doubt that the light farm tractor could have been introduced on the farm had not the farmer had his eyes opened slowly but surely by the automobile. But that is getting ahead of the story. I thought the farmer would be more interested in the tractor. I built a steam car that ran. It had a kerosene-heated boiler and it developed plenty of power and a neat control -which is so easy with a steam throttle. But the boiler was dangerous. To get the requisite power without too big and heavy a power plant required that the engine work under high pressure; sitting on a high-pressure steam boiler is not altogether pleasant. To make it even reasonably safe required an excess of weight that nullified the economy of the high pressure. For two years I kept experimenting with various sorts of boilers - the engine and control problems were simple enough - and then I definitely abandoned the whole idea of running a road vehicle by steam. I knew that in England they had what amounted to locomotives running on the roads hauling lines of trailers and also there was no difficulty in designing a big steam tractor for use on a large farm. But ours were not then English roads; they would have stalled or racked to pieces the strongest and heaviest road tractor. And anyway the manufacturing of a big tractor which only a few wealthy farmers could buy did not seem to me worth while. But I did not give up the idea of a horseless carriage. The work with the Westinghouse representative only served to

confirm the opinion I had formed that steam was not suitable for light vehicles. That is why I stayed only a year with that company. There was nothing more that the big steam tractors and engines could teach me and I did not want to waste time on something that would lead nowhere. A few years before - it was while I was an apprentice I read in the World of Science, an English publication, of the "silent gas engine" which was then coming out in England. I think it was the Otto engine. It ran with illuminating gas, had a single large cylinder, and the power impulses being thus intermittent required an extremely heavy fly-wheel. As far as weight was concerned it gave nothing like the power per pound of metal that a steam engine gave, and the use of illuminating gas seemed to dismiss it as even a possibility for road use. It was interesting to me only as all machinery was interesting. I followed in the English and American magazines which we got in the shop the development of the engine and most particularly the hints of the possible replacement of the illuminating gas fuel by a gas formed by the vaporization of gasoline. The idea of gas engines was by no means new, but this was the first time that a really serious effort had been made to put them on the market. They were received with interest rather than enthusiasm and I do not recall any one who thought that the internal combustion engine could ever have more than a limited use. All the wise people demonstrated conclusively that the engine could not compete with steam. They never thought that it might carve out a career for itself. That is the way with wise people - they are so wise and practical that they always know to a dot just why something cannot be done; they always know the limitations. That is why I never employ an expert in full bloom. If ever I wanted to kill opposition by unfair means I would endow the opposition with experts. They

would have so much good advice that I could be sure they would do little work. The gas engine interested me and I followed its progress, but only from curiosity, until about 1885 or 1886 when, the steam engine being discarded as the motive power for the carriage that I intended some day to build, I had to look around for another sort of motive power. In 1885 I repaired an Otto engine at the Eagle Iron Works in Detroit.

No one in town knew anything about them There was a rumour that I did and, although I had never before been in contact with one, I undertook and carried through the job. That gave me a chance to study the new engine at first hand and in 1887 I built one on the Otto four-cycle model just to see if I understood the principles. "Four

cycle" means that the piston traverses the cylinder four times to get one power impulse. The first stroke draws in the gas, the second compresses it, the third is the explosion or power stroke, while the fourth stroke exhausts the waste gas. The little model worked well enough; it had a one-inch bore and a three-inch stroke, operated with gasoline, and while it did not develop much power, it was slightly lighter in proportion than the engines being offered commercially. I gave it away later to a young man who wanted it for something or other and whose name I have forgotten; it

was eventually destroyed. That was the beginning of the work with the internal combustion engine. I was then on the farm to which I had returned, more because I wanted to experiment than because I wanted to farm, and, now being an all-around machinist, I had a first-class workshop to replace the toy shop of earlier days. My father offered me forty acres of timber land, provided I gave up being a machinist. I agreed in a provisional way, for cutting the timber gave me a chance to get married. I fitted out a sawmill and a portable engine and started to cut out and saw up the timber

on the tract. Some of the first of that lumber went into a cottage on my new farm and in it we began our married life. It was not a big house - thirty-one feet square and only a story and a half high - but it was a comfortable place. I added to it my workshop, and when I was not cutting timber I was working on the gas engines - learning what they were and how they acted. I read everything I could find, but the greatest knowledge came from the work. A gas engine is a mysterious sort of thing - it will not always go the way it should. You can imagine how those first engines acted

It was in 1890 that I began on a double-cylinder engine. It was quite impractical to consider the single cylinder for transportation purposes -the fly-wheel had to be entirely too heavy. Between making the first four-cycle engine of the Otto type and the start on a double cylinder I had made a great many experimental engines out of tubing. I fairly knew my way about. The double cylinder I thought could be applied to a road vehicle and my original idea was to put it on a bicycle with a direct connection to the crankshaft and allowing for the rear wheel of the bicycle to act as the balance wheel. The speed was going to be varied only by the throttle. I never carried out this plan because it soon became apparent that the engine, gasoline tank, and the various necessary controls would be entirely too heavy for a bicycle. The plan of the two opposed cylinders was that, while one would be delivering power the other would be exhausting. This naturally would not require so heavy a fly-wheel to even the application of power. The work started in my shop on the farm. Then I was offered a job with the Detroit Electric Company as an engineer and machinist at forty-five dollars a month. I took it because that was more money than the farm was bringing me and I had decided to get away from farm life anyway. The timber had all been cut.

We rented a house on Bagley Avenue, Detroit. The workshop came along and I set it up in a brick shed at the back of the house. During the first several months I was in the night shift at the electric-light plant - which gave me very little time for experimenting - but after that I was in the day shift and every night and all of every Saturday night I worked on the new motor. I cannot say that it was hard work. No work with interest is ever hard. I always am certain of results. They always come if you work hard enough. But it was a very great thing to have my wife even more confident than I was. She has always been that way. I had to work from the ground up -that is, although I knew that a number of people were working on horseless carriages, I could not know what they were doing. The hardest problems to overcome were in the making and breaking of the spark and in the avoidance of excess weight. For the transmission, the steering gear, and the general construction, I could draw on my experience with the steam tractors. In 1892 I completed my first motor car, but it was not until the spring of the following year that it ran to my satisfaction. This first car had something of the appearance of a buggy. There were two cylinders with a two-and-a-half-inch bore and a six-inch stroke set side by side and over the rear axle. I made them out of the exhaust pipe of a steam engine that I had bought. They developed about four horsepower. The power was transmitted from the motor to the countershaft by a belt and from the countershaft to the rear wheel by a chain. The car would hold two people, the seat being suspended on posts and the body on elliptical springs. There were two speeds - one of ten and the other of twenty miles per hour - obtained by shifting the belt, which was done by a clutch lever in front of the driving seat. Thrown forward, the lever put in the high speed; thrown back, the low speed;

with the lever upright the engine could run free. To start the car it was necessary to turn the motor over by hand with the clutch free. To stop the car one simply released the clutch and applied the foot brake. There was no reverse, and speeds other than those of the belt were obtained by the throttle. I bought the iron work for the frame of the carriage and also the seat and the springs. The wheels were twenty-eight-inch wire bicycle wheels with rubber tires. The balance wheel I had cast from a pattern that I made and all of the more delicate mechanism I made myself. One of the features that I discovered necessary was a compensating gear that permitted the same power to be applied to each of the rear wheels when turning corners. The machine altogether weighed about five hundred pounds. A tank under the seat held three gallons of gasoline which was fed to the motor through a small pipe and a mixing valve. The ignition was by electric spark. The original machine was air-cooled - or to be more accurate, the motor simply was not cooled at all. I found that on a run of an hour or more the motor heated up, and so I very shortly put a water jacket around the cylinders and piped it to a tank in the rear of the car over the cylinders. Nearly all of these various features had been planned in advance. That is the way I have always worked. I draw a plan and work out every detail on the plan before starting to build. For otherwise one will waste a great deal of time in makeshifts as the work goes on and the finished article will not have coherence. It will not be rightly proportioned.

Many inventors fail because they do not distinguish between planning and experimenting. The largest building difficulties that I had were in obtaining the proper materials. The next were with tools. There had to be some adjustments and changes in details of the design, but what held me up most was that I had neither the time nor the

money to search for the best material for each part. But in the spring of 1893 the machine was running to my partial satisfaction and giving an opportunity further to ..test out the design and material on the road.

WHAT I LEARNED ABOUT BUSINESS

My "gasoline buggy" was the first and for a long time the only automobile in Detroit.

It was considered to be something of a nuisance, for it made a racket and it scared horses. Also it blocked traffic. For if I stopped my machine anywhere in town a crowd was around it before I could start up again. If I left it alone even for a minute some inquisitive person always tried to run it. Finally, I had to carry a chain and chain it to a lamp post whenever I left it anywhere. And then there was trouble with the police. I do not know quite why, for my impression is that there were no speed-limit laws in those days. Anyway, I had to get a special permit from the mayor and thus for a time enjoyed the distinction of being the only licensed chauffeur in America. I ran that machine about one thousand miles through 1895 and 1896 and then sold it to Charles Ainsley of Detroit for two hundred dollars. That was my first sale. I had built the car not to sell but only to experiment with. I wanted to start another car. Ainsley wanted to buy. I could use the money and we had no trouble in agreeing upon a price. It was not at all my idea to make cars in any such petty fashion. I was looking ahead to production, but before that could come I had to have something to produce. It does not pay to hurry. I started a second car in 1896; it was much like the first but a little lighter. It also had the belt drive which I did not give up until some time later; the

belts were all right excepting in hot weather. That is why I later adopted gears. I learned a great deal from that car. Others in this country and abroad were building cars by that time, and in 1895 I heard that a Benz car from Germany was on

exhibition in Macy's store in New York. I traveled down to look at it but it had no features that seemed worth while. It also had the belt drive, but it was much heavier than my car. I was working for lightness; the foreign makers have never seemed to appreciate what light weight means. I built three cars in all in my home shop and all of them ran for years in Detroit. I still have the first car; I bought it back a few years later from a man to whom Mr. Ainsley had sold it. I paid one hundred dollars for it.

During all this time I kept my position with the electric company and gradually advanced to chief engineer at a salary of one hundred and twenty-five dollars a month. But my gas-engine experiments were no more popular with the president of the company than my first mechanical leanings were with my father. It was not that my employer objected to experiments - only to experiments with a gas engine. I can still hear him say: "Electricity, yes, that's the coming thing. But gas - no." He had ample grounds for his skepticism - to use the mildest terms. Practically no one had the remotest notion of the future of the internal combustion engine, while we were just on

the edge of the great electrical development. As with every comparatively new idea, electricity was expected to do much more than we even now have any indication that it can do. I did not see the use of experimenting with electricity for my purposes. A road car could not run on a trolley even if trolley wires had been less expensive; no storage battery was in sight of a weight that was practical. An electrical car had of necessity to be limited in radius and to contain a large amount of motive machinery in proportion to the power exerted. That is not to say that I held or now hold electricity cheaply; we have not yet begun to use electricity. But it has its place, and the internal combustion engine has its place. Neither can substitute for the other - which is

exceedingly fortunate. I have the dynamo that I first had charge of at the Detroit Edison Company. When I started our Canadian plant I bought it from an office building to which it had been sold by the electric company, had it revamped a little, and for several years it gave excellent service in the Canadian plant. When we had to build a new power plant, owing to the increase in business, I had the old motor taken out to my museum - a room out at Dearborn that holds a great number of my mechanical treasures. The Edison Company offered me the general superintendency of the company but only on condition that I would give up my gas engine and devote

myself to something really useful. I had to choose between my job and my automobile. I chose the automobile, or rather I gave up the job - there was really nothing in the way of a choice. For already I knew that the car was bound to be a success. I quit my job on August 15, 1899, and went into the automobile business. It might be thought something of a step, for I had no personal funds. What money was left over from living was all used in experimenting. But my wife agreed that the automobile could not be given up - that we had to make or break. There was no "demand" for automobiles—there never is for a new article. They were accepted in much the fashion as was more recently the airplane. At first the "horseless carriage" was considered merely a freak notion and many wise people explained with particularity why it could never be more than a toy. No man of money even thought of it as a commercial possibility. I cannot imagine why each new means of transportation meets with such opposition. There are even those to-day who shake their heads and talk about the luxury of the automobile and only grudgingly admit that perhaps the motor truck is of some use. But in the beginning there was hardly any one who sensed that the automobile could be a large factor in industry. The most optimistic hoped only for a development akin to that of the bicycle. When it was found that an

automobile really could go and several makers started to put out cars, the immediate query was as to which would go fastest. It was a curious but natural development—that racing idea. I never thought anything of racing, but the public refused to consider the automobile in any light other than as a fast toy. Therefore later we had to race. The industry was held back by this initial racing slant, for the attention of the makers was diverted to making fast rather than good cars. It was a business for speculators. A group of men of speculative turn of mind organized, as soon as I left the electric company, the Detroit Automobile Company to exploit my car. I was the chief engineer and held a small amount of the stock. For three years we continued making cars more or less on the model of my first car. We sold very few of them; I could get no support at all toward making better cars to be sold to the public at large. The whole thought was to make to order and to get the largest price possible for each car. The main idea seemed to be to get the money. And being without authority other than my engineering position gave me, I found that the new company was not a vehicle for realizing my ideas but merely a money-making concern - that did not make much money. In March, 1902, I resigned, determined never again to put myself under orders. The Detroit Automobile Company later became the Cadillac Company under the ownership of the Lelands, who came in subsequently. I rented a shop - a one-story brick shed - at 81 Park Place to continue my experiments and to find out what

business really was. I thought that it must be something different from what it had proved to be in my first adventure. The year from 1902 until the formation of the Ford

Motor Company was practically one of investigation. In my little one-room brick shop I worked on the development of a four-cylinder motor and on the outside I tried to find out what business really was and whether it needed to be quite so selfish a scramble for money as it seemed to be from my first short experience. From the period of the first car, which I have described, until the formation of my present company I built in all about twenty-five cars, of which nineteen or twenty were built with the Detroit Automobile Company. The automobile had passed from the initial stage where the fact that it could run at all was enough, to the stage where it had to show speed. Alexander Winton of Cleveland, the founder of the Winton car, was then the track champion of the country and willing to meet all comers. I designed a two-cylinder enclosed engine of a more compact type than I had before used, fitted it into a skeleton chassis, found that I could make speed, and arranged a race with Winton. We met on the Grosse Point track at Detroit. I beat him. That was my first race, and it brought advertising of the only kind that people cared to read. The public thought nothing of a car unless it made speed -unless it beat other racing cars. My ambition to

build the fastest car in the world led me to plan a four-cylinder motor. But of that more later. The most surprising feature of business as it was conducted was the large attention given to finance and the small attention to service. That seemed to me to be reversing the natural process which is that the money should come as the result of work and not before the work. The second feature was the general indifference to better methods of manufacture as long as whatever was done got by and took the money. In other words, an article apparently was not built with reference to how greatly it could serve the public but with reference solely to how much money could

be had for it - and that without any particular care whether the customer was satisfied.

To sell him was enough. A dissatisfied customer was regarded not as a man whose trust had been violated, but either as a nuisance or as a possible source of more money in fixing up the work which ought to have been done correctly in the first place. For instance, in automobiles there was not much concern as to what happened to the car once it had been sold. How much gasoline it used per mile was of no great moment; how much service it actually gave did not matter; and if it broke down and had to have parts replaced, then that was just hard luck for the owner. It was considered good business to sell parts at the highest possible price on the theory that, since the man had

already bought the car, he simply had to have the part and would be willing to pay for it. The automobile business was not on what I would call an honest basis, to say nothing of being, from a manufacturing standpoint, on a scientific basis, but it was no worse than business in general. That was the period, it may be remembered, in which many corporations were being floated and financed. The bankers, who before then had confined themselves to the railroads, got into industry. My idea was then and still is that if a man did his work well, the price he would get for that work, the profits and all financial matters, would care for themselves and that a business ought to start small and build itself up and out of its earnings. If there are no earnings then that is a signal to the owner that he is wasting his time and does not belong in that business. I have never found it necessary to change those ideas, but I discovered that this simple formula of doing good work and getting paid for it was supposed to be slow for modern business. The plan at that time most in favor was to start off with the largest possible capitalization and then sell all the stock and all the bonds that could be sold.

Whatever money happened to be left over after all the stock and bond-selling expenses and promoters, charges and all that, went grudgingly into the foundation of the business. A good business was not one that did good work and earned a fair profit.

A good business was one that would give the opportunity for the floating of a large amount of stocks and bonds at high prices. It was the stocks and bonds, not the work, that mattered. I could not see how a new business or an old business could be expected to be able to charge into its product a great big bond interest and then sell the product at a fair price. I have never been able to see that. I have never been able to understand on what theory the original investment of money can be charged against a business. Those men in business who call themselves financiers say that money is "worth" 6 per cent, or 5 per cent, or some other per cent, and that if a business has one hundred thousand dollars invested in it, the man who made the investment is entitled to charge an interest payment on the money, because, if instead of putting that money into the business he had put it into a savings bank or into certain securities, he could have a certain fixed return. Therefore they say that a proper charge against the operating expenses of a business is the interest on this money. This idea is at the root of many business failures and most service failures. Money is not worth a particular amount. As money it is not worth anything, for it will do nothing of itself. The only use of money is to buy tools to work with or the product of tools. Therefore money is worth what it will help you to produce or buy and no more. If a man thinks that his money will earn 5 per cent, or 6 percent, he ought to place it where he can get that return, but money placed in a business is not a charge on the business - or, rather, should not be. It ceases to be money and becomes, or should become, an engine of

production, and it is therefore worth what it produces - and not a fixed sum according to some scale that has no bearing upon the particular business in which the money has been placed. Any return should come after it has produced, not before. Business men believed that you could do anything by "financing" it. If it did not go through on the first financing then the idea was to "refinance." The process of "refinancing" was simply the game of sending good money after bad. In the majority of cases the need of refinancing arises from bad management, and the effect of refinancing is simply to pay the poor managers to keep up their bad management a little longer. It is merely a postponement of the day of judgment. This makeshift of refinancing is a device of speculative financiers. Their money is no good to them unless they can connect it up with a place where real work is being done, and that they cannot do unless, somehow, that place is poorly managed. Thus, the speculative financiers delude themselves that they are putting their money out to use. They are not; they are putting it out to waste. I determined absolutely that never would I join a company in which finance came before the work or in which bankers or financiers had a part. And further that, if there were no way to get started in the kind of business that I thought could be managed in the interest of the public, then I simply would not get started at all. For my own short experience, together with what I saw going on around me, was quite enough proof

that business as a mere money-making game was not worth giving much thought to and was distinctly no place for a man who wanted to accomplish anything. Also it did not seem to me to be the way to make money. I have yet to have it demonstrated that it is the way. For the only foundation of real business is service. A manufacturer is not through with his customer when a sale is completed. He has then only started with his

customer. In the case of an automobile the sale of the machine is only something in the nature of an introduction. If the machine does not give service, then it is better for the manufacturer if he never had the introduction, for he will have the worst of all advertisements - a dissatisfied customer. There was something more than a tendency in the early days of the automobile to regard the selling of a machine as the real accomplishment and that thereafter it did not matter what happened to the buyer. That is the shortsighted salesman-on-commission attitude. If a salesman is paid only for what he sells, it is not to be expected that he is going to exert any great effort on a customer out of whom no more commission is to be made. And it is right on this point that we later made the largest selling argument for the Ford. The price and the quality of the car would undoubtedly have made a market, and a large market. We went beyond that. A man who bought one of our cars was in my opinion entitled to

continuous use of that car, and therefore if he had a breakdown of any kind it was our duty to see that his machine was put into shape again at the earliest possible moment.

In the success of the Ford car the early provision of service was an outstanding element. Most of the expensive cars of that period were ill provided with service stations. If your car broke down you had to depend on the local repair man -when you were entitled to depend upon the manufacturer. If the local repair man were a forehanded sort of a person, keeping on hand a good stock of parts (although on many of the cars the parts were not interchangeable), the owner was lucky. But if the repair man were a shiftless person, with an adequate knowledge of automobiles and an inordinate desire to make a good thing out of every car that came into his place for repairs, then even a slight breakdown meant weeks of laying up and a whopping big

repair bill that had to be paid before the car could be taken away. The repair men were for a time the largest menace to the automobile industry. Even as late as 1910 and 1911 the owner of an automobile was regarded as essentially a rich man whose money ought to be taken away from him. We met that situation squarely and at the very beginning. We would not have our distribution blocked by stupid, greedy men. That is getting some years ahead of the story, but it is control by finance that breaks up

service because it looks to the immediate dollar. If the first consideration is to earn a certain amount of money, then, unless by some stroke of luck matters are going especially well and there is a surplus over for service so that the operating men may have a chance, future business has to be sacrificed for the dollar of to-day. And also I noticed a tendency among many men in business to feel that their lot was hard - they worked against a day when they might retire and live on an income - get out of the strife. Life to them was a battle to be ended as soon as possible. That was another point I could not understand, for as I reasoned, life is not a battle except with our own tendency to sag with the downpull of "getting settled." If to petrify is success all one has to do is to humour the lazy side of the mind but if to grow is success, then one must wake up anew every morning and keep awake all day. I saw great businesses become but the ghost of a name because someone thought they could be managed just as they were always managed, and though the management may have been most excellent in its day, its excellence consisted in its alertness to its day, and not in slavish following of its yesterdays. Life, as I see it, is not a location, but a journey. Even the man who most feels himself "settled" is not settled - he is probably sagging back. Everything is in flux, and was meant to be. Life flows. We may live at the same

number of the street, but it is never the same man who lives there. And out of the delusion that life is a battle that may be lost by a false move grows, I have noticed, a great love for regularity. Men fall into the half-alive habit. Seldom does the cobbler take up with the new-fangled way of soling shoes, and seldom does the artisan willingly take up with new methods in his trade. Habit conduces to a certain inertia, and any disturbance of it affects the mind like trouble. It will be recalled that when a study was made of shop methods, so that the workmen might be taught to produce with less useless motion and fatigue, it was most opposed by the workmen themselves. Though they suspected that it was simply a game to get more out of them, what most irked them was that it interfered with the well-worn grooves in which they had become accustomed to move. Business men go down with their businesses because they like the old way so well they cannot bring themselves to change. One sees them all about - men who do not know that yesterday is past, and who woke up this morning with their last year's ideas. It could almost be written down as a formula that when a man begins to think that he has at last found his method he had better begin a most searching examination of himself to see whether some part of his brain has not gone to sleep. There is a subtle danger in a man thinking that he is "fixed" for life. It indicates that the next jolt of the wheel of progress is going to fling him off. There is also the great fear of being thought a fool. So many men are afraid of being considered fools. I grant that public opinion is a powerful police influence for those

who need it. Perhaps it is true that the majority of men need the restraint of public opinion. Public opinion may keep a man better than he would otherwise be - if not better morally, at least better as far as his social desirability is concerned. But it is not

a bad thing to be a fool for righteousness' sake. The best of it is that such fools usually live long enough to prove that they were not fools - or the work they have begun lives long enough to prove they were not foolish. The money influence - the pressing to make a profit on an "investment" - and its consequent neglect of or skimping of work and hence of service showed itself to me in many ways. It seemed to be at the bottom of most troubles. It was the cause of low wages - for without well-directed work high wages cannot be paid. And if the whole attention is not given to the work it cannot be well directed. Most men want to be free to work; under the system in use they could not be free to work. During my first experience I was not free - I could not give full play to my ideas. Everything had to be planned to make money; the last consideration was the work. And the most curious part of it all was the insistence that it was the money and not the work that counted. It did not seem to strike any one as illogical that money should be put ahead of work - even though everyone had to admit that the profit had to come from the work. The desire seemed to be to find a short cut to

money and to pass over the obvious short cut - which is through the work. Take competition; I found that competition was supposed to be a menace and that a good manager circumvented his competitors by getting a monopoly through artificial means. The idea was that there were only a certain number of people who could buy and that it was necessary to get their trade ahead of someone else. Some will remember that later many of the automobile manufacturers entered into an association under the Selden Patent just so that it might be legally possible to control the price and the output of automobiles. They had the same idea that so many trades unions have - the ridiculous notion that more profit can be had doing less work than more.

The plan, I believe, is a very antiquated one. I could not see then and am still unable to see that there is not always enough for the man who does his work; time spent in fighting competition is wasted; it had better be spent in doing the work. There are always enough people ready and anxious to buy, provided you supply what they want and at the proper price -and this applies to personal services as well as to goods.

During this time of reflection I was far from idle. We were going ahead with a four-cylinder motor and the building of a pair of big racing cars. I had plenty of time, for I never left my business. I do not believe a man can ever leave his business. He ought

to think of it by day and dream of it by night. It is nice to plan to do one's work in office hours, to take up the work in the morning, to drop it in the evening - and not have a care until the next morning. It is perfectly possible to do that if one is so constituted as to be willing through all of his life to accept direction, to be an employee, possibly a responsible employee, but not a director or manager of anything. A manual labourer must have a limit on his hours, otherwise he will wear himself out. If he intends to remain always a manual labourer, then he should forget about his work when the whistle blows, but if he intends to go forward and do anything, the whistle is only a signal to start thinking over the day's work in order to discover how it might be done better. The man who has the largest capacity for work and thought is the man who is bound to succeed. I cannot pretend to say, because I do not know, whether the man who works always, who never leaves his business, who is absolutely intent upon getting ahead, and who therefore does get ahead - is happier than the man who keeps office hours, both for his brain and his hands. It is not necessary for any one to decide the question. A ten-horsepower engine will not pull as much as a twenty. The man who keeps brain office hours limits his horsepower. If he is satisfied to pull only the load that he has, well and good, that is his affair - but he must not

complain if another who has increased his horsepower pulls more than he does.

Leisure and work bring different results. If a man wants leisure and gets it - then he

has no cause to complain. But he cannot have both leisure and the results of work.

STARTING THE REAL BUSINESS.

In the little brick shop at 81 Park Place I had ample opportunity to work out the design and some of the methods of manufacture of a new car. Even if it were possible to organize the exact kind of corporation that I wanted - one in which doing the work well and suiting the public would be controlling factors - it became apparent that I never could produce a thoroughly good motor car that might be sold at a low price

.under the existing cut-and-try manufacturing methods

Everybody knows that it is always possible to do a thing better the second time. I do not know why manufacturing should not at that time have generally recognized this as a basic fact - unless it might be that the manufacturers were in such a hurry to obtain

something to sell that they did not take time for adequate

preparation. Making "to order" instead of making in volume is, I suppose, a habit, a tradition, that has descended from the old handicraft days. Ask a hundred people how they want a particular article made. About eighty will not know; they will leave it to you. Fifteen will think that they must say something, while five will really have preferences and reasons. The ninety-five, made up of those who do not know and

admit it and the fifteen who do not know but do not admit it, constitute the real market for any product. The five who want something special may or may not be able to pay the price for special work. If they have the price, they can get the work, but they constitute a special and limited market. Of the ninety-five perhaps ten or fifteen will

pay a price for quality. Of those remaining, a number will buy solely on price and without regard to quality. Their numbers are thinning with each day. Buyers are learning how to buy. The majority will consider quality and buy the biggest dollar's worth of quality. If, therefore you discover what will give this 95 per cent. of people the best all-round service and then arrange to manufacture at the very highest quality and sell at the very lowest price, you will be meeting a demand which is so large that

it may be called universal. This is not standardizing. The use of the word "standardizing" is very apt to lead one into trouble, for it implies a certain freezing of design and method and usually works out so that the manufacturer selects whatever article he can the most easily make and sell at the highest profit. The public is not considered either in the design or in the price. The thought behind most standardization is to be able to make a larger profit. The result is that with the

economies which are inevitable if you make only one thing, a larger and larger profit is continually being had by the manufacturer. His output also becomes larger - his facilities produce more - and before he knows it his markets are overflowing with goods which will not sell. These goods would sell if the manufacturer would take a lower price for them. There is always buying power present - but that buying power will not always respond to reductions in price. If an article has been sold at too high a price and then, because of stagnant business, the price is suddenly cut, the response is sometimes most disappointing. And for a very good reason. The public is wary. It thinks that the price-cut is a fake and it sits around waiting for a real cut. We saw much of that last year. If, on the contrary, the economies of making are transferred at once to the price and if it is well known that such is the policy of the manufacturer, the public will have confidence in him and will respond. They will trust him to give honest value. So standardization may seem bad business unless it carries with it the plan of constantly reducing the price at which the article is sold. And the price has to be reduced (this is very important) because of the manufacturing economies that have come about and not because the falling demand by the public indicates that it is not satisfied with the price. The public should always be wondering how it is possible to give so much for the money. Standardization (to use the word as I understand it) is not just taking one's best selling article and concentrating on it. It is planning day and

night and probably for years, first on something which will best suit the public and then on how it should be made. The exact processes of manufacturing will develop of themselves. Then, if we shift the manufacturing from the profit to the service basis, we shall have a real business in which the profits will be all that any one could desire.

All of this seems self-evident to me. It is the logical basis of any business that wants to serve 95 per cent. of the community. It is the logical way in which the community can serve itself. I cannot comprehend why all business does not go on this basis. All

that has to be done in order to adopt it is to overcome the habit of grabbing at the nearest dollar as though it were the only dollar in the world. The habit has already to an extent been overcome. All the large and successful retail stores in this country are on the one-price basis. The only further step required is to throw overboard the idea of

pricing on what the traffic will bear and instead go to the common-sense basis of pricing on what it costs to manufacture and then reducing the cost of manufacture. If the design of the product has been sufficiently studied, then changes in it will come

very slowly. But changes in manufacturing processes will come very rapidly and wholly naturally. That has been our experience in everything we have undertaken.

How naturally it has all come about, I shall later outline. The point that I wish to

impress here is that it is impossible to get a product on which one may concentrate unless an unlimited amount of study is given beforehand. It is not just an afternoon's work. These ideas were forming with me during this year of experimenting. Most of the experimenting went into the building of racing cars. The idea in those days was that a first-class car ought to be a racer. I never really thought much of racing, but following the bicycle idea, the manufacturers had the notion that winning a race on a track told the public something about the merits of an automobile - although I can hardly imagine any test that would tell less. But, as the others were doing it, I, too, had to do it. In 1903, with Tom Cooper, I built two cars solely for speed. They were quite alike. One we named the "999" and the other the "Arrow." If an automobile were going to be known for speed, then I was going to make an automobile that would be known wherever speed was known. These were. I put in four great big cylinders giving 80 H.P. - which up to that time had been unheard of. The roar of those cylinders alone was enough to half kill a man. There was only one seat. One life to a car was enough. I tried out the cars. Cooper tried out the cars. We let them out at full speed. I cannot quite describe the sensation. Going over Niagara Falls would have been but a pastime after a ride in one of them. I did not want to take the responsibility of racing the "999" which we put up first, neither did Cooper. Cooper said he knew a man who lived on speed, that nothing could go too fast for him. He wired to Salt Lake City and on came a professional bicycle rider named Barney Oldfield. He had never

driven a motor car, but he liked the idea of trying it. He said he would try anything once. It took us only a week to teach him how to drive. The man did not know what fear was. All that he had to learn was how to control the monster. Controlling the fastest car of to-day was nothing as compared to controlling that car. The steering wheel had not yet been thought of. All the previous cars that I had built simply had tillers. On this one I put a two-handed tiller, for holding the car in line required all the strength of a strong man. The race for which we were working was at three miles on the Grosse Point track. We kept our cars as a dark horse. We left the predictions to the others. The tracks then were not scientifically banked. It was not known how much speed a motor car could develop. No one knew better than Oldfield what the turns meant and as he took his seat, while I was cranking the car for the start, he remarked cheerily: "Well, this chariot may kill me, but they will say afterward that I was going like hell when she took me over the bank." And he did go.... He never dared to look around. He did not shut off on the curves. He simply let that car go - and go it did. He was about half a mile ahead of the next man at the end of the race! The "999" did what it was intended to do: It advertised the fact that I could build a fast motorcar. A week after the race I formed the Ford Motor Company. I was vice-president, designer, master mechanic, superintendent, and general manager. The capitalization of the

company was one hundred thousand dollars, and of this I owned 25 1/2 per cent. The total amount subscribed in cash was about twenty-eight thousand dollars - which is the only money that the company has ever received for the capital fund from other than operations. In the beginning I thought that it was possible, notwithstanding my former experience, to go forward with a company in which I owned less than the

controlling share. I very shortly found I had to have control and therefore in 1906, with funds that I had earned in the company, I bought enough stock to bring my holdings up to 51 per cent, and a little later bought enough more to give me 58-1/2 per cent. The new equipment and the whole progress of the company have always been financed out of earnings. In 1919 my son Edsel purchased the remaining 41-1/2 per cent of the stock because certain of the minority stockholders disagreed with my policies. For these shares he paid at the rate of \$12,500 for each \$100 par and in all paid about seventy-five millions. The original company and its equipment, as may be gathered, were not elaborate. We rented Strelow's carpenter shop on Mack Avenue. In making my designs I had also worked out the methods of making, but, since at that time we could not afford to buy machinery, the entire car was made according to my designs, but by various manufacturers, and about all we did, even in the way of

assembling, was to put on the wheels, the tires, and the body. That would really be the most economical method of manufacturing if only one could be certain that all of the various parts would be made on the manufacturing plan that I have above outlined.

The most economical manufacturing of the future will be that in which the whole of an article is not made under one roof—unless, of course, it be a very simple article.

The modern—or better, the future—method is to have each part made where it may

best be made and then assemble the parts into a complete unit at the points of consumption. That is the method we are now following and expect to extend. It would make no difference whether one company or one individual owned all the factories fabricating the component parts of a single product, or whether such part were made

in our independently owned factory, if only all adopted the same

service methods. If we can buy as good a part as we can make ourselves and the supply is ample and the price right, we do not attempt to make it ourselves—or, at any rate, to make more than an emergency supply. In fact, it might be better to have the ownership widely scattered people in the first year, built 1,708 cars, and had one branch house. In 1908, the factory space had increased to 2.65 acres and we owned the building. The average number of employees had increased to 1,908. We built

6,181 cars and had fourteen branch houses. It was a prosperous business. During the season 1908-1909 we continued to make Models "R" and "S," four-cylinder runabouts and roadsters, the models that had previously been so successful, and which sold at \$700 and \$750. But "Model T" swept them right out. We sold 10,607 cars - a larger number than any manufacturer had ever sold. The price for the touring car was \$850. On the same chassis we mounted a town car at \$1,000, a roadster at \$825, a coupe at \$950, and a landaulet at \$950. This season demonstrated conclusively to me that it was time to put the new policy in force. The salesmen, before I had announced the policy, were spurred by the great sales to think that even greater sales might be had if

only

we had more models. It is strange how, just as soon as an article becomes successful, somebody starts to think that it would be more successful if only it were different.

There is a tendency to keep monkeying with styles and to spoil a good thing by changing it. The salesmen were insistent on increasing the line. They listened to the 5 per cent., the special customers who could say what they wanted, and forgot all about the 95 per cent. who just bought without making any fuss. No business can improve unless it pays the closest possible attention to complaints and suggestions. If there is

any defect in service then that must be instantly and rigorously investigated, but when the suggestion is only as to style, one has to make sure whether it is not merely a personal whim that is being voiced. Salesmen always want to cater to whims instead of acquiring sufficient knowledge of their product to be able to explain to the customer with the whim that what they have will satisfy his every requirement - that is, of course, provided what they have does satisfy these requirements. Therefore in 1909 I announced one morning, without any previous warning, that in the future we were going to build only one model, that the model was going to be "Model T," and that the chassis would be exactly the same for all cars, and I remarked: "Any customer can have a car painted any colour that he wants so long as it is black." I cannot say that any one agreed with me. The selling people could not of course see the advantages that a single model would bring about in production. More than that, they did not particularly care. They thought that our production was good enough as it was and there was a very decided opinion that lowering the sales price would hurt sales, that the people who wanted quality would be driven away and that there would be none to replace them. There was very little conception of the motor industry. A motor car was still regarded as something in the way of a luxury. The manufacturers did a good deal to spread this idea. Some clever persons invented the name "pleasure car" and the advertising emphasized the pleasure features. The sales people had ground for their objections and particularly when I made the following announcement: "I will

build a motor car for the great multitude. It will be large enough for the family but small enough for the individual to run and care for. It will be constructed of the best materials, by the best men to be hired, after the simplest designs that modern engineering can devise. But it will be so low in price that no man making a good salary will be unable to own one - and enjoy with his family the blessing of hours of pleasure in God's great open spaces." This announcement was received not without pleasure. The general comment was: "If Ford does that he will be out of business in six months." The impression was that a good car could not be built at a low price, and that, anyhow, there was no use in building a low-priced car because only wealthy people were in the market for cars. The 1908-1909 sales of more than ten thousand cars had convinced me that we needed a new factory. We already had a big modern factory - the Piquette Street plant. It was as good as, perhaps a little better than, any automobile factory in the country. But I did not see how it was going to care for the sales and production that were inevitable. So I bought sixty acres at Highland Park, which was then considered away out in the country from Detroit. The amount of ground bought and the plans for a bigger factory than the world has ever seen were opposed. The question was already being asked: "How soon will Ford blow up?"

Nobody knows how many thousand times it has been asked since. It is asked only because of the failure to grasp that a principle rather than an individual is at work, and the principle is so simple that it seems mysterious. For 1909-1910, in order to pay for the new land and buildings, I slightly raised the prices. This is perfectly justifiable and results in a benefit, not an injury, to the purchaser. I did exactly the same thing a few years ago - or rather, in that case I did not lower the price as is my annual custom, in order to build the River Rouge plant. The extra money might in each case have been had by borrowing, but then we should have had a continuing charge upon the business and all subsequent cars would have had to bear this charge. The price of all the

models was increased \$100, with the exception of the roadster, which was increased only \$75 and of the landaulet and town car, which were increased \$150 and \$200 respectively. We sold 18,664 cars, and then for 1910-1911, with the new facilities, I cut the touring car from \$950 to \$780 and we sold 34,528 cars. That is the beginning of the steady reduction in the price of the cars in the face of ever-increasing cost of materials and ever-higher wages. Contrast the year 1908 with the year 1911. The factory space increased from 2.65 to 32 acres. The average number of employees from 1,908 to 4,110, and the cars built from a little over six thousand to nearly thirty-

five thousand. You will note that men were not employed in proportion to the output.

We were, almost overnight it seems, in great production. How did all this come about? Simply through the application of an inevitable principle. By the application of intelligently directed power and machinery. In a little dark shop on a side street an old

man had laboured for years making axe handles. Out of seasoned hickory he fashioned them, with the help of a draw shave, a chisel, and a supply of sandpaper. Carefully was each handle weighed and balanced. No two of them were alike. The curve must exactly fit the hand and must conform to the grain of the wood. From dawn until dark the old man laboured. His average product was eight handles a week,

for which he received a dollar and a half each. And often some of these were

unsaleable -because the balance was not true

Abstract

There is a new public health crisis threatening the world with the emergence and spread of 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus originated in bats and was transmitted to humans through yet unknown intermediary animals in Wuhan, Hubei province, China in December 2019. There have been around 96,000 reported cases of coronavirus disease 2019 (COVID-2019) and 3300 reported deaths to date (05/03/2020). The disease is transmitted by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 d. The symptoms are usually fever, cough, sore throat, breathlessness, fatigue, malaise among others. The disease is mild in most people; in some (usually the elderly and those with comorbidities), it may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction. Many people are asymptomatic. The case fatality rate is estimated to range from 2 to 3%. Diagnosis is by demonstration of the virus in respiratory secretions by special molecular tests. Common laboratory findings include normal/low white cell counts with elevated C-reactive protein (CRP). The computerized tomographic chest scan is usually abnormal even in those with no symptoms or mild disease. Treatment is essentially supportive; role of antiviral agents is yet to be

established. Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. The virus spreads faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but has lower .fatality. The global impact of this new epidemic is yet uncertain

Introduction

The 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) as it is now called, is rapidly spreading from its origin in Wuhan City of Hubei Province of China to the rest of the world [1]. Till 05/03/2020 around 96,000 cases of coronavirus disease 2019 (COVID-19) and 3300 deaths have been reported [2]. India has reported 29 cases till date. Fortunately so far, children have been infrequently affected with no deaths. But the future course of this virus is unknown. This article gives a bird's eye view about this new virus. Since knowledge about this virus is rapidly evolving, readers are urged to update themselves .regularly

History

Coronaviruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance under the electron microscope; hence the name coronavirus [3]. Four corona viruses namely HKU1, NL63, 229E and OC43 have been in circulation in humans, and generally cause mild respiratory disease

There have been two events in the past two decades wherein crossover of animal betacoronavirus to humans has resulted in severe disease. The first such instance was in 2002–2003 when a new coronavirus of the β genera and with origin in bats crossed over to humans via the intermediary host of palm civet cats in the Guangdong province of China. This virus, designated as severe acute respiratory syndrome coronavirus affected 8422 people mostly in China and Hong Kong and caused 916 deaths (mortality rate 11%) before being contained [4]. Almost a decade later in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected 2494 people and caused 858 deaths (fatality rate 34%) [5]

Origin and Spread of COVID-19 [1, 2, 6

In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals. The surveillance system (put into place after the SARS outbreak) was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7th January the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and > 70% similarity with the SARS- CoV. Environmental samples from the Huanan sea food market also tested positive, signifying that the virus originated from there [7]. The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring [8]. The first fatal case was reported on 11th Jan 2020. The massive migration of Chinese during the Chinese New Year fuelled the epidemic. Cases in other provinces of China, other countries (Thailand, Japan and South Korea in quick succession) were reported in people who were returning from Wuhan. Transmission to healthcare workers caring for patients was described on 20th Jan, 2020. By 23rd January, the 11 million population of Wuhan was placed under lock down with restrictions of entry and exit from the region. Soon this lock down was extended to other cities of Hubei province. Cases of COVID-19 in countries outside

China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries [9]. Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. Soon it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had travellers returning from China, placed all people symptomatic or otherwise in isolation for 14 d and tested them for the virus. Cases continued to increase exponentially and modelling studies reported an epidemic doubling time of 1.8 d [10]. In fact on the 12th of February, China changed its definition of confirmed cases to include patients with negative/ pending molecular tests but with clinical, radiologic and epidemiologic features of COVID-19 leading to an increase in cases by 15,000 in a single day [6]. As of 05/03/2020 96,000 cases worldwide (80,000 in China) and 87 other countries and 1 international conveyance (696, in the cruise ship Diamond Princess parked off the coast of Japan) have been reported [2]. It is important to note that while the number of new cases has reduced in China lately, they have increased exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died [2]. India, which had reported only 3 cases till 2/3/2020, has also seen a sudden spurt in cases. By 5/3/2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One

case was reported in an Indian who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of .these cases have been quarantined

These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain.

Pangolins and snakes are the current suspects

[Epidemiology and Pathogenesis [10, 11

All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic people and before onset of symptoms [9]. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people [12]. Patients can be infectious for as long as the symptoms last and even on clinical recovery. Some people may act as super spreaders; a UK citizen who attended a conference in Singapore infected 11 other people while staying in a resort in the French Alps and upon return to the UK [6]. These infected droplets can spread 1–2 m and deposit on surfaces. The virus can remain viable on surfaces for days in favourable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. [13]. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them and then touching the nose, mouth and eyes. The virus is also present in the stool and contamination of the water supply and subsequent transmission via aerosolization/feco oral route is also hypothesized [6]. As per current information, transplacental transmission from pregnant women to their fetus has not been

described [14]. However, neonatal disease due to post natal transmission is described [14]. The incubation period varies from 2 to 14 d [median 5 d]. Studies have identified angiotensin receptor 2 (ACE2) as the receptor through which the virus enters the respiratory mucosa [11]

The basic case reproduction rate (BCR) is estimated to range from 2 to 6.47 in various modelling studies [11]. In comparison, the BCR of SARS was 2 and 1.3 for pandemic flu H1N1 2009 [2]

[Clinical Features [8, 15–18

The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The common clinical features include fever (not in all), cough, sore throat, headache, fatigue, headache, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF α [15]. The median time from onset of symptoms to dyspnea was 5 d, hospitalization 7 d and acute respiratory distress syndrome (ARDS) 8 d. The need for intensive care admission was in 25–30% of affected patients in published series. Complications witnessed included acute lung injury, ARDS, shock and acute kidney injury. Recovery started in the 2nd or 3rd wk. The median duration of hospital stay in those who recovered was 10 d. Adverse outcomes and death are more common in the elderly and those with underlying co-morbidities (50–75% of fatal cases). Fatality rate in hospitalized adult patients ranged from 4 to 11%. The overall case fatality rate is estimated to range .[between 2 and 3% [2

Interestingly, disease in patients outside Hubei province has been reported to be milder than those from Wuhan [17]. Similarly, the severity and case fatality rate in patients outside China has been reported to be milder [6]. This may either be due to selection bias wherein the cases reporting from Wuhan included only the severe cases

or due to predisposition of the Asian population to the virus due to higher expression
[of ACE2 receptors on the respiratory mucosa [11

Disease in neonates, infants and children has been also reported to be significantly milder than their adult counterparts. In a series of 34 children admitted to a hospital in Shenzhen, China between January 19th and February 7th, there were 14 males and 20 females. The median age was 8 y 11 mo and in 28 children the infection was linked to a family member and 26 children had history of travel/residence to Hubei province in China. All the patients were either asymptomatic (9%) or had mild disease. No severe or critical cases were seen. The most common symptoms were fever (50%) and cough (38%). All patients recovered with symptomatic therapy and there were no deaths. One case of severe pneumonia and multiorgan dysfunction in a child has also been reported [19]. Similarly the neonatal cases that have been reported have been mild [20

[Diagnosis [21

A suspect case is defined as one with fever, sore throat and cough who has history of travel to China or other areas of persistent local transmission or contact with patients with similar travel history or those with confirmed COVID-19 infection. However cases may be asymptomatic or even without fever. A confirmed case is a suspect case .with a positive molecular test

Specific diagnosis is by specific molecular tests on respiratory samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage). Virus may also be detected in the stool and in severe cases, the blood. It must be remembered that the multiplex PCR panels currently available do not include the COVID-19. Commercial tests are also not available at present. In a suspect case in India, the appropriate sample has to be sent to designated reference labs in India or the National Institute of Virology in Pune. As the epidemic progresses, commercial tests .will become available

Other laboratory investigations are usually non specific. The white cell count is usually normal or low. There may be lymphopenia; a lymphocyte count <1000 has been associated with severe disease. The platelet count is usually normal or mildly low. The CRP and ESR are generally elevated but procalcitonin levels are usually normal. A high procalcitonin level may indicate a bacterial co-infection. The

ALT/AST, prothrombin time, creatinine, D-dimer, CPK and LDH may be elevated
.and high levels are associated with severe disease

The chest X-ray (CXR) usually shows bilateral infiltrates but may be normal in early disease. The CT is more sensitive and specific. CT imaging generally shows infiltrates, ground glass opacities and sub segmental consolidation. It is also abnormal in asymptomatic patients/ patients with no clinical evidence of lower respiratory tract involvement. In fact, abnormal CT scans have been used to diagnose COVID-19 in suspect cases with negative molecular diagnosis; many of these patients had positive
.[molecular tests on repeat testing [22

[Differential Diagnosis [21

The differential diagnosis includes all types of respiratory viral infections [influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, non COVID-19 coronavirus], atypical organisms (mycoplasma, chlamydia) and bacterial infections. It is not possible to differentiate COVID-19 from these infections clinically or through routine lab tests. Therefore travel history becomes important. However, as the epidemic spreads, the travel history will become .irrelevant

Treatment [21, 23]

The first step is to ensure .Treatment is essentially supportive and symptomatic adequate isolation (discussed later) to prevent transmission to other contacts, patients and healthcare workers. Mild illness should be managed at home with counseling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. Routine use of antibiotics and antivirals such as oseltamivir should be avoided in confirmed cases. In hypoxic patients, provision of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is indicated. Mechanical ventilation and even extra corporeal membrane oxygen support may be needed. Renal replacement therapy may be needed in some. Antibiotics and antifungals are required if co-infections are suspected or proven. The role of corticosteroids is unproven; while current international consensus and WHO advocate against their use, Chinese guidelines do recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS [24, 25]. Detailed guidelines for critical care management for COVID-19 have been published by the WHO [26]. There is, as of now, no approved treatment for COVID-19. Antiviral drugs such as ribavirin, lopinavir-ritonavir have been used based on the experience with SARS and MERS. In a historical control study in patients with

SARS, patients treated with lopinavir-ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone [15]

In the case series of 99 hospitalized patients with COVID-19 infection from Wuhan, oxygen was given to 76%, non-invasive ventilation in 13%, mechanical ventilation in 4%, extracorporeal membrane oxygenation (ECMO) in 3%, continuous renal replacement therapy (CRRT) in 9%, antibiotics in 71%, antifungals in 15%, glucocorticoids in 19% and intravenous immunoglobulin therapy in 27% [15]. Antiviral therapy consisting of oseltamivir, ganciclovir and lopinavir-ritonavir was given to 75% of the patients. The duration of non-invasive ventilation was 4–22 d [median 9 d] and mechanical ventilation for 3–20 d [median 17 d]. In the case series of children discussed earlier, all children recovered with basic treatment and did not need intensive care [17]

There is anecdotal experience with use of remdesvir, a broad spectrum anti RNA drug developed for Ebola in management of COVID-19 [27]. More evidence is needed before these drugs are recommended. Other drugs proposed for therapy are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferons, chloroquine and plasma of patients recovered from COVID-19 [21, 28, 29]. Additionally, recommendations about using traditional Chinese herbs find place in the Chinese guidelines [21]

[Prevention [21, 30

Since at this time there are no approved treatments for this infection, prevention is crucial. Several properties of this virus make prevention difficult namely, non-specific features of the disease, the infectivity even before onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness and transmission even after clinical recovery

Isolation of confirmed or suspected cases with mild illness at home is recommended. The ventilation at home should be good with sunlight to allow for destruction of virus. Patients should be asked to wear a simple surgical mask and practice cough hygiene. Caregivers should be asked to wear a surgical mask when in the same room as patient and use hand hygiene every 15–20 min

The greatest risk in COVID-19 is transmission to healthcare workers. In the SARS outbreak of 2002, 21% of those affected were healthcare workers [31]. Till date, almost 1500 healthcare workers in China have been infected with 6 deaths. The doctor who first warned about the virus has died too. It is important to protect healthcare workers to ensure continuity of care and to prevent transmission of infection to other patients. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission, infection control measures recommended are those for category A agents (cholera, plague). Patients should be placed in separate rooms or cohorted

together. Negative pressure rooms are not generally needed. The rooms and surfaces and equipment should undergo regular decontamination preferably with sodium hypochlorite. Healthcare workers should be provided with fit tested N95 respirators and protective suits and goggles. Airborne transmission precautions should be taken during aerosol generating procedures such as intubation, suction and tracheostomies. All contacts including healthcare workers should be monitored for development of symptoms of COVID-19. Patients can be discharged from isolation once they are afebrile for at least 3 d and have two consecutive negative molecular tests at 1 d sampling interval. This recommendation is different from pandemic flu where patients were asked to resume work/school once afebrile for 24 h or by day 7 of illness.

.Negative molecular tests were not a prerequisite for discharge

At the community level, people should be asked to avoid crowded areas and postpone non-essential travel to places with ongoing transmission. They should be asked to practice cough hygiene by coughing in sleeve/ tissue rather than hands and practice hand hygiene frequently every 15–20 min. Patients with respiratory symptoms should be asked to use surgical masks. The use of mask by healthy people in public places has not shown to protect against respiratory viral infections and is currently not recommended by WHO. However, in China, the public has been asked to wear masks in public and especially in crowded places and large scale gatherings are prohibited (entertainment parks etc). China is also considering introducing legislation to prohibit .[selling and trading of wild animals [32

The international response has been dramatic. Initially, there were massive travel restrictions to China and people returning from China/ evacuated from China are

being evaluated for clinical symptoms, isolated and tested for COVID-19 for 2 wks even if asymptomatic. However, now with rapid world wide spread of the virus these travel restrictions have extended to other countries. Whether these efforts will lead to .slowing of viral spread is not known

.A candidate vaccine is under development

Practice Points from an Indian Perspective

At the time of writing this article, the risk of coronavirus in India is extremely low. :But that may change in the next few weeks. Hence the following is recommended

Healthcare providers should take travel history of all patients with respiratory symptoms, and any international travel in the past 2 wks as well as contact with sick .people who have travelled internationally

They should set up a system of triage of patients with respiratory illness in the outpatient department and give them a simple surgical mask to wear. They should use surgical masks themselves while examining such patients and practice hand hygiene .frequently

Suspected cases should be referred to government designated centres for isolation and testing (in Mumbai, at this time, it is Kasturba hospital). Commercial kits for testing .are not yet available in India

Patients admitted with severe pneumonia and acute respiratory distress syndrome should be evaluated for travel history and placed under contact and droplet isolation. Regular decontamination of surfaces should be done. They should be tested for etiology using multiplex PCR panels if logistics permit and if no pathogen is identified, refer the samples for testing for SARS-CoV-2

All clinicians should keep themselves updated about recent developments including global spread of the disease

Non-essential international travel should be avoided at this time

People should stop spreading myths and false information about the disease and try to allay panic and anxiety of the public

Conclusions

This new virus outbreak has challenged the economic, medical and public health infrastructure of China and to some extent, of other countries especially, its neighbours. Time alone will tell how the virus will impact our lives here in India. More so, future outbreaks of viruses and pathogens of zoonotic origin are likely to continue. Therefore, apart from curbing this outbreak, efforts should be made to devise comprehensive measures to prevent future outbreaks of zoonotic origin

Coronaviruses are a diverse group of viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans. In 2002 and 2012, respectively, two highly pathogenic coronaviruses with zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in humans and caused fatal respiratory illness, making emerging coronaviruses a new public health concern in the twenty-first century¹. At the end of 2019, a novel coronavirus designated as SARS-CoV-2 emerged in the city of Wuhan, China, and caused an outbreak of unusual viral

pneumonia. Being highly transmissible, this novel coronavirus disease, also known as coronavirus disease 2019 (COVID-19), has spread fast all over the world^{2,3}. It has overwhelmingly surpassed SARS and MERS in terms of both the number of infected people and the spatial range of epidemic areas. The ongoing outbreak of COVID-19 has posed an extraordinary threat to global public health^{4,5}. In this Review, we summarize the current understanding of the nature of SARS-CoV-2 and COVID-19. On the basis of recently published findings, this comprehensive Review covers the basic biology of SARS-CoV-2, including the genetic characteristics, the potential zoonotic origin and its receptor binding. Furthermore, we will discuss the clinical and epidemiological features, diagnosis of and countermeasures against COVID-19

Emergence and spread

In late December 2019, several health facilities in Wuhan, in Hubei province in China, reported clusters of patients with pneumonia of unknown cause⁶. Similarly to patients with SARS and MERS, these patients showed symptoms of viral pneumonia, including fever, cough

and chest discomfort, and in severe cases dyspnea and bilateral lung infiltration^{6,7}.

Among the first 27 documented hospitalized patients, most cases were epidemiologically linked to Huanan Seafood Wholesale Market, a wet market located in downtown Wuhan, which sells not only seafood but also live animals, including poultry and wildlife^{4,8}. According to a retrospective study, the onset of the first known case dates back to 8 December 2019 (ref.⁹). On 31 December, Wuhan Municipal Health Commission notified the public of a pneumonia outbreak of (unidentified cause and informed the World Health Organization (WHO)⁹ (fig. 1

By metagenomic RNA sequencing and virus isolation from bronchoalveolar lavage fluid samples from patients with severe pneumonia, independent teams of Chinese

scientists identified that the causative agent of this emerging disease is a betacoronavirus that had never been seen before^{6,10,11}. On 9 January 2020, the result of this etiological identification was publicly announced (fig. 1). The first genome sequence of the novel coronavirus was published on the Virological website on 10 January, and more nearly complete genome sequences determined by different research institutes were then released via the GISAID database on 12 January⁷. Later, more patients with no history of exposure to Huanan Seafood Wholesale Market were identified. Several familial clusters of infection were reported, and nosocomial infection also occurred in health-care facilities. All these cases provided clear evidence for human-to-human transmission of the new virus^{4,12–14}. As the outbreak coincided with the approach of the lunar New Year, travel between cities before the festival facilitated virus transmission in China. This novel coronavirus pneumonia soon spread to other cities in Hubei province and to other parts of China. Within 1 month it had spread massively to all 34 provinces of China. The number of confirmed cases suddenly increased, with thousands of new cases diagnosed daily during late January¹⁵. On 30 January, the WHO declared the novel coronavirus outbreak a public health emergency of international concern¹⁶. On 11 February, the International Committee on Taxonomy of Viruses named the novel coronavirus ‘SARS-CoV-2’, (and the WHO named the disease ‘COVID-19’ (ref.¹⁷

The outbreak of COVID-19 in China reached an epidemic peak in February.


According to the National Health Commission of China, the total number of cases continued to rise sharply in early February at an average rate of more than 3,000 newly confirmed cases per day. To control COVID-19, China implemented unprecedentedly strict public health measures. The city of Wuhan was shut down on 23 January, and all travel and transportation connecting the city was blocked. In the following couple of weeks, all outdoor activities and gatherings were restricted, and public facilities were closed in most cities as well as in countryside¹⁸. Owing to these measures, the daily number of new cases in China started to decrease steadily¹⁹

However, despite the declining trend in China, the international spread of COVID-19 accelerated from late February. Large clusters of infection have been reported from an increasing number of countries¹⁸. The high transmission efficiency of SARS-CoV-2 and the abundance of international travel enabled rapid worldwide spread of COVID-19. On 11 March 2020, the WHO officially characterized the global COVID-19 outbreak as a pandemic²⁰. Since March, while COVID-19 in China has become effectively controlled, the case numbers in Europe, the USA and other regions have jumped sharply. According to the COVID-19 dashboard of the Center for System Science and Engineering at Johns Hopkins University, as of 11 August 2020 countries and regions from all six continents had reported more than 20 million ²¹ cases of COVID-19, and more than 733,000 patients had died²¹. High mortality

occurred especially when health-care resources were overwhelmed. The USA is the .country with the largest number of cases so far

Although genetic evidence suggests that SARS-CoV-2 is a natural virus that likely originated in animals, there is no conclusion yet about when and where the virus first entered humans. As some of the first reported cases in Wuhan had no epidemiological link to the seafood market²², it has been suggested that the market may not be the initial source of human infection with SARS-CoV-2. One study from France detected SARS-CoV-2 by PCR in a stored sample from a patient who had pneumonia at the end of 2019, suggesting SARS-CoV-2 might have spread there much earlier than the generally known starting time of the outbreak in France²³. However, this individual early report cannot give a solid answer to the origin of SARS-CoV-2 and contamination, and thus a false positive result cannot be excluded. To address this highly controversial issue, further retrospective investigations involving a larger number of banked samples from patients, animals and environments need to be .conducted worldwide with well-validated assays

Genomics, phylogeny and taxonomy

As a novel betacoronavirus, SARS-CoV-2 shares 79% genome sequence identity with SARS-CoV and 50% with MERS-CoV²⁴. Its genome organization is shared with other betacoronaviruses. The six functional open reading frames (ORFs) are arranged in order from 5' to 3': replicase (ORF1a/ORF1b), spike (S), envelope (E), membrane (M) and nucleocapsid . In addition, seven putative ORFs encoding accessory proteins are interspersed between the structural genes²⁵. Most of the proteins encoded by SARS-CoV-2 have a similar length to the corresponding proteins in SARS-CoV. Of the four structural genes, SARS-CoV-2 shares more than 90% amino acid identity with SARS-CoV except for the S gene, which diverges^{11,24}. The replicase gene covers two thirds of the 5' genome, and encodes a large polyprotein (pp1ab), which is proteolytically cleaved into 16 non-structural proteins that are involved in transcription and virus replication. Most of these SARS-CoV-2 non-structural proteins have greater than 85% amino acid .sequence identity with SARS-CoV²⁵

The phylogenetic analysis for the whole genome shows that SARS-CoV-2 is clustered with SARS-CoV and SARS-related coronaviruses (SARSr-CoVs) found in bats, placing it in the subgenus Sarbecovirus of the genus Betacoronavirus. Within this clade, SARS-CoV-2 is grouped in a distinct lineage together with four horse-shoe bat coronavirus isolates (RaTG13, RmYN02, ZC45 and ZXC21) as well as novel coronaviruses recently identified in pangolins, which group parallel to SARS-CoV and other SARSr-CoVs (fig. 2). Using sequences of five conserved replicative domains in pp1ab (3C-like protease (3CL^{pro}), nidovirus RNA-dependent RNA polymerase (RdRp)-associated nucleotidyltransferase (NiRAN), RdRp, zinc-binding domain (ZBD) and HEL1), the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses estimated the pairwise patristic distances between SARS-CoV-2 and known coronaviruses, and assigned SARS-CoV-2 to the existing species SARSr-CoV17. Although phylogenetically related, SARS-CoV-2 is distinct from all other coronaviruses from bats and pangolins in this species.

The SARS-CoV-2 S protein has a full size of 1,273 amino acids, longer than that of SARS-CoV (1,255 amino acids) and known bat SARSr-CoVs (1,245–1,269 amino acids). It is distinct from the S proteins of most members in the subgenus Sarbecovirus, sharing amino acid sequence similarities of 76.7–77.0% with SARS-CoVs from civets and humans

polymorphism at nucleotide position 28,144, which results in amino acid substitution of Ser for Lys at residue 84 of the ORF8 protein. Those variants with this mutation make up a single subclade labelled as 'clade S'^{33,34}. Currently, however, the available sequence data are not sufficient to interpret the early global transmission history of the virus, and travel patterns, founder effects and public health measures also strongly influence the spread of particular lineages, irrespective of potential biological differences between different virus variants

Animal host and spillover

Bats are important natural hosts of alphacoronaviruses and betacoronaviruses. The closest relative to SARS-CoV-2 known to date is a bat coronavirus detected in *Rhinolophus affinis* from Yunnan province, China, named 'RaTG13', whose full-length genome sequence is 96.2% identical to that of SARS-CoV-2 (ref.11). This bat virus shares more than 90% sequence identity with SARS-CoV-2 in all ORFs throughout the genome, including the highly variable S and ORF8 (ref.11).

Phylogenetic analysis confirms that SARS-CoV-2 closely clusters with RaTG13 (fig. 2). The high genetic similarity between SARS-CoV-2 and RaTG13 supports the hypothesis that SARS-CoV-2 likely originated from bats³⁵. Another related coronavirus has been reported more recently in a *Rhinolophus malayanus* bat sampled in Yunnan. This novel bat virus, denoted 'RmYN02

appeared asymptomatic⁴⁵. Another serological study detected SARS-CoV-2 neutralizing antibodies in cat serum samples collected in Wuhan after the COVID-19 outbreak, providing evidence for SARS-CoV-2 infection in cat populations in Wuhan, although the potential of SARS-CoV-2 transmission from cats to humans is currently uncertain⁴⁶

Receptor use and pathogenesis

SARS-CoV-2 uses the same receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2)^{11,47}. Besides human ACE2 (hACE2), SARS-CoV-2 also recognizes ACE2 from pig, ferret, rhesus monkey, civet, cat, pangolin, rabbit and dog^{11,43,48,49}. The broad receptor usage of SARS-CoV-2 implies that it may have a wide host range, and the varied efficiency of ACE2 usage in different animals may indicate their different susceptibilities to SARS-CoV-2 infection. The S1 subunit of a coronavirus is further divided into two functional domains, an N-terminal domain and a C-terminal domain. Structural and biochemical analyses identified a 211 amino acid region (amino acids 319–529) at the S1 C-terminal domain of SARS-CoV-2 as the RBD, which has a key role in virus entry and is the target of neutralizing antibodies^{50,51} (fig. 3a). The RBM mediates contact with the ACE2 receptor (amino acids 437–507 of SARS-CoV-2 S protein), and this region in SARS-CoV-2 differs from that in SARS-CoV in

the five residues critical. The pathogenesis of SARS-CoV-2 infection in humans manifests itself as mild symptoms to severe respiratory failure. On binding to epithelial cells in the respiratory tract, SARS-CoV-2 starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs. The rapid replication of SARS-CoV-2 in the lungs may trigger a strong immune response. Cytokine storm syndrome causes acute respiratory distress syndrome and respiratory failure, which is considered the main cause of death in patients with COVID-19 (refs60,61). Patients of older age (>60 years) and with serious pre-existing diseases have a greater risk of developing acute respiratory distress syndrome and death62–64 (fig. 4). Multiple organ failure has also been reported in some COVID-19 cases9,13,65

Histopathological changes in patients with COVID-19 occur mainly in the lungs.

Histopathology analyses showed bilateral diffused alveolar damage, hyaline membrane formation, desquamation of pneumocytes and fibrin deposits in lungs of patients with severe COVID-19. Exudative inflammation was also shown in some cases. Immunohistochemistry assays detected SARS-CoV-2 antigen in the upper airway, bronchiolar epithelium and submucosal gland epithelium, as well as in type I

and type II pneumocytes, alveolar macrophages and hyaline membranes in the lungs^{13,60,66,67}

Animal models used for studying SARS-CoV-2 infection pathogenesis include non-human primates (rhesus macaques, cynomolgus monkeys, marmosets and African green monkeys), mice (wild-type mice (with mouse-adapted virus) and human ACE2-transgenic or human ACE2-knock-in mice), ferrets and golden hamsters^{43,48,68–74}.

In non-human primate animal models, most species display clinical features similar to those of patients with COVID-19, including virus shedding, virus replication and host responses to SARS-CoV-2 infection^{69,72,73}. For example, in the rhesus macaque model, high viral loads were detected in the upper and

lower respiratory tracts. Acute viral interstitial pneumonia and humoral and cellular immune responses were observed^{48,75}. Moreover, prolonged virus shedding peaked early in the course of infection in asymptomatic macaques⁶⁹, and old monkeys

showed severer interstitial pneumonia than young monkeys⁷⁶, which is similar to what is seen in patients with COVID-19. In human ACE2-transgenic mice infected with SARS-CoV-2, typical interstitial pneumonia was present, and viral antigens

were observed mainly in the bronchial epithelial cells, macrophages and alveolar epithelia. Some human ACE2-transgenic mice even died after infection^{70,71}. In

wild-type mice, a SARS-CoV-2 mouse-adapted strain with the N501Y alteration in the RBD of the S protein was generated at passage 6. Interstitial pneumonia and

inflammatory responses were found in both young and aged mice after infection with the mouse-adapted strain⁷⁴. Golden hamsters also showed typical symptoms after being infected with SARS-CoV-2 (ref.⁷⁷). In other animal models, including cats and ferrets, SARS-CoV-2 could efficiently replicate in the upper respiratory tract but did not induce severe clinical symptoms^{43,78}. As transmission by direct contact and air was observed in infected ferrets and hamsters, these animals could be used to model different transmission modes of COVID-19 (refs^{77–79}). Animal models offer important information for understanding the pathogenesis of SARS-CoV-2 infection and the transmission dynamics of SARS-CoV-2, and are important to evaluate the efficacy of antiviral therapeutics and vaccines

Clinical and epidemiological feature

It appears that all ages of the population are susceptible to SARS-CoV-2 infection, and the median age of infection is around 50 years^{9,13,60,80,81}. However, clinical manifestations differ with age. In general, older men (>60 years old) with comorbidities are more likely to develop severe respiratory disease that requires hospitalization or even die, whereas most young people and children have only mild diseases (non-pneumonia or mild pneumonia) or are asymptomatic^{9,81,82}. Notably, the risk of disease was not higher for pregnant women. However, evidence of transplacental transmission of SARS-CoV-2 from an infected mother to a neonate was reported, although it was an isolated case^{83,84}. On infection, the most common symptoms are fever, fatigue and dry cough^{13,60,80,81}. Less common symptoms include sputum production, headache, haemoptysis, diarrhoea, anorexia, sore throat, chest pain, chills and nausea and vomiting in studies of patients in China^{13,60,80,81}. Self-reported olfactory and taste disorders were also reported by patients in Italy⁸⁵. Most people showed signs of diseases after an incubation period of 1–14 days (most commonly around 5 days), and dyspnoea and pneumonia developed within a median time of 8 days from illness onset⁹.

In a report of 72,314 cases in China, 81% of the cases were classified as mild, 14% were severe cases that required ventilation in an intensive care unit (ICU) and a 5% were critical (that is, the patients had respiratory failure, septic shock and/or multiple organ dysfunction or failure)^{9,86}. On admission, ground-glass opacity was the most common radiologic finding on chest computed tomography (CT)^{13,60,80,81}. Most patients also developed marked lymphopenia, similar to what was observed in patients with SARS and MERS, and non-survivors developed severer lymphopenia over time^{13,60,80,81}. Compared with non-ICU patients, ICU patients had higher levels of plasma cytokines which suggests an immunopathological process caused by a cytokine storm^{60,86,87}. In this cohort of patient, around 2.3% people died within a median time of 16 days from disease onset^{9,86}. Men older than 68 years had a higher risk of respiratory failure, acute cardiac injury and heart failure that led to death, regardless of a history of cardiovascular disease⁸⁶ (fig. 4). Most patients recovered (enough to be released from hospital in 2 weeks^{9,80} (fig. 4

Early transmission of SARS-CoV-2 in Wuhan in December 2019 was initially linked to the Huanan Seafood Wholesale Market, and it was suggested as the source of the outbreak^{9,22,60}. However, community transmission might have happened before

that⁸⁸. Later, ongoing human-to-human transmission propagated the outbreak⁹. It is generally accepted that SARS-CoV-2 is more transmissible than SARS-CoV and MERS-CoV; however, determination of an accurate reproduction number (R₀) for COVID-19 is not possible yet, as many asymptomatic infections cannot be accurately accounted for at this stage⁸⁹. An estimated R₀ of 2.5 (ranging from 1.8 to 3.6) has been proposed for SARS-CoV-2 recently, compared with 2.0–3.0 for SARS-CoV⁹⁰. Notably, most of the SARS-CoV-2 human-to-human transmission early in China occurred in family clusters, and in other countries large outbreaks also happened in other settings, such as migrant worker communities, slaughterhouses and meat packing plants, indicating the necessity of isolating infected people^{9,12,91–93}.

Nosocomial transmission was not the main source of transmission in China because of the implementation of infection control measures in clinical settings⁹. By contrast, a high risk of nosocomial transmission was reported in some other areas. For example, a cohort study in London revealed 44% of the frontline health-care workers from a hospital were infected with SARS-CoV-2 (ref.⁹⁴

The high transmissibility of SARS-CoV-2 may be attributed to the unique virological

features of SARS-CoV-2. Transmission of SARS-CoV occurred mainly after illness onset and peaked following disease severity⁹⁵. However, the SARS-CoV-2 viral load in upper respiratory tract samples was already highest during the first week of symptoms, and thus the risk of pharyngeal virus shedding was very high at the beginning of infection^{96,97}. It was postulated that undocumented infections might account for 79% of documented cases owing to the high transmissibility of the virus during mild disease or the asymptomatic period⁸⁹. A patient with COVID-19 spreads viruses in liquid droplets during speech. However, smaller and much more numerous particles known as aerosol particles can also be visualized, which could linger in the air for a long time and then penetrate deep into the lungs when inhaled by someone else^{98–100}. Airborne transmission was also observed in the ferret experiments mentioned above. SARS-CoV-2-infected ferrets shed viruses in nasal washes, saliva, urine and faeces for up to 8 days after infection, and a few naive ferrets with only indirect contact were positive for viral RNA, suggesting airborne transmission⁷⁸. In addition, transmission of the virus through the ocular surface and prolonged presence

of SARS-CoV-2 viral RNA in faecal samples were also documented^{101,102}.

Coronaviruses can persist on inanimate surfaces for days, which could also be the

case for SARS-CoV-2 and could pose a prolonged risk of infection¹⁰³. These

findings explain the rapid geographic spread of COVID-19, and public health

interventions to reduce transmission will provide benefit to mitigate the epidemic, as

has proved successful in China and several other countries, such as South

Korea^{89,104,105}

Diagnosis

Early diagnosis is crucial for controlling the spread of COVID-19. Molecular detection of SARS-CoV-2 nucleic acid is the gold standard. Many viral nucleic acid detection kits targeting ORF1b (including RdRp), N, E or S genes are commercially available^{11,106–109}. The detection time ranges from several minutes to hours depending on the technology^{106,107,109–111}. The molecular detection can be affected by many factors. Although SARS-CoV-2 has been detected from a variety of respiratory sources, including throat swabs, posterior oropharyngeal saliva, nasopharyngeal swabs, sputum and bronchial fluid, the viral load is higher in lower respiratory tract samples^{11,96,112–115}. In addition, viral nucleic acid was also found in samples from the intestinal tract or blood even when respiratory samples were negative¹¹⁶. Lastly, viral load may already drop from its peak level on disease onset^{96,97}. Accordingly, false negatives can be common when oral swabs are used, and so multiple detection methods should be adopted to confirm a COVID-19 diagnosis^{117,118}. Other detection methods were therefore used to overcome this

problem. Chest CT was used to quickly identify a patient when the capacity of molecular detection was overloaded in Wuhan. Patients with COVID-19 showed typical features on initial CT, including bilateral multilobar ground-glass opacities with a peripheral or posterior distribution^{118,119}. Thus, it has been suggested that CT scanning combined with repeated swab tests should be used for individuals with high clinical suspicion of COVID-19 but who test negative in initial nucleic acid screening¹¹⁸. Finally, SARS-CoV-2 serological tests detecting antibodies to N or S protein could complement molecular diagnosis, particularly in late phases after disease onset or for retrospective studies^{116,120,121}. However, the extent and duration of immune responses are still unclear, and available serological tests differ in their sensitivity and specificity, all of which need to be taken into account when one is deciding on serological tests and interpreting their results or potentially in the future .test for T cell responses

Therapeutics

To date, there are no generally proven effective therapies for COVID-19 or antivirals against SARS-CoV-2, although some treatments have shown some benefits in certain subpopulations of patients or for certain end points (see later). Researchers and manufacturers are conducting large-scale clinical trials to evaluate various therapies for COVID-19. As of 2 October 2020, there were about 405 therapeutic drugs in development for COVID-19, and nearly 318 in human clinical trials (COVID-19 vaccine and therapeutics tracker). In the following sections, we summarize potential therapeutics against SARS-CoV-2 on the basis of published clinical data and experience

Inhibition of virus entry.

SARS-CoV-2 uses ACE2 as the receptor and human proteases as entry activators; subsequently it fuses the viral membrane with the cell membrane and achieves invasion. Thus, drugs that interfere with entry may be a potential treatment for COVID-19. Umifenovir (Arbidol) is a drug approved in Russia and China for the treatment of influenza and other respiratory viral infections. It can target the interaction between the S protein and ACE2 and inhibit membrane fusion (fig. 5). In vitro experiments showed that it has activity against SARS-CoV-2, and current clinical data revealed it may be more effective than lopinavir and ritonavir in treating COVID-19 (refs122,123). However, other clinical studies showed umifenovir might not improve the prognosis of or accelerate SARS-CoV-2 clearance in patients with mild to moderate COVID-19 (refs124,125). Yet some ongoing clinical trials are evaluating its efficacy for COVID-19 treatment. Camostat mesylate is approved in

Japan for the treatment of pancreatitis and postoperative reflux oesophagitis.

Previous studies showed that it can prevent SARS-CoV from entering cells by blocking TMPRSS2 activity and protect mice from lethal infection with SARS-CoV

in a pathogenic mouse model (wild-type mice infected with a mouse-adapted SARS-CoV strain)^{126,127}. Recently, a study revealed that camostat mesylate blocks the entry of SARS-CoV-2 into human lung cells⁴⁷. Thus, it can be a potential antiviral drug against SARS-CoV-2 infection, although so far there are not sufficient clinical data to support its efficacy

Chloroquine and hydroxychloroquine are other potential but controversial drugs that interfere with the entry of SARS-CoV-2. They have been used in the prevention and treatment of malaria and autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis. They can inhibit the glycosylation of cellular receptors and interfere with virus–host receptor binding, as well as increase

the endosomal pH and inhibit membrane fusion. Currently, no scientific consensus has been reached for their efficacy in the treatment of COVID-19. Some studies showed they can inhibit SARS-CoV-2 infection in vitro, but the clinical data are insufficient^{128,129}. Two clinical studies indicated no association with death rates in patients receiving chloroquine or hydroxychloroquine compared with those not receiving the drug and even suggest it may increase the risk of dying as a higher risk of cardiac arrest was found in the treated patients^{130,131}. On 15 June 2020, owing to the side effects observed in clinical trials, the US Food and Drug Administration (FDA) revoked the emergency use authorization for chloroquine and hydroxychloroquine for the treatment of COVID-19. Another potential therapeutic strategy is to block binding of the S protein to ACE2 through soluble recombinant hACE2, specific monoclonal antibodies or fusion inhibitors that target the SARS-CoV-2 S protein^{132–134} (fig. 5). The safety and efficacy of these strategies need to be assessed in future clinical trials

Inhibition of virus replication. Replication inhibitors include remdesivir (GS-5734), favilavir (T-705), ribavirin, lopinavir and ritonavir. Except for lopinavir and ritonavir, which inhibit 3CL^{pro}, the other three all target RdRp^{128,135} (fig. 5).

Remdesivir has shown activity against SARS-CoV-2 in vitro and in vivo^{128,136}. A clinical study revealed a lower need for oxygen support in patients with COVID-19 (ref.137). Preliminary results of the Adaptive COVID-19 Treatment Trial (ACTT) clinical trial by the National Institute of Allergy and Infectious Diseases (NIAID) reported that remdesivir can shorten the recovery time in hospitalized adults with COVID-19 by a couple days compared with placebo, but the difference in mortality was not statistically significant¹³⁸. The FDA has issued an emergency use authorization for remdesivir for the treatment of hospitalized patients with severe COVID-19. It is also the first approved option by the European Union for treatment of adults and adolescents with pneumonia requiring supplemental oxygen. Several international phase III clinical trials are continuing to evaluate the safety and efficacy of remdesivir for the treatment of COVID-19

Favilavir (T-705), which is an antiviral drug developed in Japan to treat influenza,

has been approved in China, Russia and India for the treatment of COVID-19. A clinical study in China showed that favilavir significantly reduced the signs of improved disease signs on chest imaging and shortened the time to viral clearance¹³⁹. A preliminary report in Japan showed rates of clinical improvement of 73.8% and 87.8% from the start of favilavir therapy in patients with mild COVID-19 at 7 and 14 days, respectively, and 40.1% and 60.3% in patients with severe COVID-19 at 7 and 14 days respectively¹⁴⁰. However, this study did not include a control arm, and most of the trials of favilavir were based on a small sample size. For more reliable assessment of the effectiveness of favilavir for treating COVID-19, large-scale randomized .controlled trials should be conducted

Lopinavir and ritonavir were reported to have in vitro inhibitory activity against SARS-CoV and MERS-CoV^{141,142}. Alone, the combination of lopinavir and ritonavir had little therapeutic benefit in patients with COVID-19, but appeared more effective when used in combination with other drugs, including ribavirin and interferon beta-1b^{143,144}. The Randomized Evaluation of COVID-19 Therapy

(RECOVERY) trial, a national clinical trial programme in the UK, has stopped treatment with lopinavir and ritonavir as no significant beneficial effect was observed in a randomized trial established in March 2020 with a total of 1,596 patients¹⁴⁵.

.Nevertheless other clinical trials in different phases are still ongoing elsewhere

Immunomodulatory agents. SARS-CoV-2 triggers a strong immune response which may cause cytokine storm syndrome^{60,61}. Thus, immunomodulatory agents that inhibit the excessive inflammatory response may be a potential adjunctive therapy for COVID-19. Dexamethasone is a corticosteroid often used in a wide range of conditions to relieve inflammation through its anti-inflammatory and

immunosuppressant effects. Recently, the RECOVERY trial found dexamethasone reduced mortality by about one third in hospitalized patients with COVID-19 who received invasive mechanical ventilation and by one fifth in patients receiving .oxygen. By contrast, no benefit was found in patients without respiratory support¹⁴⁶

Tocilizumab and sarilumab, two types of interleukin-6 (IL-6) receptor-specific antibodies previously used to treat various types of arthritis, including rheumatoid arthritis, and cytokine release syndrome, showed effectiveness in the treatment of severe COVID-19 by attenuating the cytokine storm in a small uncontrolled trial¹⁴⁷.

Bevacizumab is an anti-vascular endothelial growth factor (VEGF) medication that could potentially reduce pulmonary oedema in patients with severe COVID-19.

Eculizumab is a specific monoclonal antibody that inhibits the proinflammatory complement protein C5. Preliminary results showed that it induced a drop of inflammatory markers and C-reactive protein levels, suggesting its potential to be an option for the treatment of severe COVID-19 (ref.148)

The interferon response is one of the major innate immunity defences against virus invasion. Interferons induce the expression of diverse interferon-stimulated genes,

which can interfere with every step of virus replication. Previous studies identified type I interferons as a promising therapeutic candidate for SARS149. In vitro data showed SARS-CoV-2 is even more sensitive to type I interferons than SARS-CoV, suggesting the potential effectiveness of type I interferons in the early treatment of COVID-19 (ref.150). In China, vapor inhalation of interferon- α is included in the COVID-19 treatment guideline151. Clinical trials are ongoing across the world to evaluate the efficacy of different therapies involving interferons, either alone or in combination with other agents152

Immunoglobulin therapy.

Convalescent plasma treatment is another potential adjunctive therapy for COVID-19. Preliminary findings have suggested improved clinical status after the treatment^{153,154}. The FDA has provided guidance for the use of COVID-19 convalescent plasma under an emergency investigational new drug application. However, this treatment may have adverse effects by causing antibody-mediated enhancement of infection, transfusion-associated acute lung injury and allergic transfusion reactions.

Monoclonal antibody therapy is an effective immunotherapy for the treatment of some viral infections in select patients. Recent studies reported specific monoclonal antibodies neutralizing SARS-CoV-2 infection.

in vitro and in vivo^{155–158}. Compared with convalescent plasma, which has limited availability and cannot be amplified, monoclonal antibodies can be developed in larger quantities to meet clinical requirements. Hence, they provide the possibility for the treatment and prevention of COVID-19. The neutralizing epitopes of these monoclonal antibodies also offer important information for vaccine design. However, the high cost and limited capacity of manufacturing, as well as the problem of bioavailability, may restrict the wide application of monoclonal antibody therapy

Vaccines

Vaccination is the most effective method for a long-term strategy for prevention and control of COVID-19 in the future. Many different vaccine platforms against SARS-CoV-2 are in development, the strategies of which include recombinant vectors, DNA, mRNA in lipid nanoparticles, inactivated viruses, live attenuated viruses and protein subunits^{159–161}. As of 2 October 2020, ~174 vaccine candidates for COVID-19 had been reported and 51 were in human clinical trials (COVID-19 vaccine and therapeutics tracker). Many of these vaccine candidates are in phase II testing, and some have already advanced to phase III trials. A randomized double-blinded phase II trial of an adenovirus type 5-vectored vaccine expressing the SARS-CoV-2 S protein, developed by CanSino Biologicals and the Academy of Military Medical Sciences of China, was conducted in 603 adult volunteers in Wuhan. The vaccine has proved to be safe and induced considerable humoral and cellular immune response in most recipients after a single immunization¹⁶². Another vectored vaccine, ChAdOx1, was developed on the basis of chimpanzee adenovirus by the

University of Oxford. In a randomized controlled phase I/II trial, it induced neutralizing antibodies against SARS-CoV-2 in all 1,077 participants after a second vaccine dose, while its safety profile was acceptable as well¹⁶³. The NIAID and Moderna co-manufactured mRNA-1273, a lipid nanoparticle-formulated mRNA vaccine candidate that encodes the stabilized prefusion SARS-CoV-2 S protein. Its immunogenicity has been confirmed by a phase I trial in which robust neutralizing antibody responses were induced in a dose-dependent manner and increased after a second dose¹⁶⁴. Regarding inactivated vaccines, a successful phase I/II trial involving 320 participants has been reported in China. The whole-virus COVID-19 vaccine had a low rate of adverse reactions and effectively induced neutralizing antibody production¹⁶⁵. The verified safety and immunogenicity support advancement of these vaccine candidates to phase III clinical trials, which will evaluate their efficacy in protecting healthy populations from SARS-CoV-2 infection

Future perspectives

COVID-19 is the third highly pathogenic human coronavirus disease to date.

Although less deadly than SARS and MERS, the rapid spreading of this highly contagious disease has posed the severest threat to global health in this century. The SARS-CoV-2 outbreak has lasted for more than half a year now, and it is likely that this emerging virus will establish a niche in humans and coexist with us for a long time¹⁶⁶. Before clinically approved vaccines are widely available, there is no better way to protect us from SARS-CoV-2 than personal preventive behaviours such as social distancing and wearing masks, and public health measures, including active testing, case tracing and restrictions on social gatherings. Despite a flood of SARS-CoV-2 research published every week, current knowledge of this novel coronavirus is just the tip of the iceberg. The animal origin and cross-species infection route of

SARS-CoV-2 are yet to be uncovered. The molecular mechanisms of SARS-CoV-2 infection pathogenesis and virus–host

interactions remain largely unclear. Intensive studies on these virological profiles of SARS-CoV-2 will provide the basis for the development of preventive and therapeutic strategies against COVID-19. Moreover, continued genomic monitoring of SARS-CoV-2 in new cases is needed worldwide, as it is important to promptly identify any mutation that may result in phenotypic changes of the virus. Finally, COVID-19 is challenging all human beings. Tackling this epidemic is a long-term job which requires efforts of every individual, and international collaborations by scientists, .., authorities and the public